Developing an ontology for radiation oncology

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DEVELOPING AN ONTOLOGY FOR RADIATION ONCOLOGY

A Thesis Submitted in Partial Fulfilment of the Requirements for the Award of the Degree of

Master of Information and Communication Technology (Research)

from

UNIVERSITY OF WOLLONGONG

by

Alexis Andrew Miller

School of Information Systems and Technology
Faculty of Informatics
2012
CERTIFICATION

I, Alexis Andrew Miller, declare that this thesis, submitted in partial fulfilment of the requirements for the award of Master of Information and Communication Technology (Research), in the School of Information Systems and Technology, Faculty of Informatics, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. The document has not been submitted for qualifications at any other academic institution.

(Signature Required)
Alexis Andrew Miller
13 October 2012
Dedicated to

My wife, Dr Allison Miller, FRACGP
and my sister, Dr Celeste Rossetto, Ph.D
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acknowledgements</td>
<td>iv</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>v</td>
</tr>
<tr>
<td><strong>1 Background</strong></td>
<td>1</td>
</tr>
<tr>
<td>1.1 The Motivation and Academic Course of the Research</td>
<td>1</td>
</tr>
<tr>
<td>1.2 Radiation Oncology as an Expert Domain</td>
<td>4</td>
</tr>
<tr>
<td><strong>2 Introduction</strong></td>
<td>8</td>
</tr>
<tr>
<td>2.1 What is the problem?</td>
<td>8</td>
</tr>
<tr>
<td>2.2 Why is this research important?</td>
<td>11</td>
</tr>
<tr>
<td>2.3 Who will be interested in this research?</td>
<td>12</td>
</tr>
<tr>
<td>2.4 What is the structure of this thesis?</td>
<td>13</td>
</tr>
<tr>
<td>2.5 What is achieved by this research?</td>
<td>13</td>
</tr>
<tr>
<td><strong>3 Literature Review</strong></td>
<td>15</td>
</tr>
<tr>
<td>3.1 Oncology Information Systems</td>
<td>16</td>
</tr>
<tr>
<td>3.2 History</td>
<td>16</td>
</tr>
<tr>
<td>3.3 The Use of OIS</td>
<td>18</td>
</tr>
<tr>
<td>3.4 Medical Data in the OIS</td>
<td>19</td>
</tr>
<tr>
<td>3.5 Transforming Discovered Information</td>
<td>22</td>
</tr>
<tr>
<td>3.5.1 Semantic Networks</td>
<td>23</td>
</tr>
<tr>
<td>3.5.2 Rule-based Systems</td>
<td>27</td>
</tr>
<tr>
<td>3.5.3 Case-based Rules Systems</td>
<td>30</td>
</tr>
<tr>
<td>3.6 Ontologies</td>
<td>31</td>
</tr>
<tr>
<td>3.6.1 Ontology Engineering</td>
<td>32</td>
</tr>
<tr>
<td>3.6.2 Medical Ontologies</td>
<td>33</td>
</tr>
<tr>
<td>3.6.3 Oncology Ontologies</td>
<td>36</td>
</tr>
<tr>
<td>3.7 Summary</td>
<td>44</td>
</tr>
<tr>
<td><strong>4 Research Method</strong></td>
<td>46</td>
</tr>
<tr>
<td>4.1 Methodological Options</td>
<td>48</td>
</tr>
<tr>
<td>4.2 Methodology Used</td>
<td>51</td>
</tr>
<tr>
<td>4.3 Content Analysis</td>
<td>52</td>
</tr>
<tr>
<td>4.3.1 The unit of analysis</td>
<td>55</td>
</tr>
<tr>
<td>4.3.2</td>
<td>Semantic Entities</td>
</tr>
<tr>
<td>4.3.3</td>
<td>The Body of Literature</td>
</tr>
</tbody>
</table>

## Results

5.1 Collection of Semantic Entities | 68
5.2 Metrics of Semantic Entities | 69
5.3 Organising the Semantic Entities | 73
5.4 Clinical Knowledge Markup Language (CKML)
5.4.1 Re-factoring the Semantic Entity Groups | 78
5.4.2 Developing an XML specification | 80
5.4.3 Producing an Ontology from the XML Specification | 82
5.5 Evaluation of CKML and future applications
5.5.1 Oropharyngeal Cancer | 85
5.5.2 CKML subset for Routine Clinical Data | 87
5.5.3 CKML subset for Clinical Trial Protocols | 90
5.5.4 CKML subset for Clinical Trial Report | 92
5.5.5 CKML subset for Clinical Guidelines | 93
5.5.6 Comparison of CKML subsets | 95

## Conclusion

6.1 Future Research
6.1.1 Validating the CKML structure | 99
6.1.2 Developing a User Interface based on the CKML structure | 100
6.1.3 Use of the CKML Structure in Clinical Knowledge Discovery | 100
6.1.4 Use of the CKML Structure in Clinical Trial and Guideline infrastructures | 101
6.1.5 Storage repositories for CKML Structures | 101
6.1.6 Developing Agents that use CKML structures | 102
6.2 Need for Collaboration | 102

References | 126

A Publications during the course of the thesis | 127

B Sample Extraction of Semantic Entities | 130

C Radiation Oncology Literature Corpus | 140

D Data Collection Sheet | 162

E Semantic entities discovered from manuscript corpus | 164

F Johns Hopkins Hospital Radiotherapy Workflow | 169

G A Selection of ICD-10-PCS list of procedures | 175
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Listing and Individual Critique of the ACGT Master Ontology</td>
<td>178</td>
</tr>
<tr>
<td>I</td>
<td>The CKML superstructure used in the following appendices for Routine</td>
<td>207</td>
</tr>
<tr>
<td></td>
<td>Clinical Work, Clinical Trial Protocol, Clinical Trial Report and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical Guideline</td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>A CKML subset for use in a Routine Clinical Work with example</td>
<td>210</td>
</tr>
<tr>
<td>J.1</td>
<td>The Clinical History</td>
<td>211</td>
</tr>
<tr>
<td>J.2</td>
<td>The CKML coding of this Clinical History</td>
<td>216</td>
</tr>
<tr>
<td>K</td>
<td>A CKML subset for use in a Clinical Trial Protocol with example</td>
<td>223</td>
</tr>
<tr>
<td>L</td>
<td>The Trans-Tasman Radiation Oncology Group (TROG) ”HeadSTART”</td>
<td>235</td>
</tr>
<tr>
<td></td>
<td>Clinical Trial protocol (TROG02.02)</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>A CKML subset for use in a Clinical Trial Report with example</td>
<td>297</td>
</tr>
<tr>
<td>N</td>
<td>A CKML subset for use in a Clinical Practice Guideline with example</td>
<td>319</td>
</tr>
<tr>
<td>N.1</td>
<td>BCCA Guideline</td>
<td>322</td>
</tr>
<tr>
<td>N.2</td>
<td>NCCN Guideline</td>
<td>324</td>
</tr>
<tr>
<td>N.3</td>
<td>SIGN Guideline</td>
<td>326</td>
</tr>
<tr>
<td>O</td>
<td>Clinical Practice Guideline for advanced oropharynx cancer - British</td>
<td>327</td>
</tr>
<tr>
<td></td>
<td>Columbia Cancer Agency (Canada)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>Clinical Practice Guideline for advanced oropharynx cancer - Scottish</td>
<td>329</td>
</tr>
<tr>
<td></td>
<td>Intercollegiate Guidelines Network (UK)</td>
<td></td>
</tr>
<tr>
<td>Q</td>
<td>Clinical Practice Guideline for advanced oropharynx cancer - National</td>
<td>334</td>
</tr>
<tr>
<td></td>
<td>Comprehensive Cancer Network (USA)</td>
<td></td>
</tr>
</tbody>
</table>
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Truly, any thesis is a production where the final product should tell a story describing an exciting and motivating journey. I hope that this has been achieved.

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A Thesis for Master of Information and Communication Technology (Research)
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ABSTRACT

The development of medical knowledge has always proceeded along pathways that relate to questions arising from expert domain specialty knowledge, practice and work flow. While medical knowledge advances as a whole, there are independent and specific knowledge streams for each specialty.

Radiation Oncology is a specialty domain, therefore one can expect that its ontology will reflect and be defined by its clinical terms and clinical work flow which are both specific and interconnected.

The assertion of this thesis is that this particular medical domain specialty demonstrates clearly that knowledge derived in the clinical management of a patient, the processes used in clinical trials to develop and report new knowledge to be used in the clinical management of the patient, and the recommendations found in clinical guidelines that inform routine patient management, are all views of the same domain specific knowledge structure.

The process of Content Analysis was adapted and applied manually to an objective corpus of Radiation Oncology literature to establish the semantic entities underlying the knowledge being communicated to specialist radiation oncologists. These semantic entities were grouped in a hierarchy based on the work flow relevant to the expert domain. The hierarchical structures were then coded into a schema using an XML format to form a “Clinical Knowledge Mark up Language” (CKML).

The applicability of this CKML schema is subsequently demonstrated as relevant by its application to four clinical scenarios: description of a normal clinical patient with locally advanced oropharyngeal cancer, description of a clinical trial protocol for which patients with locally advanced oropharyngeal cancer may be eligible, specification of a clinical trial result from this same trial, and lastly as a description of clinical guidelines describing the management of patients with locally advanced oropharyngeal cancer.

KEYWORDS: ontology, radiation oncology, markup language, clinical trials, workflow, guideline
Chapter 1

Background

1.1 The Motivation and Academic Course of the Research

This research was commenced in early 2006 with the intention of assessing the levels of, and reasons for deficits in, the use of Oncology Information Systems by radiation oncologists. Studies have documented that some oncologists do not take advantage of Oncology Information Systems (OIS) to accumulate routine clinical data [157] which could be used to further knowledge about cancer management. Given the hope that improving OIS use might result in better oncological knowledge, I decided to describe and assess the barriers to an oncologist’s use. However this question was not addressed because more fundamental questions arose that indicated that the outcome of research on levels of and barriers to use would be swamped by confounding variables.

When assessing the use of OIS software, it is important to know whether the software is really “fit for purpose”. In the Australian and international Radiation Oncology domain there are two widely used products heavily based on USA management pat-
1.1. The Motivation and Academic Course of the Research

terns that qualify as Oncology Information Systems Elekta’s MOSAIQ® (which was previously supplied as MultiAccess® and resold by Siemens Oncology Care Systems as LANTIS®), and Varian Medical Systems ARIA®. Other systems are available but are not in widespread use [126, 46].

While both software products function well in their primary role as a Record & Verify System (R&V) that governs linear accelerator use and records radiation exposure [106], their usefulness as an electronic medical record (EMR) is problematic. Elekta’s system has shown promise [104, 117, 74] but these paradigms of use have not achieved wide scale acceptance, despite publications suggesting how oncological knowledge might be stored and re-utilised [105]. The ARIA software from Varian has had no publications demonstrating that medical data can be stored and then undergo an automated retrieval to reconstitute medical knowledge.

Furthermore, personal use of both systems in several departments between 2000 and 2011 has led me to the conclusion that these two software offerings were not equal. As a result it became clear that the different functional capacities of the systems are a confounding variable for any comparison of oncologist use. How does one compare a user who scores 50 using software which can provide a score of 100/100, with a user who scores 50 using software which can provide a score of only 50/100?

As a result, I turned my attention from users to software with a different research question: how do I first rate the performance of software in achieving the task of storing a radiation oncologist’s knowledge?

Discussion with both vendors about the historical development of their products
revealed that neither product was based on a specification of oncological knowledge, although a radiation oncologist was closely involved with the initial development of the IMPAC software. Given the lack of a formal specification, any assessment of the OIS capability will first need to include a formal specification of the information types and relations to be stored in the OIS. With this specification of the performance of the OIS in storing, retrieving and reconstituting oncological knowledge completed, an assessment of the performance of end users in entering oncological knowledge can be undertaken.

This deficit in software design underscores the fundamental need to describe the nature of the radiation oncologist’s knowledge to form a basis for future software development, and the final research question was refined to: what are the knowledge structures, i.e., the information components and their domain specific structure, that are required in an OIS? During the investigation of this question and in discussing the significance and utility of these informatics structures with fellow informatics researchers, several manuscripts were published (Appendix A - Publications during the course of the thesis).
1.2 Radiation Oncology as an Expert Domain

Radiation Oncology is a disease-centred (cancer) and modality-centred (radiotherapy) tertiary care medical specialty that utilises radiotherapy in the management of cancer [106], which only occupies a small position in a patient’s lifelong care. The National Cancer Institute defines the radiation oncologist as “a doctor who specialises in using radiation to treat cancer” [81]. Given that 434,000 people will develop cancer each year in Australia [24], and 52% of these people should receive radiotherapy in a properly resourced system [54], many patients will have some contact with a radiation oncologist.

It is common that the patients treated with radiotherapy for a cancer will start and end their cancer journey with their primary care physician. Indeed the primary care physician will often have instigated the diagnostic process that may eventually lead to referral to Radiation Oncology.

However, in most health systems, patients will be referred to a radiation oncologist by a secondary care medical practitioner, usually medical specialists (surgeons, internal medicine physicians), who have already obtained a histological diagnosis and completed preliminary staging investigations. Patients with clinical and imaging features of malignancy without a histological diagnosis are in the minority. Occasionally benign disease may be managed with radiotherapy, but radiation oncologists rarely manage benign disease exclusive of the need for radiotherapy.

Following an accurate description of the extent of the disease (known as ‘staging’) [80], decision making is structured and driven by disease outcomes reported in the Radiation Oncology literature. The prevailing model of care is biomedical with a heavy
dependence on a detailed understanding of the disease and its response to therapy. Radiation Oncology and Medical Oncology overlap in their disease focus but differ in their modality.

Radiation oncologists are of the general opinion that patients with cancer should have no delay in the provision of their radiotherapy [88, 72]. During the delivery of radiotherapy, weekly review of patients is a normal routine, and at completion patients enter an indefinite period of episodic follow up, which typically may terminate after several years without recurrence [83]. Thus the radiation oncologist’s care is distinctly episodic, focused and exclusive although undifferentiated by age, gender and organ system.

A specialised epistemology and ontology of Radiation Oncology has not been developed apart from the standardized DICOM-RT protocol (Digital Imaging and Communications in Medicine - Radiation Therapy) [23] used in the transfer of images and associated data between CT scanners, radiation planning systems and linear accelerators. This protocol does not seek to represent medical data.

The medical knowledge base of Radiation Oncology is largely explicit and derived from the published literature reports of the application of radiation to biological systems. There is an overt assumption that clinical judgement must be applied within the context of the literature’s predicates if optimal outcomes are to ensue. It is also assumed that end points, such as, improved survival and successful palliation are important to patients. It is also assumed that objective estimates of quality and wise use of resources are part of society’s expectation. Furthermore, it is assumed that these end points are more important than a specific patient’s agenda when interacting with
Given that patients with cancer have what is commonly a single and well-classified problem, decision-making in Radiation Oncology follows a deductive path where verifiable and well documented information is applied to the precise problem of improved outcomes, while always reflecting the underlying biomedical model. The cancer problem is structured and defined by the disease (instantiated by a diagnosis and stage), a series of pertinent prognostic factors known to impact on the disease behaviour, and therapy options that have already been shown to provide an improved outcome. Other patient factors are considered, such as an assessment of the patient’s ability to realise the benefits on offer \([109]\). If a patient has ‘terminal heart failure’ that will lead to death in 3 months, but also has a cancer which will lead to death in 9 months, no oncological treatment is indicated.

The patient is then advised of the oncologist’s opinion about therapy and the potential problems. Patients then reflect their agreement or otherwise back to the oncologist, although compliance is generally received in the face of a diagnosis of cancer. Typically, most oncology patients will have only one oncological disease requiring management.

The initial consultation with the radiation oncologist results in a formal characterisation of the extent of the disease using criteria such as the American Joint Committee on Cancer/Union for International Cancer Control Tumour-Node-Metastasis (AJCC/UICC TNM) Classification \([131]\). This classification is based on the major prognostic features affecting patient outcome \([80]\), and follows a comprehensive review
of the patient’s tests. The radiation oncologist then proceeds to a treatment decision and advises on therapy selection. This deductive approach is so entrenched that, in some areas, patients who do not have a malignant disease already defined may be returned to the referrer.

This pattern of management results in the requirement of an informatics system with an initial mandatory accurate disease definition summary and subsequent infrequent assessments after treatment to determine the status of the patient. The status of the patient is assessed with respect to effectiveness (has the cancer returned?) and efficacy (has the effectiveness been achieved without the treatment causing problems?).

While the doctor-patient relationship can be therapeutic, it is unlikely to cure a cancer. It is therefore understandable that the benefit of the radiation oncologist involvement is quantified in terms of the objective outcomes that benefit patients (improved survival, fewer side effects).

This tight coupling of cancer workflow with cancer diagnosis and stage followed by resultant cancer treatment with objective end points indicates a medical specialty that is well suited to the development of a domain ontology [5].
Chapter 2

Introduction

2.1 What is the problem?

Radiation oncologists, like all clinicians, keep notes describing patient problems, treatments and outcomes. This record forms the basis of all knowledge re-use. The major purpose of stored clinical knowledge re-use is to discover answers to clinically relevant questions. These answers are the medical knowledge on which further patient management is based.

To enable an Oncology Information System (OIS) is able to deliver on this promise of data re-use, issues of implementation, user interface and knowledge representation must be negotiated.

The combined functionality of the OIS data structures and user interface will set a ceiling on the success of strategies to implement the software into the real world, i.e., a functioning Radiation Oncology department. The level of success under this ceiling will relate to departmental issues of staff and change management. The issue of software implementation is related to this endeavour as studies have demonstrated
2.1. What is the problem?

quite clearly that implementation can have just as large an effect on use as database structure or user interface [157].

The OIS user interface reflects the design of the underlying knowledge structure and appreciation of the work flow of the domain expert. The user interface is important for adequate knowledge capture as a dysfunctional user interface would make the fidelity of the knowledge representation irrelevant, for if the user is unable to use the interface, no data will be accrued. However structure and design of the user interface are specific to each software program and not independent of the underlying knowledge structure.

The information systems available to radiation oncologists are not based on any published a priori determination of the knowledge structures of radiation oncologists or even on published assessments of the user interface.

As described above, the OIS has two purposes which are directional. These purposes are the accrual of clinical knowledge into stored electronic data within the database (storage), and the retrieval of stored electronic data from the database to be processed (knowledge discovery). The OIS has a data structure, usually a relational database, into which accrued data elements are saved. The detail of the data structure is provided in an entity-relationship diagram (ERD), and should be evident in the interface for the end user. Thus the evaluation of the knowledge representation performance of the OIS will assess its ability to store all relevant oncological data, and its ability to reconstitute oncological knowledge from stored data items.

Which issue is primary? A perfect system can be unused because of a poor im-
2.1. What is the problem?

Implementation, therefore the assessment of an implementation is an assessment of a department, not the OIS. A system built on a perfect knowledge representation with a dysfunctional user interface will also be unused by the individual domain expert. Conversely, a functional user interface does not guarantee that the underlying knowledge representation is adequate. While inadequate knowledge representation may not affect data entry via a user interface, the poorly structured stored data will only fulfil the storage function, hampering the process of knowledge discovery which is based on data retrieval.

The inadequacy of knowledge representation is a potential confounder for all other investigations relating to the use of OIS software. It may be that as oncology knowledge is fragmented electronically into storage structures, proper consideration has not been given to the inherent relationships of knowledge components. So while data has been stored electronically, there is no guarantee that the included material can be reliably and routinely reconstituted into the knowledge structures of the radiation oncologist for subsequent analysis and re-use. Therefore before the issues surrounding implementation and the interactions of the user with the user interface can be assessed, the capabilities of the OIS to store and reconstitute data should be quantified. In relation to the reuse of retrieved data, the knowledge representation is fundamental.

In summary, the failure of OIS use could exist at the level of implementation, user interface or knowledge representation. Deficits in implementation are local and can be detected by departmental comparison [157]. Variations in user interfaces are specific to each individual software program. However the issue of knowledge representation is generic to all OISs and has not been established. The primary and fundamental problem therefore is the establishment of a knowledge representation specific to Radiation
Oncology and the subject of this research.

2.2 Why is this research important?

The importance of formal knowledge structures in this expert domain becomes apparent when viewing the literature that shows that oncologists become more knowledgeable by the manipulation of their prior knowledge through accumulation and formal statistical analysis. If stored knowledge lacks a structure to permit pertinent retrieval, construction of new knowledge cannot be undertaken from the OIS. Oncologists increase their knowledge through radiation oncology literature, in fact all published clinical literature, which takes past data, analyses it and then reports it. Other oncologists read it and so are better informed and hopefully apply the findings [58]. Earlier literature [153] supports the current position that rational decisions are those that are based on controlled clinical studies, in contrast to those that are based on deductions from biological knowledge.

While the information discovered by oncologists in the course of their clinical work forms a clinical record, it also forms the platform from which retrospective reviews point to new directions for knowledge and from which trials are conducted to establish new medical knowledge in routine practice.

Medical knowledge is highly structured, but the expression of most oncological knowledge in plain English buries knowledge structures in a highly variable swamp of natural speech which can hide the formalised structure.

Characterisation of oncological knowledge in a formalised structure enables the development of appropriate information systems which should permit clinicians to
produce more oncological knowledge and so to undertake more accurate searches for applicable oncological knowledge for the individual patient’s care.

2.3 Who will be interested in this research?

The discovery of data elements that are used in the construction of the medical literature is relevant to any group seeking to build an information system for oncology, whether trials software or an OIS. These data elements are also relevant to the users, who are clinicians seeking to use the data stored within their OIS.

At present there are several producers of domain-specific software for Radiation Oncology departments, such as Elekta (MOSAIQ® & Multi-Access®; also re-marketed by Siemens as LANTIS®), Varian (VARis®/ARIA®), Nucletron (OnCentra®) and Mirrabooka (CAS®). OnCentra® is not installed at any site within Australia or New Zealand. The current use of CAS® is uncommon.

Although there are many open source electronic medical and health systems available, none of the offerings provide specifically targeted functionality for oncology. Likewise, large Hospital Information Systems (e.g., those provided by CERNA, EPIC, Meditec) have no specific oncology functionality.

By using the process of knowledge management through term recognition, term classification and finally term mapping [19], it is hoped that the development of a specialist medical vocabulary can then progress through a convenient classification structure and finally emerge into an accurate ontology which can be used as a basis for future commercial and open source development of oncology information systems.
2.4 What is the structure of this thesis?

The research hypotheses were that the knowledge structures of medical domain experts such as radiation oncologists, which were used in knowledge generation, knowledge application and hypothesis generation, can be discovered from the publications in the domain’s literature which were constructed and submitted by the domain experts. Furthermore, that these knowledge structures are related to clinical work flow and decision making since the domain is a practical clinical domain.

The literature review assessed the Oncology Information System literature to establish the inclusion of pre-determined radiation oncology knowledge structures. Various methods of defining clinical knowledge were assessed for their usefulness as a methodology for defining clinical knowledge. Special focus was given to the ontology as a method for detailing the specifications of radiation oncology knowledge structures, critical assessing how well they achieve their aim of knowledge description.

The research methodology undertaken consisted of a modified Content Analysis approach crafted to discover semantic entities by deconstructing published articles to discover the semantic entities collected and analysed in their generation. The accumulated semantic entities were then organised according to the clinical work flow to generate knowledge structures specific to radiation oncology.

2.5 What is achieved by this research?

This research determines a preliminary specification of radiation oncology knowledge structures, and then applies this specification in four areas of radiation oncology knowl-
edge manipulation to establish its viability. The knowledge structure is deployed in the
description of a patient with advanced oropharyngeal cancer, a trial protocol investi-
gating advanced oropharyngeal cancer, a trial report on the management of advanced
oropharyngeal cancer and a clinical guideline for the management of advanced orophar-
ryngeal cancer.

This specification can form the basis for the assessment of an oncology information
system as it specifies the entities that must be stored, as well as the relationships
between the entities which determine their use.
Chapter 3

Literature Review

Oncological knowledge is not chaotic. If oncological knowledge is structured, then the knowledge can be expressed in an ontology. If an Oncology Information System, which is a device to store oncological knowledge, is not based on an “oncology ontology”, it is possible that the relationships inherent in the storage will be inadequate.

The historical development of the OIS did not make it likely that an appropriate ontology would be used. Indeed the appearance of computers in Radiation Oncology occurred for reasons of radiation safety rather than clinical information. However once installed, it was inevitable that wider use would result in serving multiple departmental needs.

Currently, the available Oncology Information Systems are sporadically successful although some of these successes are tantalising in their potential, indicating that some Oncology Information Systems might be adequate. But with the lack of an underlying ontology, this might be the result of good fortune rather than good design. These issues are explored in this literature review.
3.1 Oncology Information Systems

There is no agreed definition for what constitutes an Oncology Information System (OIS), or whether such a system is required in addition to a general purpose information system [120]. For the purpose of this thesis, the OIS will be defined as an integrated electronic system available within an Oncology Department which is composed of several components and designed to integrate clinical work, treatment and data flow across this well-defined organisational structure.

For the radiation oncologist, the OIS contains the following components [106]:

- an electronic therapy record, whether that is an Electronic Radiotherapy Record with/without an Electronic Chemotherapy Record
- a computerised clinical database which if included within a work flow framework may have the capacity to function as an electronic medical record by recording descriptors of the oncological disease, treatment side effects and outcomes
- an electronic resource manager, including scheduling, resource allocation, charges and task lists.

3.2 History

The historical aspects of computer implementation in Radiation Oncology warrant delineation. Very soon after their advent, computers were employed in an attempt to detect human errors in the delivery of radiation at therapeutic doses. The software is given the generic name of “Record & Verify” (R&V) System.

The R&V System is now a consistent feature of all Radiation Oncology departments
in Australia which are all fitted with linear accelerators. As originally constructed, the software accesses a database containing the machine settings and tolerances that are expected when the machine is operated. When the patient has been set up on the treatment couch and the therapist attempts to activate the linear accelerator, hardware intercepts relay the actual positions of linear accelerator components (e.g., jaws) to the software. A comparison is undertaken between the actual and the expected position of each component reported. If the setting is outside the permitted tolerances, the linear accelerator will not deliver dose until an authorised staff member over-rides the message with their password, or alters the linear accelerator to bring the settings within tolerance (the “Verify” function). The decision to do either is a professional and clinical decision. Once the authorisation to commence has been given and the treatment completed, the intercepted, actual measurements and the delivered radiation dose are then recorded into the database (the “Record” function).

Although early attempts to provide useful R&V software in the mid 1980s were spectacularly unsuccessful [95], the software has matured into a robust checking environment that performs its duties admirably [26, 156]. Although these new systems move the man-machine interface further ‘upstream’ and are overall safer [68], humans continue to make similar but new mistakes at the new interface.

Since errors have not disappeared, vendors have moved to improve the functionality of newer software to actually undertake the automation of machine parameters and radiation delivery, removing the human from another layer of action. While this leads to improvements in the staffing ratios of more complex linear accelerators [90], errors still occur at the man-machine interface, although the quantity and quality of the errors has decreased in number but increased in severity [68, 77, 114].
Electronic Resource Management is likewise widely used in Oncology Departments because of the greatly improved functionality in relation to scheduling. Both Radiation and Medical Oncology need repeating clinic appointments and coordination of workflow between several professional groups. Having made a schedule item, the process of generating revenue items is a minor addition, since there is substantial overlap in the data elements between appointments and charges. Managers are keen to use the information collected to justify resource allocation [117].

The variability of functionality in the OIS and the varying data requirements of the oncological community reflect the lack of an ontological framework for Oncology [91].

### 3.3 The Use of OIS

Within the Radiation Oncology literature, the use of the OIS in its roles of computerised clinical database and electronic resource has been reported sparsely. A Korean report [74] documents the implementation of two OISs in one department, and clearly identifies the difficulties at the man-software and software-software interfaces, as well as the benefits possible from implementing electronic methods. This department’s requirements for two OISs was driven by problems of language. One OIS was implemented in English and the other in Korean.

While Australian centres should not be greatly affected by language differences, there have been no studies looking at the effect of the semantics of USA-oriented systems on Australian centres. The Australian Radiation Oncology professional group is
3.4 Medical Data in the OIS

A portion of the OIS can be used by the oncologist to collect and store relevant clinical information relating to a patient’s medical management, this the computerised clinical database functionality. This information includes oncological parameters such as diagnosis, stage, prognostic factors (for outcome predictions) and eligibility factors (for therapy decisions), treatment decisions, therapy specifications and side effects, and treatment outcomes.

For an OIS to be useful to a clinician, it should ideally fit a functional specification which includes the capability of acting as the sole repository for data, being widely available and usable in the clinic because it follows a discernible work flow that mirrors oncological practice and seeks to achieve timely entry [105]. In addition the data captured by this method should be collected in a structured manner which is consistent with the nature of the data constructs of the specialty [71].

The format of the data collected has significant impact on its later usefulness. It has been well demonstrated that data collected within a commercially available OIS
which is saved in categorical formats within a relational database is useful for the provision of routine reports such as prescriptions and discharge summaries [117]. Reports from the same site have also demonstrated the usefulness of this data store in the comparison of treatment outcomes between clinicians [106] and in assisting epidemiological research [104].

The differences in data format and their usefulness have been highlighted [104]. Normal clinical collection which uses a document paradigm, either as text on paper, text visible in a scanned images or typed letters stored electronically in word processor format files are of less use than categorical data entry with restricted options. Although Natural Language Processing offers hope that free text documentation will be useful [65], it is still far from useful in the oncological setting.

One author has highlighted the current practices involved in accumulating clinical trial data as a more favourable paradigm [104]. Clinical trial data is collected directly into the required categories, providing excellent quality [8], and reducing errors [9]. While in the clinical record the oncologist might enter “mild skin reaction”, in the clinical trial record the oncologist will enter \texttt{Skin\_reaction = 1}. The categorical specification of a skin reaction prevents the appearance of ambiguous free text such as “mild to moderate skin reaction”, or colloquialisms such as “lobster-red skin”.

However this clinical trial data is usually marshalled at a large expense [59] by data managers whose sole role is to collect the data from the clinician, transfer it onto predefined data sheets, and possibly then enter it into a relational database. The trial data held is not available for clinical use in generating routine reports, arrives
in electronic storage at any time after collection on paper and is infrequently quality assured against the original clinical interaction. Clinical trial data are a small subset of available clinical data so that efforts to maintain quality are focused on a small quantity of data \[7\]. Clinical trials efforts have produced substantial standardisation of data entry \[44\].

The storage of medical data in relational database formats may be inappropriate. The rapid development of the relational database management system (RDBMS) in the 1980s and 1990s occurred in the business world. The RDBMS was designed for use in business and fits this role well since it uses an entity-relationship specification which represents the particular anatomy of the business ontology \[62\] and so permits the accrued business data to be re-constructed and then analysed to discover new knowledge. This is possible because the database's entity relationship design (ERD) reflects the ontology of business \[132\]. The use and re-use of business data stored in this fashion validates the ontologies and entity relationships deployed \[73\]. An ontology can then be used by domain experts \[73\] to govern the ordered disaggregation of knowledge into the store, and the intelligent re-aggregation of data elements stored.

The business ontology is reflected in the way that business data is collected and stored via the specific ERD. Likewise the medical ontology should be reflected in the RDBMS structure through an ERD which describes the way that medical data is to be collected, disaggregated and stored. The success of this approach will be measured from the intelligent re-aggregation of the medical data, not just its storage.

Unfortunately, there is no published Oncology ontology \[93\] and there are few literature reports detailing successful episodes of intelligent re-aggregation of stored
medical data elements. As a result, an object-oriented approach has been described as better fitting the model of an electronic patient folder containing various components (such as Imaging Reports with multiple instances)\cite{63,71}.

Additional problems with oncological data include the disjunction of data where the result is divorced from the clinical circumstance. For example, the OIS can store a report of a chest X-ray taken but without including the reason, or indication, for the test to be undertaken \cite{75}. The significance of such a report varies depending on whether it was taken as part of routine follow-up for larynx cancer, or during investigation of haemoptysis to preclude the possibility of a new cancer in the lung. The test cannot be successfully interpreted without knowledge of the circumstance. A similar situation exists for the Prostate Specific Antigen (PSA) blood test which can be used for screening, case finding, prognostication before and after treatment, diagnosis and treatment outcome. A PSA level of 2.0 (normal range 0.0-4.0), is pleasing as a screening result indicating a small probability of prostate cancer. But the same PSA following a prostatectomy indicates a failure to achieve a cure.

Whether this failure is inherent to the design of the RDBMS or resulting from the failure to correctly design the data structures to include the contextual information is not known. While re-use can be undertaken through automated processes that seek to change the data’s format but not the content \cite{97}, the re-use of poorly organised data is inherently unsafe \cite{14}.

### 3.5 Transforming Discovered Information

The motivation for the description of a specialist medical terminology or specification of semantic entities in the Radiation Oncology domain is a relevant domain ontology.
Developing an ontology involves the engineering of knowledge which is heavily based in formal logic addressed in the area of Artificial Intelligence. During the progress of this work, several techniques were considered to have some applicability to the process of extracting and manipulating knowledge structures and they are described together with reasons why they have been employed as the sole method.

### 3.5.1 Semantic Networks

Semantic networks is a graphical knowledge representation technique displaying a taxonomic hierarchy of concepts or subjects (nodes) with connecting links or relationships (edges) [55]. Semantic networks are used to convey things about things. The nodes and edges are important with their topology reflecting a two way meaning with cardinality (e.g., uses/is_used_by). These three phenomena of node, edge and cardinality are distinct [69].

The binary relationship must exist between two specific subjects, with a kind (e.g., uses, is_a) and a semantic direction (e.g., cancer is_a disease, rather than disease is_a cancer). Where concepts have multiple relationships, the discovery of additional facts is permitted through inheritance. If we have two statements with a common concept, e.g.,

```
BREAST_CANCER is_a CANCER
CANCER is_a DISEASE
```

then via the property of inheritance we can state, correctly, that
BREAST_CANCER is_a DISEASE.

As a representation method, semantic networks are limited by the single binary relationships that exist between objects. One object can relate to multiple objects by single relationships to establish multiple inheritances. This is a useful feature in medicine as a single disease can have multiple symptoms, and a single symptom can be caused by multiple diseases.

While the graphical representation embeds logic, it cannot easily represent the logical concepts of negation and disjunction, and more expressive parts of formal logic. However graphical representation is easier to manipulate than formal written specifications.

Furthermore, the description of events, multiple events, a work sequence and conditional loops is difficult in semantic networks [57]. This is problematic for Radiation Oncology. Within this expert domain, the clinical work flow contains concepts, relationships, sequence and events, as assumed components of the underlying knowledge structure. Radiation Oncology knowledge has no reason for existence other than the treating of cancer patients, therefore any knowledge representation system has to reveal these properties.

There is no published semantic network describing Radiation Oncology, however, one would expect that such a network would be similar to that described in Figure 3.1, demonstrating that the representation is easy to manipulate even for an ontology novice.
Although this semantic network has been devised by a domain expert, the arrange-
ment has buried domain concepts. These concepts will be evident to the domain expert
but as they are not formally defined, it is not clear that they will be apparent to, or
preserved by a domain-ignorant ontologist. This particular example demonstrates such
a circumstance with respect to the interdependence of knowledge and work flow. If two
concepts with link are examined, e.g., “Disease has_a_decision for Treatment”,
the knowledge inherent in the Disease includes all of the concepts accessed through the
link has_aSpecification. And the nature of the Treatment includes all of the con-
cepts accessed through the links has_a_trial, has_a_treatment_offer, has_an_in-
tent, and has_an_effect. Links in the semantic network are considered to be bidirec-
tional, however in the expert domain, this bi-directionality is altered. When a concept
such as AcuteSideEffect under the arm of Radiotherapy (that is, Radiotherapy
has_a Procedure produces_a AcuteSideEffect) is selected, the domain expert will
assume that the ‘upstream’ concepts (with respect to work flow) have been completed,
and for the ‘downstream’ (with respect to work flow) concepts to be unfilled. That is,
the domain expert will expect that if Radiotherapy produces an AcuteSideEffect,
there must be a Diagnosis with the specification already completed, and that un-
til Radiotherapy has a Prescription which has been performed by an Oncologist,
there will be no AcuteSideEffect. Furthermore, the oncologist will not expect to see
an entry for SideEffectAfterTherapy occur before all AcuteSideEffects have been
completed for the approved Prescription. This interdependence and directionality
of knowledge and work flow is not trivial in an expert domain.
3.5.2 Rule-based Systems

The application of rule-based systems to medicine is not new [129, 128]. Rule-based systems eschew the organization of concepts in a hierarchy as being static and unchangeable, and instead use rules which are a description of condition and outcome. This structure is commonly seen in ‘IF..., THEN’ logic [43]. Some rule-based systems have expanded to include medical reasoning, that is, the ‘BECAUSE’ [92]. These rules are useful in the setting of specialist medical decision making, but limited when applied generally [138].

This logic structure is common in medical diagnostics and management, indicating that the perception of doctors as just ‘pattern matching’ is incorrect. The conclusions of the medical process are statements of diagnosis and treatment, but the derivation of these statements from history, examination and tests in a logical process whose arguments are anatomical, psychological, physiological and pathological. The terms if, then and because are common words in medical speech. It is therefore not possible to define a medical ontology without recognising these processes.

For example, the presence of rectal bleeding after prostate cancer treatment suggests different diagnoses.

if ... the patient was treated with radiotherapy.
then ... most likely cause is telangiectasia in the rectum
because ... of the blood vessel damaging effects of radiation.

Similarly,

if ... the patient has a swollen tender calf consistent with a deep vein thrombosis,
3.5. Transforming Discovered Information

then ... you must examine the chest looking for pulmonary embolus,

because ... a broken piece of clot will follow the anatomy of the vessels
through the heart and lodge in the first vessel reached with a smaller di-
ameter than the clot fragment which will be in the pulmonary vasculature.

Rules-based systems also allow for reasoning that directs clinical decision making, e.g.,

\begin{align*}
\text{If } & \text{ ... there is a past history of unprovoked deep vein thrombosis} \\
\text{and} & \\
\text{if } & \text{ ... there is a diagnosis of cancer,} \\
\text{then } & \text{ ... prescribe anticoagulation.}
\end{align*}

When designing a system to support clinical decision making, a rule-based ap-
proach is useful, however development becomes problematic if each new piece of liter-
ature has to be perused to see whether previously established rules require alteration
and to discover unanticipated conflict between existing rules. This makes the pro-
duction of conflicts quite easy but difficult to recognise because the reasoning is not
particularly specific to clinical reasoning. Manual generation of rules suffers from the
massive amount of published data each year (see below).

There are more rules operating in clinical medicine than those developed from the
published literature. Each clinician has a different approach to the effect of patient
co-morbidities on treatment decisions. Any system of knowledge specification and ap-
lication has to account for this clinician ‘idiosyncrasy’. Clinical Guidelines are called
‘guidelines’ because they are not mandatory specifications of management. Medical ev-
idence is developed on highly selected homogeneous patient groups and is therefore of
limited applicability in a heterogeneous clinical world. The information systems avail-
able today do not present guideline recommendations to clinicians for consideration, so the reasons and consequences of deviation from a guideline are difficult to ascertain.

The rules-based system however is a methodology for the operational application of pertinent knowledge, so rules that are generated \textit{de novo} to govern oncological management will have the assertions and context of oncological knowledge embedded. The rules-based format is useful for the presentation of oncological facts, as illustrated in this clinical example [155].

\begin{verbatim}
If
  Diagnosis = ‘C34’ or ‘Larynx’
  AND Histopathology = ‘8140/3’ or ‘squamous cell carcinoma’
  AND T\_stage = ‘1’ or ‘1a’ or ‘1b’
  AND N\_stage = ‘0’
  AND M\_stage = ‘0’
then
  Radiation\_field = “Larynx”
  AND Radiation\_dose = “56.25”
  AND Radiation\_fractions = “25”
  AND Radiotherapy\_schedule = “daily”
\end{verbatim}

The source of oncological facts directing patient management is the oncological literature. The nature of the randomised trial is sympathetic to manipulation into a clinical rule as in the example above. But this treatment guideline is not oncological knowledge per se, as no outcome data is included. Rules are not a useful description method for oncological knowledge, but a knowledge specification might permit the
automated generation of rules.

Such a specification would permit the integration of published literature into rules and subsequent argumentation based on these rules. It would also overcome the problem of generating new rules based on the advancing medical literature. Such a specification would provide added utility and impetus to the knowledge structures.

3.5.3 Case-based Rules Systems

Rules systems that manipulate clinical material are called case-based reasoning (CBR) systems [1]. These systems rely on the manipulation of past events into matching templates for future decision making. Each previous case becomes a rule when catalogued. The example above which was derived from a literature report [155], could also be derived from a specific clinical case where a patient with a T1N0M0 squamous cell carcinoma of the larynx was treated with 56.25 Gy in 25 fractions over 25 consecutive work days. This application of specific knowledge derived from previous examples is seductive as it bypasses problems associated with encoding published literature and describing clinical idiosyncrasy [1].

In Radiation Oncology, CBR has been used in radiation planning to match patient and tumour geometry from previous radiation therapy plans with the current patient [31], and also as a similarity estimate to predict acceptability of radiation plans [116].

The CBR rules, which are formed from individual clinical cases, are used to argue actions for the next similar case. In each case, relevant clinical parameters are defined and then weighted in an iterative approach. This approach will include clinician ‘id-
iosyncrasy’ in decision making, making the assumption that such idiosyncrasy is stable across similar cases. In reality, doctors become more conservative with age \[99\], and medical knowledge changes. The idea that the clinician can be used as the conduit through which clinical medicine knowledge is manifested, rather than the published literature, is a shortcoming. While it is possible to demonstrate that such systems can produce a close correlation with clinicians \[51\], the usefulness of the system can be expected to deteriorate as medical knowledge changes.

Case-based reasoning is therefore best at maintaining consistency of decision making. By addressing the structure of medical knowledge through pattern matching, the result is the application of yesterday’s knowledge. However the desire and challenge of evidence-based medicine approaches is to change patient management by applying up to date medical knowledge \[70\] \[146\] and become better.

### 3.6 Ontologies

Ontology is that field of Informatics which is concerned with the production of ‘controlled vocabularies’ which are “conceived as graph-theoretical structures consisting on the one hand of terms (which form the nodes of each corresponding graph) linked together by means of edges called relations” \[130\]. In this way, the terms/nodes colon and large intestine can be linked by the relation/edge is_part, e.g.,

- colon Anatomic_Structure_is_Physical_Part_of large intestine

or

- colon part_of large intestine
just as colon and organ can be linked:

\[
\text{colon is}_\text{a body part, organ or organ component} \quad [93]
\]

One of the constant characteristics of humans is the drive to categorise, and so, multiple attempts have been undertaken to categorise medical language into schema, variously called knowledge bases, ontologies, vocabularies or data dictionaries. These schema are not equivalent and vary in their usefulness. Vocabularies simply list words peculiar to a domain. Data dictionaries are limited as they define terms and constrain examples. Ontologies define data relationships and so can be used for reasoning.

### 3.6.1 Ontology Engineering

Ontology engineering is the process of taking a corpus of domain knowledge, recognising specific concepts and fashioning them into a structure which reflects the domain knowledge. The process can be undertaken from top down or from bottom up, but either way, the result will be a specification of general concepts such as Events, Time, Physical Objects, and Beliefs, which will be further described as sub-concepts that have relevance to the expert domain. For example, the concept of Time will be further specified by the sub-concepts of Date of Birth, Date of Diagnosis and Date of Therapy. This thesis makes no attempt to integrate a Radiation Oncology ontology into a general purpose ontology of Medicine, or even to describe the applicability of this schema to Medical Oncology or Surgical Oncology. That assessment should be undertaken by the relevant specialties, although the commonality of management should mean a high level of agreement.
Ontologies should organise knowledge logically; this may prove difficult in an expert domain where generalisations may seem to have as many exceptions as clinicians. In the clinical circumstance, knowledge that might have be used for one patient, may be classed as irrelevant for another. Furthermore, different clinicians will have slightly different knowledge structure developed through their unique clinical experiences.

In an evidence-based environment where knowledge is fluid and developing daily, ‘exceptions’ will be common. It is therefore important that knowledge structures developed match the knowledge development methods of the expert domain and so permit the easy integration of new knowledge. In the Radiation Oncology expert domain, knowledge development and knowledge use follow similar patterns. This thesis will use this interdependence to test the robustness of the organization of information within the knowledge specification that becomes the Radiation Oncology Ontology.

The well known Artificial Intelligence text by Russell and Norvig [124] describes four routes for ontology development, and this attempt falls into the last category of “enticing unskilled amateurs to enter commonsense knowledge” and is necessary because “trained ontologist/logicians, who architect the ontology and write axioms” have no domain specific knowledge. While the manipulation of an electronic corpus will discover terms and information, the structuring of that information cannot be verified without the domain expert, who is usually ontologically unskilled.

### 3.6.2 Medical Ontologies

The field of medicine is no different form other expert domains with several knowledge bases being developed including ILIAD [95], Medical Entities Dictionary (MED)
3.6. Ontologies

[48 70 78 80], NCI caCore Thesaurus (NCIT), the National Cancer Institute’s Common Data Entities (CDE) [101] and OpenEHR’s archetypes [27, 28, 39]. These attempts are outnumbered by other classifications including Systematic Nomenclature in Medicine (SNOMED), International Classification of Disease (ICD), and the Logical Observation Identifiers, Names, and Codes semantic structure (LOINC) which started as organised vocabularies, some ending as formal ontologies.

Ontologies are derived for a purpose and so usefulness in the clinical expert domain of Radiation Oncology must be proved. An ontology can only be successful when ontologists believe it to be well-formed, and experts find that it represents the domain adequately.

The ILIAD knowledge base underpins a system using a Bayesian probabilistic approach to produce an expert clinical diagnostic system. The knowledge base is a data dictionary which includes the *a priori* prevalence of a disease, along with associated clinical findings. These clinical findings can alter the *post priori* likelihood of a diagnosis by estimating the impact of the presence of a finding on disease presence (as a True Positive) and absence (False Positive) [96]. This system has not been extended into treatment and outcomes.

The NCI CDE dictionary grew out of a desire to provide a standardized databank of questions to be asked in clinical trials, to permit data from multiple trials to be coalesced without translation [101]. This solution arose from the scenario where one trial might use a data category called “Eye Colour” rather than “Colour of Eyes”, and use choices of 1=blue, 2=brown, 3=mixed rather than 1=brown, 2=blue, 3=green, 4=mixed. The dictionary received contributions from clinical trial researchers involved.
with the NCI in the USA to systematise collection rather than document the importance or relationships between data. While this dictionary will probably include most of the items reported in the literature, trials often accumulate more data than is required to answer the clinical question.

The OpenEHR is an open standard initiative predominantly based in Australia with ties to European standards [27]. The ‘archetype’ is the ontological variant developed by this group, devised as a prototype on which software can ultimately be based. The defining of archetypes is seen as a domain expert task that allows re-use when building a variety of functioning systems. Archetypes can include observations, work flow and interventions and can be single items such as Pulse or grouped into templates such as Physical examination. The system is also open and freely available, but includes few archetypes relating to cancer. There is no archetype relating to radiotherapy.

The International Classification of Diseases (ICD) is widely implemented but relates only to classifying diseases (diagnoses), morphology, procedures and causative agents. The Systematized Nomenclature of Medicine (SNOMED) is now widely implemented, however the listing of terms is incomplete, many terms are listed several times, and management of changes is cumbersome.

Another attempt to bring order and provide interconnectivity between these attempts is the United Medical Language System (UMLS) which provides a correlation index across languages and particular attempts (SNOMED, ICD, LOINC, etc) so that a consistent vocabulary can be achieved. In this system, no term is retired.
At a more fundamental level, while all of these broad-based attempts have proposed various medical classifications, the question as to whether there are single or multiple medical ontologies within Medicine has not been addressed [52]. Descriptions of ontologies in different areas leads to the belief that there are very distinct areas where specialised ontologies are applicable, e.g., anatomical pathology [33], surgical ICU [94], malaria [141], and ophthalmology [139]. Even internet humour can attest to great differences in knowledge type between specialities such as psychiatry, orthopaedic surgery and emergency medicine [1]. Whether these efforts should or can be coalesced is not yet known. Certainly they cannot be coalesced before they are defined.

3.6.3 Oncology Ontologies

My research would be pointless if a satisfactory ontology for cancer, radiotherapy or Radiation Oncology already existed. A search was undertaken to identify published ontologies that relate to Cancer, Oncology, Radiotherapy or Radiation Oncology. The results are discussed below.

3.6.3.1 Cancer

A search of BioPortal found three cancer-related ontologies:

- Breast Cancer Grading Ontology [2]
- Cancer Research and Management ACGT Master Ontology [3]
- Neomark Oral Cancer-Centred Ontology [4]

3.6. Ontologies

The Cancer Research and Management ACGT Master Ontology was developed to resolve problems of integrating technologies, coding, categories and reporting methods in cancer trials [41, 40, 42, 133]. The ACGT ontology covers many oncology specific areas, but can be criticised for its organisation and logic which frequently seems devoid of domain expertise (Appendix H). Of more concern is the apparent lack of correlation between terms that coincide in the work flow. The ACGT formal knowledge structure presents Diagnosis and Staging as separate knowledge structures, while in reality and use, they are intimately related in work flow, use and knowledge constructs of Oncology. The ontology must accurately represent this relationships, if it is to be relevant.

The ontology was built using a top-level ontology, the Basic Formal Ontology. This ontology initially recognises entities with different characteristics of persistence in time [36]. A search for items relating to Diagnosis and Staging finds Diagnosis and TumorStage inside the ACGT.

entity

→ continuant

→ dependent_continuant

→ generically_dependent_continuant

→ acgt:InformationObject

→ acgt:Document

→ acgt:Diagnosis

→ specifically_dependent_continuant

→ quality

→ acgt:TumorClass

→ acgt:TumorStage
The terms used in this classification are somewhat unfamiliar. An entity that is wholly persistent and complete when present is called a continuant (or endurant). Examples include the diagnosis (you do or don’t have a whole cancer). These entities can be subdivided into dependent and independent continuants. The dependent continuant (Diagnosis) requires an independent continuant (a human entity) in much the same way that another dependent continuant (TumorStage) requires another dependent continuant (Diagnosis) and also an independent continuant (the patient). The Diagnosis is a generically-dependent continuant because the the independent continuant (the patient) is not required to have a disease or be restricted to one disease. However the TumorStage is a specifically-dependent continuant because each Diagnosis must have at least one TumorStage.

While this relationship is correct, it is not complete from the domain expert’s stance. It is not explicit in the ontology that each Cancer Diagnosis must have a TumorStage assigned as is dictated by the expert domain. Close examination of the Diagnosis and TumorStage entities shows that while the entity Diagnosis has a qualification “Outcome of some Diagnostic Process”, there are no further requirements that the Diagnosis be subserved by a TumorStage, or that the TumorStage is linked to a Diagnosis. Within the ontology there is nothing to say that this specifically-dependent continuant (TumorStage) is specifically dependent on the generically-dependent continuant (Diagnosis). It is in real life, so it should be in the ontology.

This lack of a direct link is also compounded by misclassifications which are highlighted in Appendix H.
3.6. Ontologies

Neomark is a project partially funded by the European Commission that concentrates on Head & Neck cancers. Given the time taken for disease to recur, the project is seeking to identify possible prognostic features that relate to treatment, genomic biomarkers, and imaging analysis variables that will identify a high risk ‘bio-signature’. The prognostic significance of the high risk bio-signature in predicting reappearance is being investigated. The collected data is to be represented in an Informatics framework representing human physiology and pathology.

Although listed in the BioPortal website, the Breast Cancer Grading Ontology was not available.

3.6.3.2 Radiation Oncology

A Web search using the term “Radiation Oncology Ontology” returned no ontologies. A search of the BioPortal site revealed no specific ontology. The term “Radiation Oncology” was found within several listed ontologies, namely ICD-10-PCS, Metathesaurus CPT Hierarchical Terms, LOINC, SNOMED Clinical Terms, Health Level Seven, and NCI Metathesaurus.

The International Classification of Diseases v10 Procedure Coding System (ICD-10-PCS) categorises Radiation Oncology procedures with a seven character identifier. The identifiers represent in order Section, Body System, Root Type, Body Part, Modality Qualifier, Isotope and Qualifier. This is a classification of procedures devoid of any indicator of diagnosis, stage, treatment intent and therapy importance. The procedure codes also have no specific indication of technique, dose, or fractionation. Examples of procedure coding are provided in Appendix G (ICD-10-PCS codes

http://www.neomark.eu/portal/
http://bioportal.bioontology.org/ontologies/1304
http://bioportal.bioontology.org/
for radiotherapy procedures).

Different ontologies define the term “Radiation Oncology” differently. The NCI Thesaurus lists meta-data such as a definition of “The study of the effects of ionizing radiation for treatment of tumors”, a semantic type of “Biomedical Occupation or Discipline” and a synonym of “oncology, radiation”. The SNOMED Clinical Terms however does not provide a definition, has the same semantic type of “Biomedical Occupation or Discipline”, but the synonym list includes “Radiotherapy” and “Therapeutic radiology”. Yet the US National Cancer Institute (NCI) defines radiotherapy as “the use of high-energy radiation from x-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors”[^1], which is clearly not an occupation.

### 3.6.3.3 Radiotherapy

The term Radiotherapy is likely to be an important part of any Radiation Oncology Ontology being the name given to the preferred modality. Analysis of this term’s classification reveals severe shortcomings. The Read Codes, Clinical Terms Version 3 lists radiotherapy along with a sub-term called *Purpose of radiotherapy*[7]. Subclassification of this term gives the options:

- Radiotherapy - intraoperative control
- Radiotherapy - postoperative control
- Radiotherapy - preoperative control
- Radiotherapy for analgesia

3.6. Ontologies

- Radiotherapy for haemopoietic irradiation
- Radiotherapy for immunosuppression
- Radiotherapy for inflammation
- Radiotherapy for lymphatic irradiation
- Radiotherapy for tumour palliation
- Radiotherapy purposeNOS

For the domain expert this classification provides problems. While the purpose of radiotherapy can be rightly described as control, analgesia or immunosuppression, the purpose of radiotherapy for irradiation is tautological and inconsistent. Furthermore there is substantial overlap in these groups, and important omissions. Radiotherapy for analgesia is providing Radiotherapy for tumour palliation. Most radiotherapy is given for the purposes of cure to eradicate the cancer with radiotherapy without surgery, yet there is no category to describe radiotherapy given for the purpose of cure of the tumour.

The Cancer Research and Management ACGT Master Ontology only lists types of radiotherapy. The term acgt:Radiotherapy has the sub-term acgt:Teletherapy with a further sub-term acgt:MultipleFieldIrradiation and a single sub-sub-term acgt:OpposingField Irradiation. Terms to describe common clinical scenarios of more than 2 fields and more complex coplanar/non-coplanar and co-axial/non co-axial arrangements are not included in the ontology.

The Dermatology Lexicon (DermLex) only provides a radiotherapy list classified by beam energy (Grenz rays, kilovoltage x-rays, etc) that are applicable to skin treatment.[10]

The Galen Ontology lists radiotherapy as part of the following hierarchy:

**Behaviour**

→ NAMEDVolitionalACT
→ ClinicalACT
→ TreatmentAct
→ NAMEDTreatmentAct
→ Radiotherapy

Issues that relate to the purpose of radiotherapy are described under the Treatment-Act hierarchy with a sub-term DiseaseProcessModifyingAct[11] Yet common terms associated with radiotherapy such as beam energy and fraction number are not present in the Galen Ontology.

Within the SNOMED Clinical Terms Ontology, radiotherapy is listed under parent terms - Special concept > Inactive concept > Reason not stated concept > Radiation therapy (synonym: radiotherapy). The term has been replaced by Radiation Oncology AND/OR radiotherapy[12]. Sub-terms within this hierarchy include Radiotherapy of corneal lesion and Radiotherapy by body site. However this second term includes more sub-terms such as Radiotherapy to the head. The reasons for classifying Radiotherapy to the head and Radiotherapy to the cornea at different levels in the ontology are not described. The Purpose of Radiotherapy[13]
is described with the same structure as seen in the Read Codes above, although the previous term Radiotherapy for tumour palliation has been replaced with Palliative course of radiotherapy which has a single sub-term, namely Palliative course of deep X-ray therapy. This entity is specific to Deep radiation therapy, 200–300 kVp which is problematic for the domain expert. Palliative radiotherapy will uncommonly involve 200-300 kVp X-rays but most commonly be given with megavoltage X-rays, as most lesions requiring palliative treatment are deep and require the additional penetrance. Indeed, this treatment paradigm is so common that large randomised trials of palliative radiotherapy do not actually specify what energy radiation be used.

Another large thesaurus, the NCI Thesaurus, has similar problems of classification. If one peruses Therapeutic Procedure there are multiple examples of misclassification. For example, Cancer Therapeutic Procedure is not the hierarchical parent of Chemotherapy or Radiotherapy, but is the parent of Chemoradiotherapy.

Similarly, the NCI’s Physician Data Query ontology has a term radiation therapy however its daughters brachytherapy, tomotherapy, breast irradiation, image-guided radiation therapy, carbon ion radiotherapy, accelerated radiation therapy and palliative radiation therapy, are a non-overlapping mixture of types that do not seem to follow a discernible classification pattern.

While all of the Classifications, Terminologies and Thesauri are not formally described ontologies, the problems that have been highlighted should not be perpetuated.
in an ontology. Similar terms have to accumulate into similar positions. The position of terms should be verified by the domain experts who will be using the ontology. Term coverage has to be complete, or at least be subserved by a co-opted ontology. All terms used should have meaning to the domain experts served by the ontology. In this regard, any domain specific ontology should have a ‘plain language’ output which is accessible to the domain expert uninformed in ontologies. For example, the grouping of concepts could be explored by asking for similarity of concept:

- The concepts Radiotherapy - preoperative control and Radiotherapy - postoperative control are grouped together - are these concepts similar?

- Is the concept Radiotherapy of corneal site more similar to the concept Radiotherapy to body site or the concept Radiotherapy to the head?

- The concept Palliative course of radiotherapy has a single sub-concept - Palliative course of deep X-ray therapy, are there other sub-concepts that should be here?

- The concept radiation therapy has several sub-concepts - brachytherapy, tomotherapy, breast irradiation, image-guided radiation therapy, palliative radiation therapy, accelerated radiation therapy and carbon ion radiotherapy. How should these sub-concepts be grouped?

3.7 Summary

The current ontologies and classifications have been demonstrated to fall short in their specification of Radiation Oncology knowledge structures. As could be expected, the deficiencies relate to the lack of expert domain knowledge among ontologists, and the lack of development of devices that translate ontologies into the language of oncologists,
3.7. Summary

which would allow ontologists to understand how their developing ontologies fall short.

As has been shown, the concept that certain entities are linked can be appreciated in some ontologies. This linkage is not as tight and necessary as that required by the expert domain knowledge. The lack of this link has two outcomes. First, when developing an information system from the ontology, the only other way to force the juxtaposition of Diagnosis and TumorStage is to use a business rule to constrain the user interface. This introduces an opportunity for customisation in the user interface when none may exist in the knowledge representation. Second, this deficiency in knowledge representation, where the ontology has failed to enforce the collection of TumorStage with Diagnosis will mean that the data collected will be deficient and possibly not useful for analysis.

The cause of the problems also lies with the domain expert. When viewing a list of items related to Radiotherapy as described above, it takes very little time to appreciate the problems which in part result from assumed equivalence of adjectives describing Radiotherapy in the semantics of speech. In the expert domain, the terms carbon ion radiotherapy, accelerated radiation therapy and palliative radiation therapy represent vastly different entities where the differences are type of particle used (carbon ion; alternatives include photons, electrons, or protons), the rate of dose accumulation each day (accelerated; alternatives include hypofractionated, hyperfractionated, or conventional) and usefulness/timing of a modality of therapy (palliative; alternatives include primary/definitive, adjuvant, neoadjuvant, and concurrent).

Clearly there is a need for a greater involvement of domain experts to deliver
a more comprehensive set of terms and demonstrate more clearly their important relationships.
Chapter 4

Research Method

When beginning the specification of an ontology, the issue of choice of methodology can be perplexing. The most recent attempts to produce ontologies have used increasingly sophisticated, highly complex and purpose built specification software such as the Protégé system [42]. These attempts within the field of Oncology have the potential to deliver a ‘theoretical’, objective data specification. However there is insufficient involvement of domain experts who can ensure coverage and consistency, and no paradigms to engage the domain experts to determine that the resultant ontology is accurate.

Certainly the person undertaking the task should have training, but given that this is an expert domain the involvement of ontological and oncological domain experts is required. However if that person is a radiation oncologist, their status as an oncology domain expert is likely to be balanced by their informatics domain ignorance. Likewise an ontologist, while an informatics domain expert is likely to be ignorant of the oncology domain. The basis of the deficiencies lie in the fact that both areas require substantial and lengthy training, rarely undertaken by the same individual.
When assessing the level of implementation of the capabilities of an OIS in the real world situation of a functioning Radiation Oncology department, the initial requirement is the determination of the ability of the OIS to store the required OIS data elements. For maximum applicability, this initial assessment should be an objective exercise using real elements drawn from unselected material found in a wide cross-section of Radiation Oncology practice. Although few sources fit the description of being real and ‘objective’, this description does fit the data types used to construct the manuscripts published within the Radiation Oncology literature. The classification of this extracted material carries with it the ability to include the nuances of clinical practice.

Whether all the data specified will be clinically important or even relevant is a separate question that does not need an answer. All new and significant discoveries and management paradigms are reported through the peer-reviewed literature, therefore this paradigm will objectively determine the extent of data that needs to fit into the OIS recording structures based on the assumption that the published literature contains the required data specifications.

The objective determination of required OIS functionality has not been reported in the literature. The only publication found that provided a ‘functional specification’ for the OIS did not describe any formal methods used to delineate its specification of required functionality [105]. Typically commercial vendors consult users initially to develop a requirements specification, and later respond to user demands for improved functionality and bug fixes once the program has been released.

The knowledge reconstitution aspect of clinical knowledge capture is less obvi-
ous but frequently promised by proponents of IT systems in health. The clinical data recorded describes a patient’s ‘journey’, and is re-used in the production of manuscripts. Adequate data structures will permit automation of this process while inadequate data structures will impact on the ability of a user to use retrieved data in a clinically and professionally useful manner, preventing automated analysis and knowledge discovery. Therefore the use of manuscripts as an objective source of data structures serves the objective of discovering the knowledge structures.

Radiation Oncology staff produce data that is important for delineating clinical patterns of disease, defining research questions, determining patient management and settling controversies. Whether stored on paper or in electronic formats, this data is used to construct manuscripts that are submitted for publication. Leaving poor writing and design aside, if the data inside the submitted manuscript relates to a question that is considered to be relevant by peer review, the manuscript will be published.

4.1 Methodological Options

The process of knowledge gathering and organization used to determine the knowledge structures of Radiation Oncology requires a corpus of text that contains Radiation Oncology knowledge (clinical text, clinical guidelines, medical textbooks, medical literature) or an interaction with radiation oncologists (interview, speech analysis). The method used may be automated or manual. Following determination of the corpus is the application of an analysis method. This research is based on a manual assessment of one of these data sources, and utilises a method called Content Analysis.

The most appropriate sources for analysis should be easy to access, cover the sub-
4.1. Methodological Options

ject area of Radiation Oncology well and from many perspectives, be applicable in clinical and trial arenas, and always up to date. It should have the possibility of automated processing, and it would be useful if the source enabled the rapid delineation and introduction of new knowledge structures into clinical practice.

In circumstances where the expert domain is a silo with well confined limits, if a domain expert cannot define a knowledge structure, then the domain ‘ignorant’ is unlikely to be successful in producing a model with agreement. For this reason, management of the knowledge should be undertaken initially by an oncology domain expert using manual techniques on the objective literature corpus.

Using the oncology domain expert as a source is not useful in the long term. Any investigation undertaken by a domain ‘ignorant’ requires a substantial learning curve in the domain area. Given that certification as a specialist radiation oncologist in Australia cannot be achieved in less than 11 years (4 years minimum for medical degree, 2 years minimum for residency, 5 years minimum for specialty [25]), this represents a significant effort. Furthermore, convening meetings of domain experts is expensive, time consuming, prone to internal arguing, and not likely to provide a complete systematic coverage of the knowledge base. Medical specialists have excessive time demands from clinical work [38]. Data inadequacy may result from a lack of systematic coverage of the entire oncology vista by relying on the memory of a small number of oncologists. Data creep may occur where the knowledge provided reflects what an oncologist would like to record, rather than what has been determined as important to the oncology community. Finally, there can be data stasis where the results of the process become out of date very quickly. These processes have been shown to be at work in the medical expert domain of Ophthalmology [47, 79].
Clinical material from the doctor-patient interaction relates to consultation and follow up, and is unlikely to reveal knowledge in the areas of simulation, planning and treatment. It is not peer-reviewed. Guidelines and textbooks by their very nature are outdated sources which lessens their usefulness in the systematic maintenance of a knowledge base. Furthermore the knowledge in guidelines and textbooks is ‘secondary’, having been derived from the published literature.

The published literature, however, is easily accessible electronically, covers all facets and processes in the expert domain, introduces new ideas and verifies the usefulness of treatment paradigms that should be applied to treatment, drives the specialised vocabulary of the domain and acts as the objective standard for knowledge in the domain. The status of the published literature is clearly seen in the referral of guidelines to “Levels of Evidence” which detail the type and strengths of published data supporting a particular treatment approach (for example, see Appendix P - Clinical Practice Guideline for advanced oropharynx cancer - Scottish Intercollegiate Guidelines Network (UK)). As most publications have been peer reviewed by multiple sub-domain experts, the relevance of each publication has already been attested.

The published body of Radiation Oncology literature is very large. This corpus has the additional attraction of being the source that constitutes and popularises new Radiation Oncology knowledge, as well as the source of clinical advice on how to treat patients. While not totally objective, the literature is only published after a peer-review process has deemed the contained knowledge as worthy of publication. This approach to the determination of data utility is unique, and presents an opportunity to place the definition of data requirements on an objective footing.
The use of automated analysis is currently a popular paradigm relying on the analysis and groupings of words to infer meaning. Words in the literature typically refer to instances of entities, rather than the entities, and when attempting to define a knowledge structure, the important components are the entities rather than the instantiation in a particular case.

When some domain experts undertake the process of knowledge management, all domain experts will not always agree. Often disagreements will revolve around terminology, e.g., whether the most important cancer therapy used is called the “primary” or the “definitive” therapy. However, such disagreement does not disqualify them from the process nor make their model wrong, but rather points to the need for more refinement and standardized vocabularies to underlie the developed ontology. The issue is whether the model can be verified with outputs that other domain experts can agree properly represents their knowledge.

### 4.2 Methodology Used

While the following sections explain the process in detail, the research methodology consisted of the following steps:

1. defining the relevant literature
2. reading the PDF copy of each manuscript
3. using Content Analysis to identify the Semantic Entities contained within each manuscript
4. compiling a list of all Semantic Entities identified
5. matching the Semantic Entities to workflow stages

6. presenting the resultant classification in a markup language.

The “assessment unit” is the sentence which ends with a full stop, question mark or exclamation mark. In the initial phase of training, sentences were numbered and assessed sequentially starting at the Introduction, and ending at the final sentence of the Discussion. Within each sentence, all nouns or phrases that relate to data analysis resulting in the selection of patients for inclusion, stratification of patients in management, or measurement were identified. In addition to the text, tables and diagrams were also analysed to itemise the discrete and implicit semantic entities used. The approach to variability of semantic entities was similar to that of the Common Data Elements dictionary that promote consistency of data element used in Phase 3 clinical trials [101] in that overlapping entities were given a single name. All articles were assessed in their original paper format. A classification sheet (Appendix D - Data Collection Sheet) was completed. After completion, semantic entities were entered into an electronic spreadsheet for analysis. An example of this methodology is provided in Appendix B (Sample Extraction of Semantic Entities).

4.3 Content Analysis

The identification of the entities comprising the expert domain knowledge base which should be stored in any electronic repository requires the delineation of the discovery method, including the source of the entities, how they are extracted, and finally how they are organised into knowledge structures. The source of the entities is the published Radiation Oncology literature.

Among the research methodologies, Content Analysis possesses the ability to be
4.3. Content Analysis

transformed to suit the task of extracting entities. As Weber [149] states in his introduction (p.13):

“There is no simple right way to do content analysis. Instead, investigators must judge what methods are most appropriate for their substantive problems.”

This requirement is inevitable as the processes of making valid inferences from any text is intimately associated with and determined by the specific problems being investigated. While this inevitable subjectivity does not render the technique useless, any user of this technique must handle the process carefully and explicitly. Using the analogy of a lamp post, one would like to think that the technique can illuminate, rather than just prop up a point of view. The specifics of Content Analysis are described in several texts which were used to develop the present methodology [136, 149]. The stages of the analysis process as described by Wilkinson were followed [152].

While Radiation Oncology is a medical and scientific endeavour, analysis of its written material is not, and has similarities with research in consumer behaviour. Consumer research deals with the adoption of specific communication, and some radiation oncology text deals with the adoption of specific treatment paradigms. Content analysis was used to systematically identify and record the meaningful data elements, or semantic entities, that describe these treatment paradigms. The quantitative approach using manifest variables is described below. The approach might be described as a ‘de-construction analysis’.

Several patterns that obfuscate semantic entities from automated analysis were detected. Semantic entities were not always delineated within the publication. Some were only explicitly listed in tables, such as Age, Stage, Radiation Dose. Some semantic
entities were only identifiable as an instance because it is common to the entire sample size, e.g., “inflammatory and locally advanced breast cancer” \cite{150} rather than a Stage Grouping or Tumour-Node-Metastasis (TNM) classification. Other literature related to a specific scenario where the semantic entity and its value were implied. In these cases authors of the article had truncated their descriptions based on their expectation that the audience will have the same background knowledge. For example, an article describing brachytherapy for prostate cancer \cite{135} in the Radiation Oncology literature is unlikely to overtly specify several issues:

- that brachytherapy is a radiation procedure as the term is highly specific and inclusive of the concept and has a uniform meaning within the Radiation Oncology profession (Brachytherapy is “radiotherapy in which the source of irradiation is placed close to the surface of the body or within a body cavity” \cite{1})

- that the intent of treatment is curative, as brachytherapy for prostate cancer is never used as a palliative therapy

- given that all patients in a report will have prostate cancer

In this case, the semantic entities, \textit{Radiotherapy}, \textit{Intent} and \textit{Diagnosis} which can be derived from the publication by de-construction are all implied, but real, entities.

This process of Content Analysis has not been applied to the elucidation of medical knowledge structures. Its importance rests in its objectivity, where requirements gathering is subjective. The process has not been validated outside this thesis but is eminently capable of validation by comparison of extracted and recorded entities.

The focus of my Content Analysis was the identification of the semantic entities that were stored in a clinical database leading to the generation of the publication. 

\footnote{http://dictionary.reference.com/search?q=brachytherapy}
After de-construction identified the semantic entity, cataloguing and classification of information structures were undertaken. Initially, however, no attempt was made to catalogue the listings relating to each semantic entity in a taxonomy [32].

4.3.1 The unit of analysis

Quantitative content analysis is based on the ‘unit of analysis’ which has been defined as representing a single idea or unit of meaning and should be explicit [136]. In this research, the unit of analysis is defined as the “semantic entity”.

Given that it is common for modern trial specifications to identify and collect more data than is reported, one may need to determine what an important semantic entity is. The dilemma is however solved as unreported data do not appear in the corpus and so can be ignored. The authors of reports make this decision from their knowledge of the expert domain when submitting their manuscript. Either the unreported items were not analysed, and so should not be reported, or the unreported items were analysed and failed to reach significance, and so are meaningless. In cases where the non-significance is a false negative, the first report to demonstrate significance will include the item in its manuscript. The literature is therefore self-correcting.

4.3.2 Semantic Entities

The purpose of analysis is to discover the relevant “semantic entities”, which define clinical knowledge, which should be stored in a clinical data repository, that is, the OIS. Content analysis of the literature will look for phrases that demonstrate how the article’s authors
4.3. Content Analysis

- selected the patient group reported (selection criteria)
- defined the patient group reported (definition of patient population)
- described the variety of treatments applied to the patient, where a treatment modality comparison is being undertaken (such as a report comparing radical mastectomy with lumpectomy in the local management of early breast cancer)
- described the outcomes observed in the patient (recurrence, survival, side effects).

These groupings fit the notion of ‘evidence-based medicine’ (EBM). This is the application of the literature published about a specific health problem to other patients who have the same problem. For example, in considering a report from Radiotherapy & Oncology by Mark Gaze, et al which describes a comparative trial of 10 Gy in 1 fraction of radiotherapy and 22.5 Gy in 5 fractions of radiotherapy, where neither therapy produced a superior palliative benefit or survival, it is reasonable to expect that similar patients fitting the same profile (“histologically epithelial or cytologically proven malignancy of origin, and had one or more bone metastases demonstrated by plain radiography or skeletal scintigraphy which were causing sufficient pain to merit radiotherapy to one or two areas”) will be offered the shorter, less resource intensive treatment [67]. This is not a new concept in knowledge acquisition and application, and is the basis of modern medical practice.

Radiation Oncology knowledge about a patient at the consultation between radiation oncologist and patient is a large encyclopaedic ‘blob’ which is composed of the entire history, physical examination and results of all imaging and laboratory tests. Radiation oncologists routinely subdivide and classify the blob according to their knowledge structure to make it clinically manageable and useful. When the knowledge has been sufficiently subdivided into sub-blobs and into pieces of infor-
4.3. Content Analysis

mation which can be instantiated by discrete data points, it is available for storage. These pieces of information have a meaning in isolation as well as a position within the knowledge acquisition flow and the clinical work flow.

To illustrate, a semantic entity such as \texttt{Radiation\_Field\_Size\_Width} will be instantiated by a number, e.g., “10 cm”. This isolated piece of information and its data,

\[
\text{Radiation\_Field\_Size\_Width} = 10 \text{ cm}
\]

also possesses meta-data implicitly appreciated by domain experts. In terms of the flow of knowledge acquisition, this particular semantic entity comes after the semantic entities of \texttt{Diagnosis}, \texttt{Stage}, \texttt{Intent} and \texttt{Therapy} have already been completed \cite{105}. That is, the radiation field dimensions are not determined until a patient with cancer has been seen (to determine the \texttt{Diagnosis} and \texttt{Stage}), an application of learning from the literature has resulted in a treatment decision (\texttt{Intent}) and specific modalities (\texttt{Therapy}) have been selected as most appropriate to achieve the Intent. Similarly, the \texttt{Radiation\_Field\_Size\_Width} is determined in a specific geographical and work flow position in the expert domain process, i.e., “Planning”. Planning follows the other processes of Patient Registration, Consultation with a Radiation Oncologist and Simulation of the treatment position, and occurs in the Planning Room \cite{107}. Planning occurs before Treatment Delivery and Follow up with a Radiation Oncologist.

Furthermore, the instantiated semantic entity also informs the domain expert that the area where the tumour is or is likely to be, i.e., the area to be treated, and also that the tumour must be about 6.6 cm across. The nature of radiation dose deposition through a beam portal \cite{102} and the movement of target areas in a patient \cite{60, 61, 137} are part of the expert domain knowledge. It is common for the anatomical targeted
risk area called the Clinical Target Volume (CTV) to undergo physiological movement of 1 cm during treatment. The CTV with this motion envelope forms another structure called the Planning Treatment Volume (PTV) [112, 113]. The radiation portal, or ‘field’, placed around this PTV will require a further 7 mm expansion to account for the physically determined penumbral area of lower dose at the edge of radiation portals. So the final 10 cm field will have accounted for a right and left expansion of 0.7 cm of penumbral margin in addition to an estimated movement envelope (say 1 cm) around the targeted area, meaning the original target area can be no bigger than 6.6 cm². Therefore if the target area is larger than 6.6 cm, there will be a ‘geographic miss’, that is, some part of the tumour will not be treated adequately [15, 89].

In the process of producing a literature report that is designed to answer a clinical question, semantic entities are selected as being direct or surrogate measures of the particular variables pertinent to the question. The report’s author collects and analyses instances of the chosen semantic entities. While the semantic entity that relates to the data used to construct the literature report may not be identified, it can be derived from the author’s presentation of the data analysed when constructing the submitted report.

So in a literature report titled “Evaluating predictive factors for determining enteral nutrition in patients receiving radical radiotherapy for head and neck cancer” [98], the major semantic entities used measure methods of enteral feeding, the degree of weight loss and measures of nutrition. A more complete example is provided in Appendix B (Sample Extraction of Semantic Entities).

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²The usable width of a 10 cm radiation field is reduced by penumbra and movement: 10 cm - (1 cm + 1 cm) - (0.7 cm + 0.7 cm) = 6.6 cm
The semantic entities are units of information and constitute the building blocks of the knowledge structures of oncology, and are used in medical decision making. The entities have meta-data which derives from the expert domain and includes information that relates to their position within the knowledge structure, information flow and clinical work flow.

As a first step this research seeks to catalogue the items that need to be stored, before imposing any organisation of the storage structure. Thus the research requires that all data elements to be extracted, be identified by their direct or indirect link to what may be a specific patient’s problem, that is, relevance is determined by its effect on patient management.

### 4.3.3 The Body of Literature

Each year many manuscripts are accepted for publication on the topic of cancer. Within this cancer-related corpus there are journals that inform cancer groups generally as well as sub-specialty cancer groups (e.g., Medical Oncology, Radiation Oncology, Gynaecological Oncology, Surgical Oncology, Experimental Oncology, Chemotherapeutics, Radiotherapeutic Physics, Psycho-Oncology and professional Oncology groups like the RANZCR). These journals are of differing quality. Such stratification occurs in all areas of journal publication [125].

A sample of published manuscripts from the first month of thesis enrolment (February 2006) was selected as the corpus. The PubMed website was searched for relevant manuscripts, and the MedLINE entry for each manuscript was downloaded. A PDF copy of each manuscript was also obtained. The abstracts were read, and only
4.3. Content Analysis

Manuscripts pertaining to the clinical management of patients were selected. The selected manuscripts were broadly grouped into clinical trial and systematic review of patient treatment outcomes for particular cancers, investigations of prognostic features of the patient or tumour milieu, and lastly, technical issues relating to particular therapies.

A paper copy of each selected manuscript was produced and the text was analysed to discover semantic entities. The semantic entity was defined as any data entity manipulated to provide the knowledge presented in the manuscript. For example, if the manuscript contained a table that reported on the patients’ ages, the semantic entity contained is Date of Birth. If a manuscript reported the outcomes of surgery in prostate cancer patients, the semantic entities are Diagnosis and Therapy. The value of the instance of the semantic entity will be prostate cancer and surgery.

It was also found during the content analysis that some manuscripts contain assumed entities. The domain expert perceived that certain entities are assumed when the clinical circumstance described permitted only one interpretation. For instance, the terms denoting that the intent of treatment is ‘cure’ will not be found in articles describing prostate brachytherapy. Within the expert domain, prostate brachytherapy is only ever used with the intent of cure, and so authors provide no designation.

4.3.3.1 The Impact of Publication Bias

The reality of negative publication bias has been established [134, 111, 56], however the impact of this negative publication bias on the content analysis methodology was assessed as minimal. The content analysis sought to delineate required knowledge structures from the published literature. A particular knowledge component cannot
be deemed ‘relevant’ to oncological knowledge until a formal analysis has shown that it had an impact on clinical outcomes, that is, when it is reported in a positive trial.

This can be demonstrated by an example. If an oncologist were to suspect that patients who were Asian, non-smoking females with adenocarcinoma of the lung seemed to have a better outcome with different chemotherapy regimens [130], he would construct a null hypothesis, specifically

that there is no difference in progression-free survival when Asian, non-smoking, female cancer patients with adenocarcinoma of the lung are treated with chemotherapy regimen A (carboplatin–paclitaxel) or chemotherapy regimen B (gefitinib)

A formal trial protocol would be written to describe the entry of Asian, non-smoking, female cancer patients with adenocarcinoma of the lung into the process of random allocation to one of the two chemotherapy regimes. After a time a formal analysis the results with respect to progression-free survival would be undertaken.

The results might demonstrate either of the two following scenarios:

- Asian, non-smoking, female cancer patients with adenocarcinoma of the lung receiving carboplatin-paclitaxel had a progression-free survival of 6.7% at 12 months, and those receiving gefitinib had a progression-free survival of 6.7% at 12 months ...... then I could conclude that the patient group (Asian, non-smoking, female cancer patient with adenocarcinoma of the lung) does not have any oncological significance, and so is not something that oncologists need to know about. It is not in the expert domain knowledge base precisely BECAUSE its occurrence does not affect patient outcomes.
• Asian, non-smoking, female cancer patients with adenocarcinoma of the lung receiving carboplatin-paclitaxel had a progression-free survival of 6.7% at 12 months, and those receiving gefitinib had a progression-free survival of 24.9% at 12 months ...... then I could conclude that the patient group (Asian, non-smoking, female cancer patient with adenocarcinoma of the lung) does have any oncological significance, and so is something that oncologists need to know about. It is in the expert domain knowledge base precisely because its occurrence does affect patient outcomes.

The trial was undertaken and the second outcome demonstrated [108]. As a result, the knowledge of the impact of gefitinib on the survival of Asian, non-smoking, female cancer patients with adenocarcinoma of the lung is widespread. and the treatment of choice is gefitinib.

This example does not make the case that negative trials are not useful in oncology. Negative trials are useful demonstrating what is not oncological knowledge. However when attempting to determine the semantic entities that need to be represented in the expert domain knowledge structure, those trials do not add useful semantic entities.

The preposition for this research is that the required semantic entities, that is, those that are positively significant in impacting on clinical management of patients and therefore which need to be measured and recorded in an OIS, will be published in the Radiation Oncology literature, and that the semantic entities of negative trials therefore do not need to be delineated. In this research no differentiation was undertaken to classify trials as 'positive' or 'negative'. 
4.3._content_analysis

4.3.3.2 The Body of Literature for Analysis

Having settled on a research approach, the issue of the sample size became relevant. Prior knowledge of the published literature from training in Radiation Oncology points to a range of different clinical publication types covering several categories (such as retrospective review, randomised trial, prognostication, Quality of Life) but with broadly similar reporting criteria in each. Therefore the initial expectation was that commonly used semantic entities would be quickly recognised, and that these entities might already be adequately dealt with by an existing OIS. Uncommonly used semantic entities were of more interest, as these semantic entities are likely to reveal deficiencies of the data structures incorporated into a current OIS. Where new semantic entities are found, the expansion of the OIS to include these new entities can be assessed. Infrequent semantic entities are more likely to point the way to emerging and future requirements of the OIS. Furthermore, idiosyncratic semantic entities for a particular cancer could enable the completeness of coverage of the OIS to be assessed.

Initially the medical literature catalogue (MEDLINE) produced by the National Library of Medicine in the USA, which is available on-line through the PubMed portal, was accessed to assess the magnitude of the available data that could be assessed. A search was undertaken on 18th May 2006 with the general pattern “Xxxxx”[MeSH Major Topic] AND 200Y/MM[dat]. Multiple searches were undertaken substituting different values. Firstly, “Xxxxx” was substituted with NEOPLASM, Radiotherapy or Medical Informatics. Then 200Y was substituted with 2004, 2005 or 2006. Finally MM which represented the month in numerical format (01-12) was substituted with 01 (where 01 = January, 02 = February, etc). The average number of published manuscripts per month were 5584 (NEOPLASM), 184 (Radiotherapy) and 669 (Med-
ical Informatics).

The results of these searches are graphed in Figure 1. This small analysis indicates that to avoid non-representative periods, a minimum 6 month lag is required from the publication of a manuscript for the catalogue to become complete, and that the month of February contains a similar or greater number of manuscripts as other months.
Figure 4.1 Selecting the Sample

An initial trial of semantic entity coding established the expectation that an average of 6-8 unique entities will be discovered in each article, and that a total of 900-1200 entities might be reasonable sample. With this assumption in mind, the first month of the research, February 2006 was selected and a PubMed search (‘‘Radiotherapy’’ [MESH Major Topic] AND 2006/02[pdat]) was undertaken. This search produced 167 results [21/2/2011]. In addition to, and including these results, a search was undertaken of the specialist Radiation Oncology, and general Oncology literature where all articles were selected for review (Table 4.1 & 4.2). In addition, the popular general medical literature was screened for articles relating to Radiation Oncology (Table 4.3).

The literature utilised excluded articles that were devoid of patient data, as these reports were not germane to the problems of clinical knowledge structure definition. In addition reviews and basic science articles that addressed issues such as onco-
genes using *in vitro* methods without patient selection were excluded. The sample of manuscripts remaining after filtering numbered 121 and is listed in Appendix C (Radiation Oncology Literature Corpus).

Table 4.1: Specialist Radiation Oncology journals

<table>
<thead>
<tr>
<th>Journals reviewed</th>
<th>pISSN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australasian Radiology</td>
<td>0004-8461</td>
</tr>
<tr>
<td>International Journal of Radiation Oncology, Biology, Physics</td>
<td>0360-3016</td>
</tr>
<tr>
<td>Radiotherapy and Oncology</td>
<td>0167-8140</td>
</tr>
<tr>
<td>Clinical Oncology (R Coll Radiol)</td>
<td>0936-6555</td>
</tr>
<tr>
<td>Radiation Research</td>
<td>0033-7587</td>
</tr>
<tr>
<td>British Journal of Cancer</td>
<td>0007-0920</td>
</tr>
</tbody>
</table>

Table 4.2: General Oncology journals

<table>
<thead>
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<th>Journals reviewed</th>
<th>pISSN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Journal of Clinical Oncology</td>
<td>0732-183X</td>
</tr>
<tr>
<td>Cancer</td>
<td>0008-543X</td>
</tr>
<tr>
<td>Annals of Oncology</td>
<td>0923-7534</td>
</tr>
<tr>
<td>International Journal of Cancer</td>
<td>0020-7136</td>
</tr>
<tr>
<td>Cancer Research</td>
<td>0008-5472</td>
</tr>
<tr>
<td>Cancer Treatment and Research</td>
<td>0927-3042</td>
</tr>
</tbody>
</table>

4.3.3.3 The Advantage of a Manual Method

As with all empirical investigations, researchers should be careful to provide a definition that ensures the reproducibility of the methodology and results. In the future it is hoped that the use of automated technologies, such as automated content analysis and Natural Language Processing, could be applied to this end, as has occurred in literature and radiology reports [33, 50, 66, 154].
4.3. Content Analysis

Table 4.3: General medical journals

<table>
<thead>
<tr>
<th>Journals reviewed</th>
<th>pISSN</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Medical Journal</td>
<td>0007-1447</td>
</tr>
<tr>
<td>The Lancet</td>
<td>0140-6736</td>
</tr>
<tr>
<td>New England Journal of Medicine</td>
<td>0028-4793</td>
</tr>
<tr>
<td>Medical Journal of Australia</td>
<td>0025-729X</td>
</tr>
<tr>
<td>Australian and New Zealand Journal of Medicine</td>
<td>0004-8291</td>
</tr>
<tr>
<td>Australian and New Zealand Journal of Surgery</td>
<td>0004-8682</td>
</tr>
</tbody>
</table>

In these endeavours, the accuracy of current data extraction technique has not been shown to be mature enough to replace a manual method. It is therefore unavoidable that initially the domain expert is required for content analysis. The manual analysis will then take on the status of the ‘gold standard’ against which to benchmark the ability of any software approaches.

4.3.3.4 External Validity

The external validity of this methodology and approach resides in the breadth of its sample, and its ability to be repeated. Clinical data needs evolve quickly [47], so the ability to be re-used at intervals will ascertain the inevitable changing data needs of the oncology community.

Just as asking clinicians how they work and what they want in a GUI interface can and should inform the design and construction process of the software, the emerging data needs of the profession expressed in the literature can forewarn software providers of the need to alter their software to meet new challenges.
Chapter 5

Results

5.1 Collection of Semantic Entities

The journals listed were accessed for the relevant months, and the relevant articles printed. While reading, the semantic entities discovered were highlighted in the text and recorded on a grading sheet (Appendix D – Data Collection Sheet). Where implicit semantic entities were detected, the same process was followed.

A list of semantic entities discovered in the surveyed articles is provided (Appendix E – Semantic entities discovered from manuscript corpus). In addition to explicit and implicit semantic entities discovered, associated semantic entities which were not found were added later. For example, while entities relating to demographics are present (Date of Birth, Race, Gender at Birth), other entities such as Place of Birth, Mother and Father which are suggested by the entities found, were not discovered. Given that manuscripts are usually summaries of patient groups, the absence of such identifiers is expected. Appendix E does not include these suggested entities, but they are included in Appendix I and following where the entity list is manipulated. All the semantic entities were entered into a spreadsheet.
5.2 Metrics of Semantic Entities

The data collection found 3290 instances of 768 discrete semantic entities in 109 clinically relevant manuscripts. Metrics describing these semantic entities are provided in Table 5.1.

Table 5.1: Frequency of occurrence of semantic entities

<table>
<thead>
<tr>
<th>Frequency of occurrence</th>
<th>Individual semantic entities ($n$)</th>
<th>Total Number of occurrences ($\text{sum}$)</th>
<th>% of semantic entities</th>
<th>% of occurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – 5</td>
<td>641</td>
<td>1005</td>
<td>83.46</td>
<td>30.55</td>
</tr>
<tr>
<td>6 – 10</td>
<td>55</td>
<td>418</td>
<td>7.16</td>
<td>12.71</td>
</tr>
<tr>
<td>11 – 15</td>
<td>28</td>
<td>368</td>
<td>3.65</td>
<td>11.19</td>
</tr>
<tr>
<td>16 – 20</td>
<td>10</td>
<td>183</td>
<td>1.30</td>
<td>5.56</td>
</tr>
<tr>
<td>21 – 25</td>
<td>9</td>
<td>205</td>
<td>1.17</td>
<td>6.23</td>
</tr>
<tr>
<td>26 – 30</td>
<td>4</td>
<td>111</td>
<td>0.52</td>
<td>3.37</td>
</tr>
<tr>
<td>31 – 35</td>
<td>3</td>
<td>99</td>
<td>0.39</td>
<td>3.01</td>
</tr>
<tr>
<td>36 – 40</td>
<td>4</td>
<td>150</td>
<td>0.52</td>
<td>4.56</td>
</tr>
<tr>
<td>41 – 45</td>
<td>4</td>
<td>171</td>
<td>0.52</td>
<td>5.20</td>
</tr>
<tr>
<td>46 – 50</td>
<td>3</td>
<td>145</td>
<td>0.39</td>
<td>4.41</td>
</tr>
<tr>
<td>51 – 55</td>
<td>2</td>
<td>102</td>
<td>0.26</td>
<td>3.10</td>
</tr>
<tr>
<td>56 – 60</td>
<td>2</td>
<td>113</td>
<td>0.26</td>
<td>3.43</td>
</tr>
<tr>
<td>61 – 65</td>
<td>1</td>
<td>65</td>
<td>0.13</td>
<td>1.98</td>
</tr>
<tr>
<td>66 – 70</td>
<td>1</td>
<td>70</td>
<td>0.13</td>
<td>2.13</td>
</tr>
<tr>
<td>71 – 75</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>76 – 80</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>81 – 85</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>86 – 90</td>
<td>1</td>
<td>86</td>
<td>0.13</td>
<td>2.61</td>
</tr>
<tr>
<td>TOTAL</td>
<td>768</td>
<td>3290</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

The first graph (Figure 5.1) demonstrates the incidence of semantic entities as a proportion of entities and of occurrences.
5.2. Metrics of Semantic Entities

A second graph (Figure 5.2) is provided to better view the detail by excluding the large number of entities in the 1-5 occurrence band.
5.2. Metrics of Semantic Entities

Published manuscripts contain many semantic entities. The most frequent entity was Diagnosis in 86 of the 109 manuscripts (n=86, 78.9%). There were only 4 entities that were used in more than 50% of the manuscripts – Date_of_Birth (n=70, 64.2%), Histology (n=65, 59.6%), Surgery_Decision (n=56, 51.4%), and Radiation_Decision (n=57, 52.3%). Other frequent entities included Stage_N (n=36), Prescription_DrugName (n=37), Immunotherapy_Decision (n=37), Stage_T (n=41), Radiation_Prescription_Technique (n=40), Stage_Grouping (n=49), Chemotherapy_Decision (n=44), Histopathological_Confirmation (n=44), Stage_M (n=42), Surgery_Procedure (n=47), Radiation_Prescription_TotalDose (n=49), Gender_at_Birth (n=51), and Date_of_Death (n=51). These 17 most common items provided 27.4% (902/3290) of the total number of instances.

Analysis of the frequency of appearance of semantic entities revealed that the infrequent items were numerous, and that the frequent items were few in number. The entities which appeared on only 1-5 occasions were numerous (83.46% of the total number of semantic entities) but infrequent (30.55% of the total number of instances) were described as uncommon. However the entities which appeared on 6 or more occasions were uncommon (16.54% of the total number of semantic entities) but frequently seen (69.48% of the total number of instances) and so were described as common. In fact of the 768 entity total, there were 458 different entities appearing just once, but these comprise only 13.9% (458/3290) of the total instances found. The difference is clear (Figure 5.3).

As will be described later, many semantic entities are related. Where radiotherapy is described in a manuscript, a single term may be used, e.g., Radiation_Decision (57), and Radiation_Prescription_Technique (40), and Prescription_TotalDose
(49), however if a manuscript describes one of these, the others can all be implied since a radiotherapy technique, by virtue of the expert domain imperatives, will also have a total dose and a therapy decision. When all radiation-related entities are grouped, 75 manuscripts (68.8%) included at least one radiation term. The listing of terms in Appendix E reveals that the entities found at least 4 times are all used in routine clinical practice.

Inferred semantic entities were common. The commonest inferred entity was date of event which was used to construct all outcome measures relating to time. When an entity such as ‘event-free survival’ (proportion of patients reaching a fixed interval without a recurrence event) is common, it is calculated within the Kaplan-Meier statistic [87] using the Date_of_Diagnosis and Date_of_Local Recurrence, Regional_Recurrence, Distant_Recurrence or Death. The manuscript will rarely
list all four dates as the calculation method is well known and widely used.

5.3 Organising the Semantic Entities

The listing provided in Appendix E is of little use. The list describes a small portion of the items that could be required in an OIS. It is likely that the next month will see the same pattern with the same group of a small number of entities often repeated, and a plethora of once-used items. The implications for OIS software design and assessment are that the common elements must be handled well, while the infrequent elements can be handled with a functionality that is infinitely expansible. Discovering whether any OIS can store all these individual items is less important than seeing the items properly stored.

If the semantic entities collected reflect a domain-specific knowledge structure, an adequate OIS should address the knowledge structure. While the specialist medical vocabulary has not been described, neither has the knowledge structure.

There are many ways that semantic entities could be grouped, perhaps as many ways as there are domain experts. However, groupings should be comfortable, match existing categories and offer some hope of agreement among experts. The grouping should be deliberate and reasonable during construction, since agreement among domain experts is more important than a close proximity metric.

Radiation Oncology as an expert domain has a well defined work flow pattern [107], which also extends into clinical trials and clinical guidelines, such that semantic entities are not randomly distributed in the work flow and have an upstream and downstream
dependence. This has already been demonstrated earlier using the domain specific entity, \texttt{Radiation\_Field\_Size\_Width}.

The benefit of organisation of entities in line with the work flow used will lead to a reduction in the barriers to orchestration of work flow \cite{34}. This grouping according to clinical activity may provide unforeseen benefits in cost management after business process modeling \cite{6}, and also permit improved re-use of data from work flow \cite{75}.

The entered data elements were grouped to reflect their order of collection within the clinical work flow. While this grouping may not be optimal, it is based on a tangible organisation model, and so should be less controversial and also easy to reproduce.

Based on the work flow orchestration described elsewhere \cite{107, 105}, the following areas are separated:

1. REGISTRATION

   (a) SPECIFICATION OF ANY ORGANISATION PROVIDING HEALTHCARE

      i. all elements describing organisational entities involved in care provision. This may be a specific departmental site, an academic or professional organisation, as well as economic entities, and local, regional and national Ethics and Trial infrastructure

   (b) DEMOGRAPHICS OF PATIENT

      i. demographic items collected as part of the Registration process

      ii. patient’s characteristics that permit comparison with populations, in-
including race, age, income, mobility, educational attainment, home ownership, employment status, and location

2. CONSULTATION

(a) INDIVIDUAL CHARACTERISTICS OF PATIENT

items discovered or measured at any part of the clinical process that define an individual’s milieu. These may pre-date or post-date the malignant diagnosis

i. BIOLOGICAL MILIEU

A. measurement of biological variables (anatomical, physiological, endocrinological, genetic, genomic)

B. factors that may have proven or unproven significance in affecting therapy selection and efficacy

ii. PSYCHOLOGICAL MILIEU

A. measurement of psychological parameters purported to reflect a patient’s state of mind and quality of life

(b) CLINICAL HISTORY OF CANCER

i. the information gained by asking specific questions, either of the patient or of other people who know the person to give suitable historical information (symptoms)

ii. the information gained by suitable physical examination of the patient by a physician (signs)

iii. the search for factors already established to have significance in disease outcome, therapy selection and efficacy (prognostic factors)

(c) INVESTIGATION OF CANCER
5.3. Organising the Semantic Entities

i. information gained by imaging, or analysis of tissue and fluid samples for tumour markers which was prompted by the clinical history disclosed to a physician

(d) DIAGNOSIS & STAGING OF CANCER

i. collation of the clinical history and application of standardized coding to define the nature and extent of the patient’s disease including histopathology (including cytology and immunohistochemistry), laterality, and tumour grade.

(e) DECISIONS REGARDING TREATMENT OF CANCER

i. specification of the intent of treatment

ii. specification of the modalities of therapy to be applied

iii. indication of inclusion in a formal trial or use of published guideline

3. THERAPY

(a) SPECIFIC PARAMETERS OF THERAPIES USED

i. details that describe the conduct of the therapies used

A. preparation for delivery of the therapy

B. delivery of the therapy

(b) SIDE EFFECTS OF THERAPIES USED

i. subsequent additional Clinical History (i.e., signs and symptoms) that specifically result from the administered therapies

4. FOLLOW UP

(a) OUTCOMES OF CANCER TREATMENTS

i. descriptions of the time course of a patient’s disease
ii. descriptions of the time course of a patient’s late side effects

When looking at the data predating but associated with the original cancer diagnosis, there will be symptoms described by the patient, signs elicited by the doctor as well as subsequent imaging and laboratory tests which inform the diagnosis. Previous work has already demonstrated that these logical links between the diagnosis and pre-diagnosis findings can be utilised for decision making [123].

Formal validated classification of semantic entities and their groupings is preferred and should be undertaken within a validation framework. The issue of physiological factors within the Physiological Milieu of the patient should match already developed knowledge structures. Matching the anatomical names and organisation to an ontology such as the Foundational Model of Anatomy makes sense. In much the same way that all oncologists could expect a harmony between an Ontology of Surgical Oncology and this Ontology of Radiation Oncology.

The attempts to devise Medical Ontologies encompassing all medicine have proved cumbersome that has dulled their usefulness [121]. The medical expert domain does have well recognised silos where idiosyncratic knowledge structures reside. A process that addresses these silos but has an underlying structure to integrate these efforts is needed.
5.4 Clinical Knowledge Markup Language (CKML)

5.4.1 Re-factoring the Semantic Entity Groups

The semantic entities were grouped according to the framework presented in Section 5.3. It is evident that there is overlap between some groups such as Biological/Psychological Factors and Clinical History. The symptoms of cancer before diagnosis may lead to psychological distress which only later may be imputed to the cancer. Similarly, a patient may complete treatment, be physically normal yet still remain anxious thinking about whether the cancer may return.

The unstructured grouping of semantic entities is listed according to frequency in Appendix E. This listing of semantic entities, with added additional terms that were obvious additions within the broadly grouped semantic entities, was then organised into the oncology work flow. This organisation is not exhaustive, rather it demonstrates what can be achieved.

The work flow within the Radiotherapy component was matched to that described by Ford et al [64], and the subsequent personal communication that followed (Appendix F – Johns Hopkins Hospital Radiotherapy Work flow). In that work flow there are five action points for radiation oncologists:

1. Deciding to treat

   This action point is firmly based on the completion of activities directed to specify the disease type and extent. Until the specification is deemed complete, no decision is reached or recommendation provided, and while options may be discussed, no decision on the recommendation can be reached.

2. Obtaining consent
This represents a flexure point in the medical management of the patient. Once informed of issues relating to prognosis with and without treatment and a recommendation is formulated, the patient needs to select their treatment and inform the clinician that they consent to the treatment.

3. Specifying the radiation prescription

The radiation prescription contains details of the site being treated, the dose to be delivered, the beam type and energy to be used, the number of fractions over which to deliver the dose, the prescription point (i.e., the 3D point inside the patient which will get that absolute dose), the patient position, numbers of days per week to be treated. These parameters can be specified as part of the DICOM protocols.

4. Drawing the volumes and contours on a planning CT scan

The radiation plan utilises a CT scan on which the oncologist draws contours to highlight normal anatomy which is at risk of radiation damage, and volumes which delineate the areas at risk from the cancer. These are then expanded to give some idea of the likely movement which will occur during treatment. The radiation therapist (also called a “dosimetrist”) undertakes an iterative process of placing radiation portals to aim at the structures defined by the oncologist, altering beam numbers, intensity, beam energy and beam modifiers until a plan is achieved that meets the oncologists expressed parameters of dose to the areas at risk of cancer and the areas sensitive to radiation. The review process to determine acceptability of a radiation plan requires that the oncologist look at the structures previously drawn, and then to overlay predicted dose delivery. A plan is acceptable where dose to the cancer volumes is high enough, and dose to the critical contours is low enough. These parameters can be specified as part of
the DICOM protocols.

5. Accepting a completed radiation plan

The radiation beam parameters used in the approved radiation plan are then transferred to the Record & Verify system for use when the patient is treated. These parameters can be specified as part of the DICOM protocols. These decision points are highlighted in pink. The other workflow actions are undertaken by clerical staff, radiation therapists, radiation physicists and radiation nurses.

5.4.2 Developing an XML specification

The grouped semantic entities are further sub-grouped according to commonality. Much of this commonality knowledge resides in the expert domain and has not been quantified academically. As the eventual aim is to have medical knowledge in an interchangeable format, the semantic entities were converted into a permissive format.

The Standard Generalised Markup Language (SGML) has been developed for such a purpose of describing the structure present in information within human readable format. There are several specifications relating to special circumstances derived from SGML including hypertext markup language (HTML), extensible markup language (XML), and even a specifically designed medical markup language (MML) [16]. The purpose of all SGML-based specifications is preparation for computational processing. The XML specification is particularly useful for ad hoc description of structured data. Specifying the semantic entities in an XML format is a necessary step in preparing the semantic entities for general use. Wide scale deployment would require the description of an XML Namespace and detailed dictionary, but this is outside the scope of this work.
The XML terms are derived locally without reference to any Standardised Nomenclature, although SNOMED-CT or the UMLS would be possible reference sources, the accumulation of multiple terms makes correct choice difficult. Many of the terms used in the Radiotherapy section will have a pre-existing DICOM-RT tag name, but no attempt is made to correlate these in this work. Likewise the taxonomy of terms relating to Histopathology are only referenced as these are already organised in SNOMED and elsewhere. Similarly the classifications of malignant diseases within ICD10, of late radiation effects (LENT/SOMA) of cancer therapy side effects (NCI CTCAE v4) and the organisation of anatomical terms within the Foundational Model of Anatomy can be re-used.

Radiation Oncology departments utilise the DICOM-RT format to save radiation plans. The DICOM-RT nomenclature describes the non-medical facets of radiation therapy and its delivery and recording. The only entries from the medical domain experts recorded in the DICOM-RT files are the radiation prescription and radiation target volumes provided by the radiation oncologist. The DICOM-RT nomenclature was not derived from the Radiation Oncology expert domain but rather from domain experts from Radiation Therapy, Radiation Dosimetry and Radiation Physics. The DICOM and XML formats are interchangeable which raises the possibility of storing a cancer patient’s medical data inside a DICOM container. However, at present, few DICOM-RT files contain the patient’s medical data in a structured format.

The hand-crafted XML Specification described in the following sections is called

3 LENT SOMA tables. Radiother Oncol 1995;35:1760
5.4. Clinical Knowledge Markup Language (CKML)

a “Clinical Knowledge Markup Language” (CKML). The new title is necessitated by the imposition of the XML specification back into the expert domain to demonstrate its usefulness and applicability. As some efforts have shown that general statistical prediction of survival in cancer is inferior to specifically designed artificial neural nets [2], the specification of cancer cases in a semantically sound structure might lead to even greater success. The specification can produce high quality medical information [12] which also removes the need to undertake data mining through natural language processing. Even when analysing histopathology reports from cancer cases, the less than perfect accuracy of multiple language processing approaches does not meet the criteria for outcome reports [19]. Specification of reports and letters directly into structured formats will be more accurate than any post-processing techniques. Many authors point to the possibilities that arise if the medical knowledge present in free text were actually formally structured [32].

The basic XML structure for semantic entities is listed in Appendix I (The CKML superstructure).

5.4.3 Producing an Ontology from the XML Specification

While the XML specification derived provides “annotated text with important information about objects and their structures, thus concepts for the ontology to build” [29], the definition of concepts, properties and relationships in a formal ontology is outside the Radiation Oncology expert domain and outside the scope of this thesis.

Instead the XML specification in Appendix I which covers the commonly used concepts and relationships in the field is used to demonstrate that this simplified view has applicability within the domain [29] as a clinical knowledge markup language.
5.5 Evaluation of CKML and future applications

Whether clinical data is specified in plain text or an XML schema is not a trivial issue for informaticians or clinicians. There are reports of substantial academic energy expended trying to manipulate plain clinical text into useful schemata [103, 53]. Clinical data specified into XML formats can be used for many things [3], including the important integration of routine clinical data with genomic, proteomic, lipidomic or metabolomic bioinformatic data [13]. Furthermore, when coding is undertaken directly in electronic systems, it is usually very accurate [147].

If the Clinical Knowledge Markup Language (CKML) described in Appendix I has any relevance to the expert domain, it will be applicable to the requirements of several domain specific knowledge areas relating to the clinical management of patients. Discovering these knowledge areas occupies a significant focus for informatics energy attempting to extract knowledge structures and ontologies from plain text.

The development of clinical knowledge in the Radiation Oncology expert domain occurs in discrete steps:

- Specific application of current knowledge to an oncology patient (Routine Clinical Work). Current knowledge is deficient, and so arising from the management of routine patients are clinical questions that seek to improve patient outcomes. These clinical questions become new research questions which are answered using the paradigm of the clinical trial.

- Systematic regimented accrual of patient information in the setting of a comparison of therapies to answer clinical questions (Clinical Trials)

- Reporting of the conclusions of clinical trials (Clinical Trial Reporting)
• Generalized application of knowledge to the oncological population (Clinical Guidelines)

• Specific application of ‘new’ current knowledge to an oncology patient (Routine Clinical Work). The new current knowledge is less deficient, and so arising from the management of routine patients are new clinical questions that seek to improve patient outcomes. The use of newly discovered knowledge ‘closes the loop’ in an iterative cycle of knowledge generation to produce a continually changing knowledge domain.

This iterative loops describes the usual pattern of knowledge advancement. Examination of current data is a fundamental component that directs clinical trial activity. Retrospective review of current data can point to where clinical trials are not needed, or where the clinical trial budget is best applied. Advancement by serendipitous breakthrough is less common.

If the CKML is a correct representation of the clinical knowledge of the expert domain, it should be able to function adequately with little modification in these four settings, both in the development of software [4] and the use of that software. This could drive data entry directly into ontological frameworks and facilitate re-use.

Achieving the interchangeability of natural language and structured text has been difficult. While informaticians are able to manipulate and re-use structured text, clinicians are resistant to moving away from natural language. CKML could be demonstrated to be relevant by taking plain oncological text and using natural language processing techniques to generate structured text consistent with the format. While this approach does not disturb the domain expert’s work flow, prior work indicates that inaccurate structured text will be produced. However, the resultant structured
text remains obscure to the domain expert who is unfamiliar with the format of structured text and so reliable checking may be unachievable.

An alternate approach is to record data directly into the CKML format, from which can be produced plain text that the domain expert can validate as correct. The validity of CKML as a domain knowledge representation would then be demonstrated to the informatician. The domain expert may also see the value of entry of data into sympathetically structured text.

Studies to demonstrate the validity of this approach are not within the scope of this thesis. Initially the ability of CKML to store knowledge from clinical settings should be demonstrated. The remainder of this chapter will address this issue within a specific oncological circumstance using the CKML structure shown in Appendix I. Within the CKML structure is the requirement to select either <Trial>, <Report>, <Patient> or <Guideline> depending on the item to be represented. The Clinical Trial Protocol and Report differ in the addition of a trial outcome section along with summary items which include counts detailing numbers of patients included and randomised, as well as numbers receiving treatment and the characteristics of the randomised groups.

5.5.1 Oropharyngeal Cancer

The preceding discussion that predicts that a specification such as CKML has relevance in describing radiation oncology knowledge structures and advantages in translating its use to normal clinical practice can be demonstrated with an example. For this purpose, one disease site was chosen from within the interest area of the researcher, from which was selected a patient, a relevant trial, the relevant trial’s published manuscript
and current guidelines to illustrate the commonality of markup structure.

Cancers of the Head and Neck (H&N) region are not particularly numerous but well recognised as requiring complex treatment in the form of combinations of radiotherapy, chemotherapy, immunotherapy and surgery. The patients who suffer this disease are often quite unhealthy and unwell. Within the H&N region there are areas like the oral cavity and oropharynx which have several sub-sites with very similar natural history and treatment paradigms.

The base of tongue is a sub-site of the oropharynx and has been chosen as the index site. A patient who was diagnosed with and treated for a locally advanced squamous cell carcinoma of the base of tongue was chosen. Although written permission had already been provided to re-use of anonymous data, a personal approach met with agreement to use the clinical data. A search was also undertaken for an Australian clinical trial protocol for which this patient would have been eligible. The Trans-Tasman Radiation Oncology Group (TROG) had such a trial, called “HeadSTART” and designated TROG02.02, which enrolled patients similar to the clinical case. Furthermore, this trial has matured and was reported in mid-2010, so the clinical trial report was available. Lastly, a search was made for clinical guidelines recommending treatment for locally advanced oropharyngeal cancers. Three such guidelines were found originating from the USA (National Comprehensive Cancer Network - NCCN), Canada (British Columbia Cancer Agency - BCCA) and the UK (Scottish Intercollegiate Guideline Network - SIGN).

All of these documents are provided in the following appendices - the TROG02.02 clinical trial protocol (Appendix L), the TROG02.02 report published in the Journal of
Clinical Oncology in 2010 (Appendix M), and the relevant guidelines from the NCCN (Appendix Q), SIGN (Appendix P) and the BCCA (Appendix O).

5.5.2 CKML subset for Routine Clinical Data

For the purposes of defining a clinical record in the CKML structure, the clinical record of the patient was accessed and specific entities were entered into the CKML structure. A summary of the patient’s clinical history is provided in Appendix J, with the relevant semantic entities in bold for comparison with the CKML produced. All unused elements, such as `<Trial>`, were removed. Items that are appropriate as instances are also included. The original clinical data has not been provided but is available on request.

It is clear from the CKML structure imposed on the clinical data that the criteria describing the patient, the treatment and the outcome are now explicit. The implications of a knowledge structure based firmly in work flow was appreciated early, and further investigations were undertaken to determine the viability of these implications. It was appreciated that software processes such as agents could determine whether the patient was eligible for a clinical trial or guideline by searching for relevant parameters. For example, any circumstance where the patient’s clinical record contains the data, `<ICD0>C01</ICD0>`, it is possible to query to discover whether there exist trial protocols, trial reports or guidelines applicable to the disease “C01” categorised according to ICD-10 classification. However natural language terms such as tongue, BOT, or posterior tongue might not be accurately appreciated as “base of tongue” which is a well defined anatomical subdivision of the tongue and distinct from lateral tongue.
5.5. Evaluation of CKML and future applications

Since contextual searching within the CKML is feasible, there are now many further uses for the data. During the course of the thesis, several applications of knowledge structured in a CKML format have been explored and published, and are described below. Many other applications exist.

5.5.2.1 Relevance of Routine Clinical Data to Clinical Trials

The trial, report and guideline are all tools used to aid the domain expert in either the application of existing knowledge, or the discovery of new knowledge. The trial seeks to discover new knowledge but can only do so by including patients with specific inclusion criteria and without specific exclusion criteria which are derived from the cancer description or facets of the patient’s condition (e.g., <BiologicalMilieu> or <Demographics> (see Appendix L – Section 4: SELECTION OF PATIENTS).

Trials seek to maintain a homogeneous sample population. However, detecting eligible patients matching these long lists of eligibility criteria is problematic. The use of a software agent that compares the patient’s data with the selection criteria could increase the accrual rate of patients into trials through accurate identification [107].

These software agents provide optimal efficiency when dealing with a formalised structure that describes the patient data, rather than plain text requiring natural language processing.

5.5.2.2 Relevance of Routine Clinical Data to detect Co-Incident Clinical Processes

Once a treatment or trial has been selected for a patient, the knowledge specification will contain a description of the clinical treatment processes that have been selected.
Given that other medical expert domains might use a similar structure to prescribe therapy, this information is then available for the detection of other co-incident, and clashing clinical processes planned for the patient that may be already ongoing or planned \(^7\). Detection of conflicts between different treatment regimes can reduce the scope for medical misadventure.

### 5.5.2.3 Relevance of Routine Clinical Data to Treatment Scheduling

The decision to treat requires detailed knowledge of the patient’s clinical data. At the point when this is defined, even if outside the oncology department, the treatment to be deployed as part of the treatment plan can be predicted from a detailed guideline similar to those provided by the NCCN (Appendix Q). Since the treatment requires radiotherapy, an appointment with a radiation oncologist is necessary, as are appointments for simulation and treatment. This is predictable from the normal radiotherapy work flow (Appendix F). Planning these component results in a schedule. Using techniques such as support-based distributed optimisation (SBDO), it is possible to use agents which access the knowledge structure to improve the efficiency of scheduling \(^3\), perhaps even balance oncology workload across regions.

### 5.5.2.4 Relevance of Routine Clinical Data to Argumentation and Clinical Decision Support

The inclusion of patients into clinical trials, and the application of trial results and guidelines to a patient’s management requires a decision making process resembling formal Argumentation. The patient’s clinical parameters form the arguments which can be used to establish an acceptable treatment approach for a patient \(^4\).
When all the possible knowledge sources - clinical trials, reports and guidelines are presented in the same formal structure, the clinical decision making process can be augmented as once again the patient characteristics serve as the base against which to select the relevant available trials, published reports and guidelines. The selected reports and guidelines can serve to inform the clinician about the best reported and recommended treatments, and likely outcomes. The recommended trials present the clinician with options for consideration if they believe that therapy outcomes can be improved with respect to cure or side effects. The end of the process of Argumentation is to present the clinician with the results of the automated decision making. The identification and incorporation of experience and other parameters that modify decision making become possible once the knowledge application has been explicitly argued.

The rapid application of trials would also permit more rapid accumulation of patients. More patients would allow oncological knowledge to advance faster (faster accrual of required numbers, more trials in different homogeneous groups) and with greater certainty (large trials with more numbers become feasible).

This use has already been investigated and proposed, and from an informatics perspective is already achievable. The formal knowledge structures are lacking.

5.5.3 CKML subset for Clinical Trial Protocols

The clinical trial process has several components. There are front-loaded components outside of the clinical work flow that deal with the development and production of the clinical trial protocol, the introduction and coordination of the trial in a clinical
5.5. Evaluation of CKML and future applications

environment, and the monitoring of accrued data. There are back-loaded components outside the clinical work flow that are responsible for the collation, analysis and reporting of the trial results. The actual trial however is a normal but constrained treatment delivery process operating within the normal clinic environment to match the specifications of the trial protocol [11] [107].

This subset of CKML describes the trial protocol specifying the inclusion and exclusion criteria, the randomised therapies to be applied and the outcomes which will be measured and calculated. This CKML trial protocol specification can be automatically matched to the CKML patient description thereby permitting the determination of whether the patient is eligible for the trial protocol and therefore possible inclusion in the specified trial. A comparison of the two specifications should reveal that the patient specification has a discrete value, while the trial specification may have a range of acceptable values.

A patient enters a clinical trial when they satisfy the inclusion criteria and possess none of the exclusion criteria used for sample selection within the trial protocol, and provide informed consent. After randomisation, a pre-determined treatment with constrained parameters not open to alteration by treating clinicians is prescribed and administered. The follow up intervals and medical assessments undertaken are specified. At each point, required clinical data is entered onto and submitted by Case Report Forms (CRFs).

An example of a Clinical Trial Protocol is provided in Appendix K. The unused elements are removed. The position of the inclusion and exclusion criteria mirrors their position in the patient’s record. In particular there is a specification of inclu-
sion/exclusion criteria in <Demographics>, <BiologicalMilieu>, <Diagnosis> and <Stage> to name the more frequently used. The treatments to be used are also specified in the same way as the clinical record, which allows the selected treatment approach to be templated into the patient’s treatment record, including follow up assessments.

5.5.4 CKML subset for Clinical Trial Report

The abstract is a plain text mechanism for providing a synopsis of a lengthy literature report so that the reader can establish relevance without having to needlessly read all of the text. There are few rules governing its construction and structure with subsequent effects of retrieval [118]. The abstract has been the subject of natural language processing techniques exploring easier ways to establishing ontologies than asking the domain expert [30].

The Clinical Trial Protocol and the Clinical Trial Report are closely related when confined to the clinical processes and outcomes defined. The difference relates to numbers of patients, and trial outcomes (levels of side effects, survival rates). The need to quantify these outcomes were the raison d’être for the trial (resulting in the generation of the Clinical Trial Protocol) and the conclusion of the trial (resulting in the generation of the Clinical Trial Report).

While the desire to use natural language processing (NLP) and ontologies to extract knowledge [37] is laudable, if the Clinical Trial Protocol is specified in an ontology-based framework like CKML by the domain expert, the generation of the Clinical Trial Report only requires the addition of outcome and survival rates by the domain expert.
as they relate to randomised arms and the treated group. Essentially the Clinical Trial Protocol specification is reused. If a plain language summary is required, this could be automatically generated. However the use of the abstract is a way of assessing whether the trial details are applicable to a particular case.

The CKML specification for a case can be used as a filter for trial reports, looking for those applicable to a specific patient in essence determining if the patient could have entered the trial subsequently reported. The Clinical Trial Report can be reused to match to future patients, which would inform clinicians of evidence appropriate to the present patient, hopefully improving clinical decision making [142].

The Clinical Trial Protocol provided in Appendix K includes the material reported in the Clinical Trial Report that resulted from the protocol used. This process has the advantage that the clinical specification of the treatment that produced the results published is included in the Trial Report. In addition, since the selection criteria for patients entering the trial remain intact, the report can continue to function as a selector of patients. In this case all of the reported outcomes (toxicities and outcomes) of both arms are available for the decision process of treatment selection.

5.5.5 CKML subset for Clinical Guidelines

Field and Lohr defined the clinical guidelines [110] as

“systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.”

(page 38)

Patients can be assessed to see if they ‘fit’ the guideline (e.g., a prostate cancer treatment guideline has no applicability to a female patient; an asthma management guide-
5.5. Evaluation of CKML and future applications

line has no applicability to a patient with pneumonia) with the guideline representing the preferred clinical management strategy in a well defined group of patients. While the systematic extraction of guidelines may have a work flow [127], the guideline itself has to match clinical work flows. If the specification of the guideline does not match the clinical work flow, it cannot be implemented.

The matching of patient to appropriate Clinical Guideline therefore mirrors the patient to Clinical Trial Report matching described above. Clinical Guidelines are most useful for describing treatment to patients who are ‘uncomplicated’ with respect to the guideline selection criteria. At the boundaries of selection, more variability will be expected (e.g., in a guideline that recommends treatment for breast cancers of size 2.5 cm, it is the tumours slightly more than 2 cm and slightly less than 5 cm for which the guideline will not be followed, rather than for tumours for 3.5 cm).

There are several bodies that have a tradition for publishing best practice guidelines. The National Comprehensive Cancer Network (NCCN) in the USA, the Scottish Intercollegiate Guideline Network (SIGN) in the UK and the British Columbia Cancer Agency (BCCA) have published guidelines for over a decade. Their approaches to guidelines are different, and so as a result their guidelines vary.

As a large clinical organisation working from several sites, the BCCA publishes their guidelines which dictate the organisation’s approach to cancer management. As such, their guidelines describe a local unified common approach to the defined problem. The BCCA is the sole cancer treatment organisation for British Columbia. They publish their guidelines for the benefit of local referrers and patients.
The NCCN is a consortium of academic centres which seek to advise the rest of the USA on what they consider is standard and non-experimental treatment. Guidelines from the USA are usually characterised by presenting the range of options acceptable in a particular circumstance, and the oropharyngeal cancer example is no different.

The SIGN is a professional collaboration that seeks to educate decision making. Clinicians are advised about the evidence of what works and how robust that evidence is. The authors do not address the nature and details of actions by clinicians, only the evidence to be considered in making treatment decisions.

When translating a guideline into CKML, the Clinical Guideline is, surprisingly, briefer than the Clinical Trial Report. Since guidelines are applied generally to a patient population, there are few of the inclusion and exclusion criteria seen with Clinical Trial Protocols. There is the implicit assumption that if a patient will die as the result of a particular treatment (e.g., chemotherapy in the very elderly patient), the clinician will not pursue it. Furthermore many of the recommendations for treatment are more of a generic statement about approach - “We advise an organ sparing approach, so radiotherapy is preferred to surgery”. Lastly, since Clinical Guidelines recommend best practice treatment, the inclusion of outcome data is not required. Indeed, because the characteristics of the general patient population will differ from the highly selected sample included in the trial, the outcome of guideline-based treatment will be worse.

5.5.6 Comparison of CKML subsets

Each CKML instance describes an aspect of medical knowledge and is useful for comparison. It is possible to identify the different scenarios because Clinical Trial
Protocol, Clinical Trial Report and Clinical Guideline have no need for patient identifiers and can use their own unique tag. The CKML for Routine Clinical Work has no need to identify a trial arm (TrialArm) or a guideline (GuidelineID), although for the present patient, a clinical guideline may be used to determine treatment (GuidelineEligibility).

Entities within the specification may be an instance (Patient) or a range (e.g., Trial). In the Routine Clinical Work subset, an element such as Morphology will have a single instance for each patient (e.g., Mr LOLLIPOP has a SQUAMOUS CELL CARCINOMA of the base of tongue). However another clinical trial for lung cancer might include patients with ‘non-small cell lung cancer’, an entity that includes SQUAMOUS CELL CARCINOMA, ADENOCARCINOMA, and LARGE CELL CARCINOMA among others [84]. Similarly, a prior clinical trial publication may have demonstrated that 50 Gy/25 Fx has an equivalent outcome for 42.5 Gy/16 Fx for early stage breast cancer [151], and so a range of acceptable fractionation schemes would be included in any applicable Clinical Guideline.

The domain expert, when seeking to manage an individual patient, looks for applicable clinical reports. The automated comparison of the patient’s specific parameter value with the range that describes the patient group included in a trial or guideline will permit the domain expert to quickly determine whether a patient does or does not fit the profile of a clinical guideline (that is, whether the data is applicable), and also what data elements are missing.
Chapter 6

Conclusion

The research undertaken by a radiation oncology domain expert has been successful in producing a description of a radiation oncology knowledge structure. The basis of this work has been demonstrated in the merging of semantic entities into a structured work flow to provide a useful knowledge structure with several application formats. The merged knowledge structure was formalised into an XML format, called Clinical Knowledge Markup Language (CKML). It was demonstrated that the CKML specification can describe a real clinical case of oropharynx cancer, a real clinical cancer trial for oropharynx cancer patients, the published manuscript of that trial and current guidelines for the management of oropharynx cancer patients. While the knowledge structure is not a formal ontology, it provides a positive step in building the bridge between the domain experts and formal ontologists.

This thesis has described the iterative and dependent nature of knowledge development, acquisition and deployment seen in clinical work, trials, trial reports and guidelines in Radiation Oncology. This development uses clinical understanding developed from routine clinical work to drive the investigation of new knowledge through to the formal clinical trial structure. The new knowledge discovered during a clinical
trial is distributed as clinical trial reports through the peer reviewed processes of the published literature. A catalogued and abstracted version of this report is made available in repositories such as MedLINE, even though the usefulness of this abstract is limited. Finally the knowledge accumulated from multiple clinical trial reports comes to rest in conclusions that summarise the current best treatment as clinical guidelines. The entities that describe the population samples used in summarising this knowledge can be compared and then used to inform decision making in an individual patient.

The research used a modified Content Analysis process to establish the semantic entities used in producing manuscripts for publication. The objective text corpus analysed consisted of clinically oriented manuscripts drawn from a single month of published manuscripts dealing with radiation oncology. These semantic entities could be separated into the ‘few & frequent’ group and the ‘many & seldom’ group. The ‘few & frequent’ group included several facets of patients and tumours, and the normal clinical work flow in Radiation Oncology.

The usual methods for discovery and acquisition of medical knowledge in the expert domain is dependent on a clear, widely used and well established work flow. Medical knowledge is both a prerequisite for some work flow components, for example simulation or treatment, but it also is gathered from and arises from the work flow, for example, consultation and simulation. When the semantic entities are allocated to their usual position in the work flow, a hierarchy is revealed. This hierarchy was developed into a handcrafted XML-based ‘Clinical Knowledge Markup Language’ (CKML) devised and deployed into each of the knowledge development areas.

The research provides a positive contribution to the field by demonstrating the
usefulness of the published expert domain literature in discovering semantic entities rather than just processing words. Furthermore the use of the clinical work flow as the organising principle for knowledge structure is novel. While it has been attempted in the past in a limited way, the interdependence of data used in the areas of clinical work, clinical trial structure, trial reporting and clinical guidelines has been demonstrated in a way that is understandable to the domain expert.

6.1 Future Research

There are several possibilities that arise from the CKML for future development. The development of a domain specific knowledge structure grounded in the domain specific work flow enables the utilisation of technologies such as Business Process Modelling Notation and Execution to supplement and constrain knowledge discovery and elucidation. This overlap of knowledge structure and work flow can permit the construction of an electronic environment where the components of knowledge, the semantic entities, are captured at the right place by the right person within the work flow.

Furthermore, the expression of the domain specific knowledge into a mark up format permits the automated reuse of the knowledge in many areas of clinical practice, work flow process, knowledge application and new knowledge discovery. Software-based agents, mixed-initiative argumentation, support-based distributed optimisation and automated detection of interactions between co-incident clinical processes are some of the areas that have been formally investigated. Other areas such as automated clinical risk analysis using anatomical ontologies are possible areas of further application.
6.1.1 Validating the CKML structure

This work requires research to determine the veracity of the knowledge structures presented. These structures should be validated by other domain experts in Radiation Oncology to demonstrate that the CKML, or similar mark up, can actually be used for documentation of patient data, clinical trial protocols, clinical trial reports and clinical guidelines. The paradigm of constructing plain text outputs from CKML instances, and then asking domain experts whether the original documents reflect the same knowledge as the plain text output, will be more useful than natural language processing of free text.

6.1.2 Developing a User Interface based on the CKML structure

The problems of data entry must eventually be addressed in graphical user interface research. Presenting the views for data entry clearly in a user interface sympathetic to the knowledge structure and work flow may enable clinicians to translate their knowledge directly into a useful data structure with a level of configurability which ensures that complete data is collected with the least work.

6.1.3 Use of the CKML Structure in Clinical Knowledge Discovery

The translation of CKML into an XLST schema and submission as a formal template in the XML Namespace will permit research to demonstrate that it is possible to output clinical data from any OIS for the purposes of knowledge sharing and aggregation. This will allow the assessment of the OIS to establish whether a complete CKML speci-
6.1. Future Research

6.1.4 Use of the CKML Structure in Clinical Trial and Guideline infrastructures

The structure of CKML has relevance to those who build, develop and extend OISs. Several lines of research can be followed to extend and define this role. Research is required to:

- enable the trial specifications found in Clinical trial clearing houses (e.g., CancerTrials.gov) to be made available for routine clinical use in matching patients with available clinical trials without leaving the OIS and to demonstrate that this IT based approach improves trial recruitment.

- demonstrate to these clearing houses that production of trial protocols in the CKML enhances use.

- demonstrate that summaries of relevant clinical trials held in clinical data repositories such as MedLINE can be made available to clinicians in real time as they deal with new patients. It is likely that this research will be based on Natural Language Processing used to analyse and structure previously published abstracts in MedLINE into the CKML structure.

6.1.5 Storage repositories for CKML Structures

The optimal place for the storage of the populated CKML description of a patient is yet to be described. The utility of placing this data inside a separate database,
or stored inside a DICOM container with the radiation plan images has not been addressed in research.

6.1.6 Developing Agents that use CKML structures

The purpose of a standardised knowledge structure is to be able to deploy and re-apply knowledge in appropriate circumstances. In Radiation Oncology, it is typical when consulting a patient that the clinician wishes to apply previous knowledge in determining how to manage the current patient. Agents that check for important data and prompt for missing data to assist with clinical decision making will be a benefit.

6.2 Need for Collaboration

The cooperation of domain experts in knowledge engineering and medicine is problematic. Both require a decade to achieve their status and the individuals who might be considered to be active experts in both domains are rare. The situation is not helped by academic Informatics groups that produce papers and projects that are devoid of any substantive medical influence.

The advice that I would give to publishers of Medical Informatics journals is to reject Informatics articles that purport to provide a system that assists clinicians yet have no relevant clinicians in their authorship. Pure Informatics manuscripts can be devoid of clinical domain experts, but manuscripts describing Applied Informatics must include clinical domain experts.

I urge my clinical colleagues to point trainees to look at the academic area of Informatics. The area is interesting and significant. I urge my Informatics colleagues to engage clinicians until they have established meaningful academic relationships.
Without this engagement, Medical Informatics will remain irrelevant to clinicians who are the end users.

Finally, the structures described by domain experts need to be validated by ontology domain experts, translated into their specific ontological schema and once again verified by radiation oncology domain experts using natural language output statements that verify the purity of the translation. The translation from the ontology-naive language of a domain expert into a formal ontology is necessary to enable the production of oncology information systems that will allow routine clinical knowledge about patients to be used to improve the management of oncology patients.
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Appendix A

Publications during the course of the thesis
The following publications arose from collaborations that motivated the direction of research acting as proof of concept for CKML.


Appendix B

Sample Extraction of Semantic Entities
APPENDIX 6

Sample Extraction of Semantic Entities


Coding undertaken includes:

- Data parameters identified in text (italics)
- Semantic Entities used in report analysis (bold)

CLINICAL INVESTIGATION

PROSTATE

DOSIMETRY AND PRELIMINARY ACUTE TOXICITY IN THE FIRST 100 MEN TREATED FOR PROSTATE CANCER ON A RANDOMIZED HYPOFRACTIONATION DOSE ESCALATION TRIAL

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Purpose: The primary endpoint was progression-free survival. Secondary endpoints included acute toxicity, and the proportion of patients with complete response by histologic criteria, at 6 weeks after treatment. The overall goal was to identify the dose, fractionation, and schedule that optimizes tumor control while reducing normal tissue toxicity.

Patients and Methods: The trial comprised 75 Gy in 30 fractions (Arm A) vs 70.2 Gy in 26 fractions (Arm B). At the end of each treatment, patients underwent gastrointestinal endoscopy and rectoscopy. Acute toxicity was assessed using the Radiation Therapy Oncology Group (RTOG) scale. The end-point of progression-free survival was assessed using Kaplan-Meier survival analysis. Differences between arms were assessed using the log-rank test.

Results: The overall objective response rate was 85% in Arm A and 88% in Arm B. Acute toxicity was similar in both groups, with no grade 4 toxicity reported. The median time to failure for patients in Arm A was 18 months, compared to 24 months in Arm B (p = 0.03). The 5-year progression-free survival rate was 65% in Arm A and 72% in Arm B (p = 0.03).

Conclusion: The results of this study suggest that a higher dose fractionation scheme may improve the outcome for men with prostate cancer. Further studies are needed to confirm these findings and to determine the optimal dose and schedule.

INTRODUCTION

Brenner and Hall (1) calculated the risk ratio for prostate cancer to be about 1.5 using fractionation from biochemical failure (BPF) data in men treated by external beam radiotherapy (1.8-2.0 Gy) and permanent 125I seed implant. They and others have confirmed that the risk ratio is in the 1.5 range in other patient datasets; however, there is a wide range of reported risk ratios and estimates of the associated error in the assumptions made (2–11). The results of a randomized trial would provide more tangible evidence for the value of the risk ratio in prostate cancer.

Radiotherapy dose has consistently been observed to be a determinant of BPF in retrospective, prospective, and randomized studies. A priori this trial was to build on the prior randomized dose escalation trial of 70 vs. 78 Gy (51), administered in 2.0 Gy fractions and prespecified the local toxicity. (i.e., International Commission on Radiation Units and Measurements point dose). The 40 Gy difference in dose between the arms resulted in a significant improvement in BPF that was most pronounced for men with a permanent prostate-specific antigen (PSA) > 10 ng/mL. The rationale for the hypofractionation scheme described herein was that there would be a therapeutic gain if the risk ratio for prostate cancer was 1.5 and for the rectum 2.0 for late effects (13–17). The preliminary results from the Cleveland Clinic suggested that this may be true (18). Our study compares 78 Gb in 2.0 Gy fractions with 70.2 Gb in 2.7 Gy fractions, prespecified to the planning target volume (PTV). Assuming a prostate cancer risk ratio of 1.5, the delivery of 70.2 Gb in 26 fractions would be biologically equivalent to 84 Gy in 2.0 Gy fractions. Using the same 26 fraction regimen and assuming an risk ratio for late effects...
133


strategy was based in part on the Cleveland Clinic experience using a similar technique (14) and the rationale that the 99% line in the IMRT plan would fall in about the same position as the 100% line in the CRT plan. Risk that the effective PTV in the CRT plan was set (i.e., where the prescription line was located relative to the CTVs as represented on the transverse slice by a solid black line) was 8-13 mm in all dimensions, except posteriorly, in which the effective PTV was 5-8 mm. The effective PTV in the IMRT plan was 5-10 mm around the CTVs in all dimensions, except posteriorly, in which the PTV was 2-4 mm.

IMRT plan evaluation and acceptance

Step-and-shoot IMRT was planned using the Ceres (ROHMES) treatment planning system. A series of dose-volume histograms were generated and analyzed to determine the desirability of the plan. At least 95% of the PTV (D95%) was to receive the prescribed dose; a variation was noted if <15% of the PTV received the prescribed dose. There were no variations for the PTV nor CTVs (V95%). The maximum dose heterogeneity allowed in the PTV was 20%. There were 8 patterns in the IMRT overall median heterogeneity = 17.2% and 3 patterns in the CRT overall median heterogeneity = 13.9% groups that had dose gradients above 30%. These were considered violations (dose gradient > 20-29%); no violations (dose gradient > 25%) were observed. Because the dose is prescribed to the minimum inhomogeneity contour encompassing the PTV, the dose variability was seen in portions of the target volume receiving higher than the specified dose.

The normal tissue planning limits for the bladder and rectum were set based on prior studies (23, 24). The plan was deemed acceptable under the following conditions: less than or equal to 17% and 35% of the rectum should receive 285 Gy (V20 Gy) and 440 Gy (V10 Gy), respectively, for the conventionally fractionated patients (Arm I, 76 Gy total dose). The bladder V50 Gy and V64 Gy was 20% and 30% in Arm I patients. The criteria for these organs has been described previously (25-27). The criteria for the bladder were altered because a meaningful dose-response correlation has not been defined.

For Arm II, the rectal V30 Gy and V40 Gy were 17% and 35%. The bladder V50 Gy and V64 Gy were 20% and 30%. The derivation of the V50 Gy and V64 Gy criteria for the Arm II patients was based on very conservative extrapolations from the V50 Gy and V40 Gy parameters used for Arm I patients. The n/a note for the criteria was assumed to be the same as that for prostate cancer control (n/a in Arm II) and was probably too conservative, as described in the Discussion section.

If the volume of the rectum or bladder exceeded the dose limits described by <5%, this was classified as an acceptable violation. The volume of rectal volumes beyond these constraints was classified a protocol violation. The rectal (n/a in Arm I) or bladder volumes beyond these constraints were calculated as protocol violations. The rectal (n/a in Arm I) or bladder volumes beyond these constraints were calculated as protocol violations. The rectal (n/a in Arm I) or bladder volumes beyond these constraints were calculated as protocol violations.
similar methodology was used to evaluate differences in International Prostate Symptom Score according to treatment groups. Stepwise forward logistic regression modeling was used to determine independent prediction changes of QoL and GI toxicity, relative to pretreatment function measured using the same grading scale. The variable for the change in acute toxicity was coded as follows: no change; no change in toxicity severity was coded as 0; a small increase in toxicity from Grade 0 to Grade 1 was coded as 1; from Grade 1 to Grade 2 as 2; from Grade 2 to Grade 3 as 3; from Grade 3 to Grade 4 as 4; from Grade 4 to Grade 5 as 5; and Grade 0 to Grade 5 as 6. Covariates included: dose delivered to the bladder (continuous), dose volume (continuous), bladder volume (continuous), rectal V20 (continuous), rectal V40 (continuous), rectal V60 (continuous), prostate volume (continuous), PTV volume (continuous), and PSA (continuous). All multivariate models were adjusted for age, race, and medical history. The results are expressed as odds ratios (OR) and 95% confidence intervals (CI). All reported p-values were two-sided, and a p-value < 0.05 was considered statistically significant.

**Table 1.** T-stage:้านที่มีการเป็น T1, T2, T3 และ T4 ตามลำดับ.

**Table 2.** Genital and bowel toxicity: ผลข้อมูลที่เกี่ยวกับการเกิดภาวะความเสี่ยงที่เกี่ยวกับเยื่อหุ้มทางเพศและลำไส้.

**Table 3.** prostate volume: การวัดขนาดของต่อม prostatic.

**Table 4.** CTV volume: การวัดขนาดของ CTV.

**Table 5.** Bladder volume: การวัดขนาดของ Bladder.

**Table 6.** Rectum volume: การวัดขนาดของ Rectum.

**Table 7.** Interobserver variation: การวัดขนาดของ Interobserver.

**Table 8.** Intraclass correlation coefficient: การวัดขนาดของ Intraclass correlation coefficient.

**Table 9.** Receiver operating characteristic curve: การวัดขนาดของ Receiver operating characteristic curve.

**Table 10.** Univariate analysis: การวัดขนาดของ Univariate analysis.

**Table 11.** Multivariate analysis: การวัดขนาดของ Multivariate analysis.

**Table 12.** Prognostic factors: การวัดขนาดของ Prognostic factors.

**Table 13.** Clinicopathological factors: การวัดขนาดของ Clinicopathological factors.

**Table 14.** Summary table: การวัดขนาดของ Summary table.

**Table 15.** Summary of findings: การวัดขนาดของ Summary of findings.

**Table 16.** Summary of conclusions: การวัดขนาดของ Summary of conclusions.

**Table 17.** Summary of recommendations: การวัดขนาดของ Summary of recommendations.

**Table 18.** Summary of limitations: การวัดขนาดของ Summary of limitations.

**Table 19.** Summary of future research: การวัดขนาดของ Summary of future research.

**Table 20.** Summary of funding sources: การวัดขนาดของ Summary of funding sources.

**Table 21.** Summary of conflicts of interest: การวัดขนาดของ Summary of conflicts of interest.

**Table 22.** Summary of ethical considerations: การวัดขนาดของ Summary of ethical considerations.

**Table 23.** Summary of data availability: การวัดขนาดของ Summary of data availability.

**Table 24.** Summary of statistical analysis: การวัดขนาดของ Summary of statistical analysis.

**Table 25.** Summary of data interpretation: การวัดขนาดของ Summary of data interpretation.

**Table 26.** Summary of data presentation: การวัดขนาดของ Summary of data presentation.
The doxorubicin dose was significantly higher for patients in Arm II compared to Arm I. patients in Arm II received a higher dose of doxorubicin than those in Arm I, indicating a higher intensity of treatment in Arm II.

Table 2: Doxorubicin dose for the PTN system, bladder, and lumbar levels

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Arm I</th>
<th>Arm II</th>
</tr>
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<tbody>
<tr>
<td>CTD1 volume (cc)</td>
<td>56.7 ± 1.4</td>
<td>45.8 ± 2.3</td>
</tr>
<tr>
<td>PTN volume (cc)</td>
<td>145.2 ± 5.9</td>
<td>158.2 ± 7.6</td>
</tr>
<tr>
<td>Retinal volume (cc)</td>
<td>75.2 ± 2.6</td>
<td>76.5 ± 3.7</td>
</tr>
<tr>
<td>Bladder volume (cc)</td>
<td>261.0 ± 13.8</td>
<td>239.2 ± 16.7</td>
</tr>
<tr>
<td>PTN(D50%) %</td>
<td>70.4 ± 0.2</td>
<td>70.4 ± 0.3</td>
</tr>
<tr>
<td>PTN mean dose (Gy)</td>
<td>81.1 ± 0.3</td>
<td>73.8 ± 1.2</td>
</tr>
<tr>
<td>PTN max dose (Gy)</td>
<td>84.2 ± 0.3</td>
<td>82.3 ± 0.5</td>
</tr>
<tr>
<td>Retinal V40% %</td>
<td>11.7 ± 0.4</td>
<td>15.8 ± 0.5</td>
</tr>
<tr>
<td>Retinal V50% %</td>
<td>28.1 ± 1.2</td>
<td>28.9 ± 0.9</td>
</tr>
<tr>
<td>Bladder V50% %</td>
<td>16.2 ± 1.2</td>
<td>27.1 ± 1.3</td>
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<tr>
<td>Bladder V40% %</td>
<td>34.2 ± 2.2</td>
<td>43.8 ± 2.7</td>
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<tr>
<td>Retinal max dose (Gy)</td>
<td>88.0 ± 2.3</td>
<td>80.4 ± 2.1</td>
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<tr>
<td>Retinal mean dose (Gy)</td>
<td>84.2 ± 0.3</td>
<td>79.8 ± 0.5</td>
</tr>
<tr>
<td>Right femoral head V50%</td>
<td>1.0 ± 0.3</td>
<td>3.1 ± 0.5</td>
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<tr>
<td>LSI %</td>
<td>1.0 ± 0.3</td>
<td>3.4 ± 0.5</td>
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Table 3: Dosimetric parameters for the distal seminal vesicles and lymph nodes in unfavorable patients

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<th>Arm II</th>
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<tr>
<td>SV-CTV2 volume (cc)</td>
<td>10.7 ± 2.4</td>
<td>11.2 ± 2.4</td>
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<td>SV-PTV2 volume (cc)</td>
<td>51.3 ± 2.8</td>
<td>55.7 ± 2.8</td>
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<td>SV-PTV2 D95% (Gy)*</td>
<td>63.2 ± 0.6</td>
<td>56.5 ± 0.5</td>
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<tr>
<td>SV-PTV2 mean dose (Gy)*</td>
<td>74.6 ± 0.3</td>
<td>67.8 ± 0.3</td>
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<tr>
<td>LRS-CTV3 volume (cc)</td>
<td>30.4 ± 2.6</td>
<td>30.7 ± 2.6</td>
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<tr>
<td>LRS-PTV3 volume (cc)</td>
<td>133.9 ± 3.5</td>
<td>142.7 ± 3.5</td>
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<tr>
<td>LRS-PTV3 D95% (Gy)*</td>
<td>53.3 ± 2.4</td>
<td>54.5 ± 2.5</td>
</tr>
<tr>
<td>LRS-PTV3 mean dose (Gy)*</td>
<td>63.3 ± 0.6</td>
<td>64.2 ± 0.3</td>
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</tbody>
</table>

*Abbreviations: SV-PTV2 = seminal vesicle planning target volume; D95% = dose to 95% of the volume; LRS-PTV3 = lymph node planning target volume; SV = seminal vesicles; LRS = lymph nodes; PTV = planning target volume; CTN = clinical target volume.

Interaction analysis via logistic regression was used to determine covariates associated with an increase in acute GI and GU morbidity over pretreatment estimates. When possible, the covariates were included as continuous variables. The only covariate shown to be related to increased acute rectal reactions was the composite DVH V65 Gy vs V90 Gy parameter (Table 7). The rectal high dose percent volume constraints, the V60 Gy and V50 Gy for Arms I and II, were put together as a single continuous variable. The higher the percentages of rectum exposed to these threshold doses, the greater the risk of Grade 2 or higher acute rectal reaction. Neither treatment arm, nor any of several other doxorubicin or volume parameters were significant. Risk group designation (intermediate vs. high risk), and the administration of androgens for the patients was not significant.

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bladder volume at planning was independently associated with an increase in acute effects.

**DISCUSSION**

The biochemical response of prostate cancer to RT dose escalation is pronounced. The randomized trials from the M.D. Anderson Cancer Center (12) and Proton Radiation Oncology Group (51), and the supportive prospective sequential and retrospective series provide rather convincing evidence that RT doses above 75.6 Gy to the PTV are essential in men at intermediate-to-high risk. Given the prohibitive cost of extending IMRT treatments to 9 weeks or more and the different radiobiologic properties of prostate cancer and the surrounding normal tissues, hypofractionation is an attractive strategy that should be investigated in randomized trials.

Hypofractionation for prostate cancer has been used for many years without substantial toxicity (52-55, 58-59). An extreme example is an older regimen of 36 Gy given in 6 Gy fractions administered twice weekly (53). More commonly, 3-4.5 Gy fractions have been used. A similar hypofractionation strategy was recently tested in a randomized trial of 66 Gy in 33 fractions vs. 52.5 Gy in 20 fractions, which in the preliminary report of this trial, there was no statistically significant difference in biochemical failure. The Christie, Royal Marsden, and Princess Margaret Hospitals are all looking at 45 Gy fractions to 53.5 Gy (55, 56, 58).

In the trial described above, the PTV1 dose of 70.5 Gy in 26 fractions is equivalent to 84.4 Gy in 2 Gy fractions using an a/f ratio of 1.5 (1.1). Recently, Brenner (17) summarized the evidence indicating that the a/f ratio for late rectal effects is 5.4. Thus the equivalent dose in 2 Gy fractions for rectal late effects, at least in the anterior rectal wall, would be 76.9 Gy. The approach used in developing the dosimetric constraints applied in this study was that hypofractionation was no safer than standard fractionation. Considering that the rectal dosimetric constraints were calculated using an a/f ratio of 1.5 for the rectum, and that the biologically equivalent dose for late effects to the rectum is probably similar for both protocol arms, adherence to the protocol constraints for the rectum, and possibly the bladder as well, could result in fewer late rectal reactions.

The a/f ratio for late genitourinary side effects is not known and may be different. However, Table 2 shows that the proportions of the rectum and bladder treated to the ≥50 Gy (V50 Gy) and ≥31 Gy (V31 Gy) in Arm II were higher than to the V5.5 Gy and V40 Gy in Arm I. In addition, there were significantly more protocol violations for the rectal and bladder V50 and V31 Gy in Arm II than in Arm I, indicating that the constraints used were more difficult to adhere to and possibly too strict. These factors and the use of smaller PTV margins in the HMRRT arm should be considered.

### Table 4. Maximum acute genitourinary toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Group</th>
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<th>2</th>
<th>3</th>
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<tbody>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Arm I</td>
<td>During radiation therapy</td>
<td>8 (6%)</td>
<td>14 (28%)</td>
<td>27 (54%)</td>
<td>1 (2%)</td>
<td></td>
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<tr>
<td>Arm II</td>
<td>During radiation therapy</td>
<td>4 (8%)</td>
<td>22 (44%)</td>
<td>20 (40%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Arm I</td>
<td>At 3-month follow-up</td>
<td>8 (6%)</td>
<td>15 (31%)</td>
<td>4 (8%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Arm II</td>
<td>At 3-month follow-up</td>
<td>25 (46%)</td>
<td>15 (38%)</td>
<td>5 (8%)</td>
<td>0</td>
<td></td>
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</table>

There were no significant differences between the arms.

### Table 5. International prostate symptom score evaluation

<table>
<thead>
<tr>
<th>Group</th>
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<th>After radiation therapy</th>
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</thead>
<tbody>
<tr>
<td>Arm I</td>
<td>7.3 ± 0.4</td>
<td>6.8 ± 0.7</td>
</tr>
<tr>
<td>Arm II</td>
<td>8.4 ± 1.0</td>
<td>6.9 ± 0.7</td>
</tr>
</tbody>
</table>

There were no significant differences between the arms.

1 At 3-month follow-up.
in interpreting the results that overall acute effects were not significantly different between the treatment arms.

**Incidence of acute toxicity**

The acute effects observed for the patients treated herein were comparable for the most part to those reported by others (23, 30–40), although there were some differences. We describe about a 48% rate of Grade 2 or higher maximum gastrointestinal reactions (Table 6), whereas the average in the other reports is 35% (range, 28–50%). The slightly higher than average incidence of gastrointestinal reactions may be related to our use of a modified RTOG scale, the inclusion of lymph nodes in the high-risk patients and that mean biologic doses to the prostate, and hence rectum, were in excess of 80 Gy. The drop that occurred in Grade 2 or higher acute gastrointestinal toxicity to <10% by 3 months after the completion of radiotherapy is noteworthy. In terms of Grade 2 or higher maximum gastrointestinal reactions, the average reported by others is about 30% (range, 14–52%) (23, 30–40). Our finding of about 13% (Table 6) is at the low end. By 3 months after completion of radiotherapy, only 1 patient still had Grade 2 gastrointestinal toxicity.

We observed a slightly higher frequency of gastrointestinal acute toxicity in the hypofractionation arm during Weeks 2–4 of radiotherapy, although the maximum mean grade of reactions was less than 0.5. Yang et al. (50) described weekly GI toxicity in men treated with three-dimensional conformal radiotherapy to 65.20 Gy for prostate cancer and found slightly higher mean reactions that peaked between Weeks 4–6 of treatment. Proctor et al. (49) also found that peak GI toxicity was seen in the latter weeks of treatment with standard fractionation to 68–78 Gy. In our study, the peak mean GI reactions were at 3 weeks for Arm II and 5–6 weeks for Arm I.

Lukka et al. (51) compared 66 Gy in 33 fractions to 52.2 Gy in 20 fractions and found increases in both acute urinary (5.1 to 9.2%) and rectal (2.8 to 4.2%) toxicity in the men randomized to the hypofractionation arm. Kaplan et al. (51) contrasted the acute toxicity in men with prostate cancer treated sequentially using three-dimensional conformal radiotherapy to 78 Gy in 39 fractions and later with IMRT to 70 Gy in 25 fractions. They found comparable rates of Grade 2 or higher acute urinary (20% conformal vs 23% IMRT) and rectal (12% conformal vs 14% IMRT) toxicity. Kliman et al. (52) used the same hypofractionation scheme of 70 Gy in 25 fractions combined with real-time tumor tracking and reported even lower acute reactions. With the limited data available, there is no consistent pattern of the degree of acute reactions from the hypofractionation treatment of prostate cancer, probably because

**Table 6: Maximum acute gastrointestinal toxicity**

<table>
<thead>
<tr>
<th>Group</th>
<th>Timing</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
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<tbody>
<tr>
<td>Arm I</td>
<td>During radiation therapy</td>
<td>26 (52%)</td>
<td>20 (40%)</td>
<td>4 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Arm II</td>
<td>During radiation therapy</td>
<td>21 (42%)</td>
<td>20 (40%)</td>
<td>9 (18%)</td>
<td>0</td>
</tr>
<tr>
<td>Arm I</td>
<td>At 3-month follow-up</td>
<td>42 (84%)</td>
<td>6 (12%)</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Arm II</td>
<td>At 3-month follow-up</td>
<td>42 (84%)</td>
<td>6 (12%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

There were no significant differences between the arms. * One patient had an extracolonic perineural reaction and could not be assessed.

**Fig. 1. Mean maximum gastrointestinal (GI) toxicity is plotted by weeks of treatment. The x-axis is scaled from 0 to 8. The toxicity at the 3-month follow-up is displayed at the far right (hatched PU).**

The conventional fractionation intensity-modulated radiation therapy (76 Gy in 38 fractions; solid circles) patients are compared to the hypofractionation intensity-modulated radiation therapy (79.2 Gy in 26 fractions; solid diamonds) patients. Statistically different points are labeled with the respective p value. CVMRT = conventional fractionated intensity-modulated radiation therapy; IMRT = intensity-modulated radiation therapy.

**Table 7: Multivariate analysis of maximum acute gastrointestinal toxicity**

<table>
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<th>Variable</th>
<th>Chi-square</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal V4550</td>
<td>3.9</td>
<td>1.109 (0.002 to 2.28)</td>
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</table>

Covariates used: significant bladder maximum dose; rectal maximum dose; rectal volume; rectal V4550; PTW (volume); PTW (area); PTW (mean dose); PIAS (area vs. y-axis); Tongue (T1-T2 vs. T3); risk group (intermediate vs. high); treatment group (Arm I vs. Arm II). Covariates were continuous unless indicated otherwise.

The increase in acute toxicity over pretreatment values was not used (see Patients and Methods) in stepwise ordinal logistic regression.
Table 2. Multivariate analysis of maximum acute gastrointestinal toxicity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chi-square</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder volume</td>
<td>0.9</td>
<td>0.998 (0.994-0.999)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

---

cause of differences in treatment methods, target and normal tissue definitions, and normal tissue constraints used.

Dose-volume histogram associations

Dose-volume histogram parameters were included in logistic regression analyses to identify correlates of acute normal tissue toxicity. The only significant determinant of increased gastrointestinal reactions was the high-dose rectal constraint (V65 Gy for Arm 1 and V50 Gy for Arm II, see Table 7); the complication risk was greater when the volumetric dose was higher. A consideration in interpreting these data are that for the HIMRT patients the V50 endpoint was stricter because the extrapolation from the V50 endpoint for the CBRT patients was based on an ad ratio of 1.5 for late rectal toxicity. Nayyar et al. (41), Kadosh et al. (47), and Porters et al. (49) found that patients in the higher dose—volume groups had more acute GI toxicity. Others have not found any relationships between acute GI toxicity and dose—volume parameters (23, 40, 46, 53, 54).

Acute gastro-intestinal toxicity was found to be most dependent on the bladder volume at planning (Table 5), the complication risk was greater when the bladder volume was smaller. Kadosh et al. (47) and Michalski et al. (54) observed that the distance of the bladder receiving over a reference dose was an independent correlate of acute GI reactions. Reckendorf et al. (45) reported that acute GI reactions were dependent on the volume of the CTV1 and PTV1. Others have not observed any target volume or normal tissue dose—volume dosimetric relationships with acute GI toxicity (23, 41, 46, 49, 53).

In conclusion, there was a small, but significant increase in acute GI reactions at Week 2—4 of treatment in the HIMRT arms. Overall, there was little difference in acute morbidity between the standard and hypofractionation randomization arms of the HIMRT-based treatments used here, although PTV margins were slightly smaller in the hypofractionation arms. Dose—volume criteria were related to treatment—related increases in acute GI and GU reactions. Longer follow—up is needed to determine the significance of these associations with late toxicity.

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Appendix D

Data Collection Sheet
Appendix E

Semantic entities discovered from manuscript corpus

\[ n = \text{Frequency of occurrence} \]
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TetanusToxoidAb
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VEGF-A_LI
VEGFR2_LI
ViableTumour
VisualAcuity
VisualEvokedPotentials
VisualFieldDeficit
Vomiting
weight loss
Xerostomia
YearsOfSmoking
Appendix F

Johns Hopkins Hospital
Radiotherapy Workflow
OVERVIEW

The original file obtained lacked sufficient resolution and was not suitable for display. The workflow modelling contained within the original has been reproduced in software designed for business process modelling. The process map displayed in the following four pages remains "not for distribution".
Appendix G

A Selection of ICD-10-PCS list of procedures
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Appendix H

Listing and Individual Critique of the ACGT Master Ontology
The following is a listing of all the items from the "Advancing Clinico-Genomic Trials on Cancer" (ACGT) Master Ontology (MO). A selection of criticisms are present as footnotes to establish that this ontology is incomplete and inconsistent. Most of the terms used in the ontology are undefined.

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   acgt:MammaryCarcinomaClass
acgt:ClinicalClassTNM
  acgt:MClass
    acgt:M0
    acgt:M1
    acgt:MX
  acgt:NClass
    acgt:N0
    acgt:NodalStatusNegative
    acgt:N1
    acgt:N2
      acgt:N2a
      acgt:N2b
    acgt:N3
      acgt:N3a
      acgt:N3b
      acgt:N3c
    acgt:NX
  acgt:TClass
    acgt:T0
    acgt:T1
      acgt:T1a
      acgt:T1b
      acgt:T1c
      acgt:T1mic
    acgt:T2
    acgt:T3
    acgt:T4
      acgt:T4a
      acgt:T4b
      acgt:T4c
      acgt:T4d
    acgt:Tis
      acgt:TisDCIS
      acgt:TisLCIS
      acgt:TisPaget
    acgt:TX
acgt:PathologicClasspTNM
  acgt:pMClass
    acgt:pM0
    acgt:pM1
    acgt:pMX
  acgt:pNClass
    acgt:pN0
    acgt:pCRStatus
    acgt:pN1
      acgt:pN1a
      acgt:pN1b
      acgt:pN1c
    acgt:pN1mi
    acgt:pN2
    acgt:pN2a
    acgt:pN2b
    acgt:pN3
    acgt:pN3a
    acgt:pN3b
    acgt:pN3c
    acgt:pNX
  acgt:pTClass
acgt:pT0
cagt:pT1
  acgt:pT1a
  acgt:pT1b
  acgt:pT1c
  acgt:pT1mic
acgt:pT2
acgt:pT3
acgt:pT4
  acgt:pT4a
  acgt:pT4b
  acgt:pT4c
  acgt:pT4d
acgt:pTis
  acgt:pTisDCIS
  acgt:pTisLCIS
  acgt:pTisPaget
acgt:pTX
acgt:RClass
  acgt:R0
  acgt:R1
  acgt:R2
  acgt:RX
acgt:WilmsTumorStage
  acgt:WilmsTumorStageI
  acgt:WilmsTumorStageII
  acgt:WilmsTumorStageIII
  acgt:WilmsTumorStageIV
  acgt:WilmsTumorStageV
acgt:TumorHomogeneity
  acgt:CysticTumor
  acgt:HomogenousTumor
  acgt:InhomogenousTumor
acgt:TumorSituation
  acgt:LocallyAdvancedSituation
acgt:TwinType
  acgt:TwinCount
  acgt:TriPletOrMultiPlet
  acgt:TwoPlet
  acgt:TwinGeneticType
     acgt:BiZygotic
     acgt:MonoZygotic
acgt:VisualAcuity
  acgt:CanonicalVisualAcuity
  acgt:PathologicalVisualAcuity
acgt:VitalityLevel
  acgt:Avital
  acgt:Vital
realizable_entity
disposition
dacgt:Disease
  acgt:InfectiousDisease
     acgt:BacterialInfection
     acgt:ViralInfection
     acgt:ChronicViralInfection
  acgt:NonInfectiousDisease
  acgt:Alcoholism
  acgt:Allergy
acgt:HematologicalDisease
acgt:Coagulopathy
acgt:HematologicalMalignancy
acgt:Hypertonia
acgt:Neuropathy
acgt:MotorNeuropathy
acgt:SensoryNeuropathy
acgt:Neutropenia
acgt:SIOPRelevantHistory
acgt:Syndrome
  acgt:Aniridia
  acgt:BuddChiariSyndrome
  acgt:Drash
  acgt:HemiHypertrophy
  acgt:Perlman
  acgt:RhabdoidTumorPredispositionSyndrome
  acgt:StuartBrasSyndrome
  acgt:WAGR
  acgt:WiedemannBeckwithEMG
acgt:SystemicNonInfectiousDisease
acgt:Tabagism
function
role
  acgt:AdministrativeRole
  acgt:Director
  acgt:LegalGuardianRole
  acgt:Patient
  acgt:ProtocolPatient
  acgt:ResponsibleITPerson
  acgt:StudyNurse
acgt:CancerTreatment
acgt:Complication
  acgt:LateComplication
  acgt:NeurologicalComplication
acgt:ContrastMedium
acgt:Criterion
  acgt:EligibilityCriterion
  acgt:ExclusionCriterion
  acgt:InclusionCriterion
acgt:Drug
  acgt:AnalgeticDrug
  acgt:AntibioticDrug
  acgt:AntimycoticDrug
  acgt:Betablocker
  acgt:ChemotherapyDrug
    acgt:AntiTumorAntibiotic
    acgt:AromataseInhibitor
    acgt:Cytostatic
  acgt:SERM
  acgt:Diuretic
    acgt:HighCeilingLoopDiuretic
    acgt:OsmoticDiuretic
    acgt:PotassiumSparingDiuretic
  acgt:HormoneTherapyDrug
    acgt:GnRHAnalog
    acgt:LHRHAnalog
  acgt:ImmunotherapyDrug
acgt:EmergencySurgeryRole
acgt:SubstanceSample
acgt:BloodPlasmaSample
acgt:BloodSample
acgt:PeripheralBloodSample
acgt:BloodSerumSample
acgt:CerebrospinalLiquidSample
acgt:HistologicalSample
acgt:TissueSample
acgt:TumorSample
acgt:ProgenitorCellSample
acgt:BoneMarrowProgenitorCellSample
acgt:PeripheralProgenitorCellSample
acgt:StemCellSample
acgt:PeripheralBloodStemCellSample
acgt:TumorDNASample
acgt:TumorRNASample
acgt:UrineSample

object
acgt:BiologicalIndependentContinuant
acgt:ExtraOrganismalIndependentContinuant
acgt:Population
acgt:PopulationSubgroup
acgt:Organism
acgt:HumanBeing
acgt:FemaleHumanBeing
acgt:MaleHumanBeing
acgt:OrganismalIndependentContinuant
acgt:ImmaterialOrganismalIndependentContinuant
acgt:OrganismalSpace
acgt:CanonicalOrganismalSpace
acgt:CanonicalAnatomicalCavity
acgt:SubdivisionOfCavityOfOrganSystemSubdivision
acgt:AnteriorCranialFossa
acgt:MiddleCranialFossa
acgt:PathologicalOrganismalSpace
acgt:Abscess
acgt:OrganismalSurface
acgt:CanonicalOrganismalSurface
acgt:PathologicalOrganismalSurface
acgt:MaterialOrganismalIndependentContinuant
acgt:CanonicalMaterialOrganismalIndependentContinuant
acgt:AnatomicalSet
acgt:AnatomicalStructure
acgt:AcellularAnatomicalStructure
acgt:AnatomicalCluster
acgt:BiologicalMacromolecule
acgt:Body
acgt:CardinalBodyPart
acgt:CardinalCellPart
acgt:CardinalOrganPart
acgt:CardinalTissuePart
acgt:Cell
acgt:Organ
acgt:OrganSystem
acgt:OrganSystemSubdivision
acgt:PortionOfTissue
acgt:SubdivisionOfCardinalBodyPart
acgt:LimbSegment
malignant Neoplasm has multiple suboptions including carcinomatous, sarcoma and neuroendocrine tumour. However, carcinoma is an instance of a primary tumour.

The division of malignant Neoplasm into primary tumour should follow a different division as shown below:

1. Malignant Neoplasm
   - Primary Tumour
     - Carcinoma
     - Sarcoma
     - Dysontogenetic Tumour
     - Haematological Tumour
     - Neuroendocrine Tumour
     - Mixed Tumour
   - Metastasis
acgt:InflammatoryCarcinoma
acgt:InvasiveDuctalCarcinoma
acgt:ComedoCarcinoma
acgt:MixedCarcinoma
acgt:SchirrousCarcinoma
acgt:InvasiveLobularCarcinoma
acgt:MedullaryCarcinoma
acgt:TubularCarcinoma
acgt:NonInvasiveMammaryCarcinoma
acgt:DCIS
acgt:LCIS
acgt:PagetNippleTumor
acgt:RenalCellCarcinoma
acgt:ChromophobeRenalCarcinoma
acgt:ClearCellCarcinoma
acgt:PapillaryRenalCellCarcinoma
acgt:DysontogeneticTumor
acgt:Nephroblastoma
acgt:HighRiskNephroblastoma
acgt:DiffuseAnaplasticNephroblastoma
acgt:HighRiskBlastemaRichNephroblastoma
acgt:IntermediateRiskNephroblastoma
acgt:EpithelialNephroblastoma
acgt:FocalAnaplasticNephroblastoma
acgt:IntermediateRiskBlastemaRichNephroblastoma
acgt:MixedNephroblastoma
acgt:RegressiveTypeNephroblastoma
acgt:StromaRichNephroblastoma
acgt:LowRiskNephroblastoma
acgt:CompletelyNecroticNephroblastoma
acgt:CysticPartiallyDifferentiatedNephroblastoma
acgt:RhabdoidTumor
acgt:MRT
acgt:RTK
AT:RT
acgt:Haematoo oncologicalTumor
acgt:Metastasis
acgt:SecondaryMetastasis
acgt:PrimaryTumor
acgt:ExtrarenalPrimaryTumor
acgt:Haematoo oncologicalTumor
acgt:SemiMalignNeoplasm
acgt:Nephroblastomatosis

\(^2\)acgt:Metastasis has a single suboption called acgt:SecondaryMetastasis. This is a tautology or nonsensical. Metastases are also called ‘secondaries’, and the concept of a ‘primary’ metastasis is foreign.

\(^3\)acgt:Haematoo oncologicalTumor occurs in two places, firstly as a suboption for acgt:MalignNeoplasm, and secondly here as a suboption below acgt:PrimaryTumor. It is unclear why acgt:Carcinoma or acgt:MammaryCarcinoma do not also qualify as acgt:MalignNeoplasm and acgt:PrimaryTumor, which is most certainly applicable.
acgt:Quantum
acgt:TechnicalObject
acgt:BiopsyNeedle
acgt:DigitalFile
acgt:HearingDevice
acgt:ImplantObject
acgt:LinearParticleAccelerator
acgt:Mask
acgt:PlasterFrame
acgt:ProthesisObject
acgt:VenaCavaProthesisObject
acgt:VacuumCushion
object_aggregate
acgt:Microarray
acgt:AntibodyMicroarray
acgt:DNAMicroarray
acgt:ProteinMicroarray
acgt:TissueMicroarray
acgt:TransfectionMicroarray
object_boundary
site
spatial_region
snap:one_dimensional_region
snap:three_dimensional_region
acgt:RadiationField
snap:two_dimensional_region
acgt:Isodose
snap:zero_dimensional_region
occurrent
processual_entity
acgt:StateOfAffairs
acgt:AdhesionIleus
acgt:Alopecia
acgt:Anemia
acgt:Arrhythmia
acgt:Arthralgia
acgt:Asthenia
acgt:Ataxia
acgt:CardiacArrest
acgt:CardiacMurmur
acgt:Fever
acgt:Glomerulopathy
acgt:HearingLoss
acgt:HearingLoss16To30dB
acgt:HearingLoss31To60dB
acgt:HearingLossGreater60dB

4 snap:three_dimensional_region has a single suboption, acgt:RadiationField, which is a 2D structure presented as a field aperture. The relevant snap:three_dimensional_region would be acgt:IrradiatedVolume which already has a standardised definition courtesy of the International Commission on Radiation Units (ICRU).

5 snap:two_dimensional_region has a single suboption called acgt:Isodose. This is ambiguous as acgt:Isodose can be considered a 3D structure with a volume in mLs, that is the volume receiving 95% of the reference dose that should cover the entire target volume.

6 acgt:HearingLoss while this option characterises dB loss levels it should also include laterality (right/left) as occurs with acgt:Hemiparesis
Hearing Loss Less 15 dB
Hematuria
Hemiparesis
  - Left Hemiparesis
  - Right Hemiparesis
Hypertension
Hypotension
Immune Deficiency
Lost To Follow Up
Monoparesis
Myalgia
Nausea
Papilledema
Paraparesis
Paraplegia
  - Complete Paraplegia
  - Incomplete Paraplegia
Proteinuria
Pulmonary Edema
Sensory Disturbance
Skin Edema
Tetraparesis
Thrombosis
  - Hepatic Vein Occlusion
  - Tubulopathy
Unconsciousness
  - Coma
  - Somnolence
  - Stupor
FiAT Process Part
  - Cycle
    - Cardiac Cycle
    - Menstrual Cycle
    - Treatment Cycle
      - Pharmacotherapy Cycle
      - Chemotherapy Cycle
      - Docetaxel Cycle
      - Epirubicin Cycle
Process
  - Intentional Process
  - Administrative Process
  - Care Process
    - Nursing Care
    - Parenteral Feeding
    - Psychosocial Care
  - Medical Process
  - Diagnostic Process
    - Audiometry
    - Autopsy
    - Biopsy
      - Biopsy With Incision
      - Biopsy Without Incision
        - Core Needle Biopsy
        - Suction Assisted Core Biopsy
        - Endoscopic Biopsy
        - Fine Needle Biopsy
        - Punch Biopsy
acgt:SurfaceBiopsy
acgt:TrucutBiopsy
acgt:BloodPressureMeasuringProcess
acgt:CellCounting
  acgt:TumorCellCounting
acgt:CerebrospinalLiquidPuncture
  acgt:LumbarCerebrospinalFluidPuncture
  acgt:VentricularCerebrospinalFluidPuncture
acgt:ClinicalExamination
acgt:CytogeneticExamination
acgt:CytologicalExamination
acgt:ECG
acgt:HematologicalBiochemicalTest
  acgt:AlkalinePhosphataseTest
  acgt:ANC
acgt:CountingPlatelets
acgt:CountingRedBloodCells
acgt:EPOLevelTest
acgt:HbTest
acgt:SerumCreatinineTest
acgt:TotalBilirubinTest
acgt:TransaminaseBiochemistry
acgt:TroponinTest
acgt:WBC
acgt:HistologicalExamination
  acgt:DCISHistologicalAssessment
  acgt:ERHistologicalAssessment
  acgt:HistopathologicTypeAssessment
  acgt:InvasiveDuctalCarcinomaAssessment
  acgt:InvasiveLobularCarcinomaAssessment
acgt:LCISHistologicalAssessment
acgt:PRHistologicalAssessment
acgt:Imaging
  acgt:Comptertomography
  acgt:MagneticResonanceImaging
  acgt:NuclearImaging
  acgt:MUGAScan
acgt:RoentgenologicalImaging
  acgt:ReferenceRoentgenologicalImaging
acgt:Scintigraphy
  acgt:BoneScintigraphy
  acgt:Utrasound
  acgt:Echocardiography
acgt:ImmunohistochemicalExamination
acgt:Inking
acgt:MacropathologicalExamination
acgt:MalignancyRelatedDiagnosticProcess
acgt:MicropathologicalExamination

7acgt:HistologicalExamination has a number of suboptions which all relate to BREAST cancer only. The acgt:HistologicalExamination of other cancers such as prostate brain oesophagus lung and pancreas are not included. Even within the setting of acgt:HistologicalExamination of breast cancers there is no acgt:TumourGradeAssessment or acgt:TumourLymphaticInvasionAssessment.

8acgt:Imaging has a wide range of suboptions however the subsuboptions are not comprehensive. For example there is no acgt:PETScan. Furthermore, acgt:Scintigraphy does not include acgt:ThyroidScan, acgt:GalliumScan or acgt:sestamibiScan. There are even more.
Pharmacotherapy has a number of suboptions which do not include small molecule therapies (erlotinib etc) or the monoclonal antibodies (trastuzumab etc).

It is debatable whether the options listed under Chemotherapy represent correct knowledge engineering. ABVDChemo is actually a combination of four drugs each with their own dosing and scheduling which can vary from institution to institution. There is even no guarantee that the ABVDChemo of two oncologists in the Illawarra Cancer Care Centre will be identical.
acgt:ELFChemo
acgt:ESHAPandR-ESHAPChemo
acgt:EtoposideCisplatinChemo
acgt:FECChemo
acgt:GemCapChemo
acgt:GemCarboChemo
acgt:GemcitabineCisplatinChemo
acgt:GemTaxolChemo
acgt:ICEChemo
acgt:IrinotecanWithDeGramontChemo
acgt:MayoChemo
acgt:MICChemo
acgt:MMChemo
acgt:MMMCChemo
acgt:MTXChemo
acgt:MVPChemo
acgt:OralMaintenanceChemo
acgt:TEOralMaintenanceChemo
acgt:TIOralMaintenanceChemo
acgt:TMZOralMaintenanceChemo
acgt:Oxaliplatin5FUChemo
acgt:PaclitaxelCarboplatinChemo
acgt:PCVChemo
acgt:PemetrexedCisplatinChemo
acgt:PMitCEBOChemo
acgt:TACChemo
acgt:TandemChemotherapy
acgt:VADChemo
acgt:VAPEC-BChemo
acgt:VCDChemo
acgt:VDChemo
acgt:VinorelbineCarboplatinChemo
acgt:VinorelbineCisplatinChemo
acgt:w-VDChemo
acgt:HormonalTreatment
acgt:HRT
acgt:ERT
acgt:LHRHAnalogTreatment
acgt:Immunotherapy
acgt:SupportivePharmacotherapy
acgt:Physiotherapy
acgt:Purging
acgt:CD34SelectionPurging
acgt:Radiotherapy
acgt:Brachytherapy
acgt:Teletherapy
acgt:BathIrradiation

This section is grossly incomplete. There is no commonality in the concepts of acgt:Brachytherapy and acgt:BoostIrradiation. The former is a method of delivering dose using radioactive implants, while the latter relates to a method called “shrinking field technique” where the radiation dose is escalated in the area of highest risk through any delivery method. acgt:BathIrradiation is not a generally accepted term. Finally both acgt:MultipleFieldIrradiation and acgt:OpposingFieldIrradiation describe radiation beam arrangements and since acgt:OpposingFieldIrradiation uses TWO fields, it is an example of acgt:MultipleFieldIrradiation.
Lymph Node Dissection has a single suboption, **axgt:AxillaryNodeDissection**. There is the possibility of lymph node dissection in any of the nodal bearing areas of the body, e.g., **axgt:PelvicNodeDissection**, **axgt:ParaAorticDissection**, **axgt:MediastinalNodeDissection**, **axgt:HilarNodeDissection**, **axgt:CervicalNodeDissection**, **axgt:PortaHepatisNodeDissection**.
acgt:Pneumonectomy
acgt:TumorResection
acgt:PartialTumorResection
acgt:SubtotalTumorResection
acgt:TotalTumorResection
acgt:ExcisionalBiopsy
acgt:Transplantation
acgt:SurgicalSuture
acgt:Transfusion
acgt:ErythrocyteTransfusion
acgt:ThrombocyteTransfusion
acgt:MolecularBiologyTechnique
acgt:DNAReplication
acgt:PCR
acgt:Immunostaining
acgt:ELISA
acgt:FlowCytometry
acgt:ICC
acgt:IHC
acgt:ImmmunoEM
acgt:WesternBlotting
acgt:MicroarrayHybridization
acgt:ResearchProcess
acgt:Experiment
acgt:MicroarrayExperiment
acgt:Suicide
acgt:NaturalProcess
acgt:IonizingRadiation
acgt:OrganisinalProcess
acgt:Adhesion
acgt:PathologicalAdhesion
acgt:PlateletAdhesion
acgt:Bleeding
acgt:CerebralHemorrhage
acgt:SkinHemorrhage
acgt:Bulging
acgt:CerebralSeizure
acgt:CharacterChange
acgt:ChromsomeAberration
acgt:ConvulsiveSeizure
acgt:Coughing
acgt:CreatinineClearance
acgt:Deglutition

13 acgt:TotalTumourResection has one suboption, acgt:ExcisionalBiopsy which is not an example of total tumour resection. A biopsy, by its very nature, is not an attempt at complete tumour resection. It is at best a acgt:PartialTumourResection.

14 acgt:ResearchProcess has the suboptions, acgt:Experiment and acgt:MicroArrayExperiment. This is only one type of research process that might be undertaken in an oncological setting. More prevalent would be a subsuboption like acgt:ClinicalExperiment further characterised with the subsubsuboption acgt:RandomisedClinicalExperiment. This area might also be expanded to include the concepts of the various Phase I-III designations.

15 acgt:Bleeding has the suboptions of acgt:CranialBleeding and acgt:SkinBleeding. Bleeding can occur in all organs which are supplied by blood, therefore the pattern, acgt:[Organ]Bleeding, should be used with organ name substitution.
204

acgt:Desquamation
acgt:Diarrhea
acgt:DiseaseProcess
  acgt:InfectiousDiseaseProcess
    acgt:BacterialInfectionProcess
    acgt:ViralInfectionProcess
      acgt:ChronicViralInfectionProcess
    acgt:NonInfectiousDiseaseProcess
    acgt:AlcoholismProcess
    acgt:HematologicalDiseaseProcess
      acgt:CoagulopathyProcess
      acgt:HematologicalMalignancyProcess
      acgt:LeukemiaProcess
    acgt:HypertoniaProcess
  acgt:NeuropathyProcess
    acgt:MotorNeuropathyProcess
    acgt:SensoryNeuropathyProcess
  acgt:NeutropeniaProcess
  acgt:SIOPRelevantHistoryProcess
  acgt:SyndromeProcess
    acgt:AniridiaProcess
    acgt:BuddChiariSyndromeProcess
    acgt:DrashProcess
    acgt:HemiHypertrophyProcess
    acgt:PerlmanProcess
    acgt:RhabdoidTumorPredispositionSyndromeProcess
    acgt:StuartBrasSyndromeProcess
    acgt:WAGRProcess
    acgt:WiedemannBeckwithEMGProcess
  acgt:SystemicNonInfectiousDiseaseProcess
    acgt:TabagismProcess
  acgt:Dyspnea
  acgt:Enanthema
  acgt:Engraftment
  acgt:Epitheliolysis
  acgt:ErythemaDevelopment
  acgt:Fibrosis
  acgt:GeneExpression
  acgt:GeneticMutation
    acgt:GeneticDelationMutation
  acgt:Headache
  acgt:Hearing
  acgt:HeartFunctioning
  acgt:Hernia

16 acgt:ViralInfectionProcess has one suboption, acgt:ChronicViralInfectionProcess. There should also be an acgt:AcuteViralInfectionProcess option.
17 acgt:NeuropathyProcess has the suboptions of acgt:MotorNeuropathyProcess and acgt:SensoryNeuropathyProcess which is incomplete. There should also be acgt:AutonomicNeuropathyProcess
18 acgt:SyndromeProcess lists formally recognised eponymous medical patterns, however the list is very limited as there are many more syndromic names.
19 acgt:GeneticMutation has a suboption, acgt:GeneticDelationMutation, which is misspelt (acgt:GeneticDeletionMutation), but should include other mutational mechanisms like acgt:GeneticSubstitutionMutation and acgt:GeneticInsertionMutation.
20 acgt:Hernia has the suboption of acgt:DiaphragmaticHernia but this is poorly organ-
ised. The suboption, acgt:AnatomicHernia, should be expanded with subsuboptions including acgt:DiaphragmaticHernia, acgt:InguinalHernia and acgt:FemoralHernia, among others.

21 acgt:Infection has a single suboption - acgt:WoundInfection. However should there also be acgt:SpontaneousInfection for infections that do not occur at a wound site.

22 acgt:Inflammation has a single suboption - acgt:Stomatitis. Other inflammations should be included e.g., acgt:Dermatitis, acgt:Mucositis, acgt:Nephritis acgt:Nephritis, and more.

23 acgt:Infarction or death of tissue has a single suboption (acgt:IntestinalInfarction) but none for the more common acgt:CardiacInfarction and acgt:LungInfarction. Other organs could also be included.

24 acgt:Obstruction has a single sub-option - acgt:VenaCavaObstruction. Other obstructions such as acgt:IntestinalObstruction, acgt:UretericObstruction acgt:LymphaticObstruction, acgt:TrachealObstruction, acgt:OesophagealObstruction, acgt:GastricObstruction, acgt:BiliaryTreeObstruction, acgt:CSFObstruction are not included.
TumorRelapse has a single sub-option called LocalTumorRelapse excluding equivalent categories like RegionalTumorRelapse and DistantTumorRelapse.

EndOfCranialPressureMeasuringProcess has no corresponding entity to start the cranial pressure measuring process; there should be an entry called StartOfCranialPressureMeasuringProcess.
acgt:ProcessStart
acgt:Birth
acgt:MeasuringProcessStart
  acgt:StartOfDensityMeasuringProcess
  acgt:StartOfFrequencyMeasuringProcess
  acgt:StartOfLengthMeasuringProcess
  acgt:StartOfPressureMeasuringProcess
    acgt:StartOfBloodPressureMeasuringProcess
    acgt:StartOfRoomPressureMeasuringProcess
    acgt:StartOfTirePressureMeasuringProcess
  acgt:StartOfTemperatureMeasuringProcess
acgt:RecordingProcessStart
  acgt:StartOfDensityRecordingProcess
  acgt:StartOfFrequencyRecordingProcess
  acgt:StartOfPressureRecordingProcess
    acgt:StartOfBloodPressureRecordingProcess
    acgt:StartOfRoomPressureRecordingProcess
    acgt:StartOfTirePressureRecordingProcess
  acgt:StartOfTemperatureRecordingProcess
    acgt:StartOfPatientTemperatureRecordingProcess
    acgt:StartOfRoomTemperatureRecordingProcess
    acgt:StartOfSampleTemperatureRecordingProcess
processual_context
spatiotemporal_region
  connected_spatiotemporal_region
  spatiotemporal_instant
  spatiotemporal_interval
scattered_spatiotemporal_region
temporal_region
  connected_temporal_region
  temporal_instant
  temporal_interval
    acgt:Day
    acgt:Hour
    acgt:Minute
    acgt:Month
    acgt:Second
    acgt:Week
    acgt:Year
scattered_temporal_region
owl:AllDisjointClasses
owl:AsymmetricProperty
owl:IrreflexiveProperty
Appendix I

The CKML superstructure used in the following appendices for Routine Clinical Work, Clinical Trial Protocol, Clinical Trial Report and Clinical Guideline
The Clinical Knowledge Markup Language can be used to provide the workflow-oriented structure to the knowledge contained in Routine Clinical Work, a Clinical Trial Protocol, the subsequent Clinical Trial Report in the literature and a Clinical Practice Guideline.

<Organisation>

** REGISTRATION

<Department>
<Doctor>
<Trial> | <Guideline> | <Patient> | <Report>

** CONSULTATION

<BiologicalMilieu>
<PsychologicalMilieu>
<Diagnosis>
<Cancer>
<CancerDiagnosisDate>
<CancerSymptoms>
<CancerSigns>
<CancerPrognosis>
<CancerImaging>
<CancerMarkers>
<CancerDiagnosis>
<Histopathology>
<Cytology>
<CancerStage>
<TrialEligibility>
<GuidelineEligibility>
<TreatmentIntent>
<TrialArm>
<TrialArmName>
<TrialArmSummary>
<Therapy>

** TREATMENT PREPARATION

** TREATMENT DELIVERY
<Surgery>
<Radiotherapy>
<Chemotherapy>

** FOLLOW UP

<CancerOutcome>
<PsychologicalMilieu>
<CancerResponse>
<CancerLocalRecurrence>
<CancerRegionalRecurrence>
<CancerDistantRecurrence>
<CancerDeath>
<TrialOutcome>
<LateSideEffects>
Appendix J

A CKML subset for use in a Routine Clinical Work with example
The patient data reported here is anonymous and is derived from the chart of a patient treated locally. The names and dates pertaining to the patient have been changed. The patient whose data is displayed has granted permission to use this data, firstly in the form of a departmental release to use data for research purposes which is held in the clinical record, as well as a subsequent verbal confirmation in 2011 before thesis submission.

**J.1 The Clinical History**

The following clinical history may require input from a domain expert to assert that it is a consistent account of a patient’s cancer journey. If the reader finds the domain specific terms unfamiliar, a brief reading of this text by a radiation oncologist will confirm that it is intelligible.

The patient was treated at the *Illawarra Cancer Care Centre* by Dr *Alexis Andrew Miller*. The patient, *LARRY LOLLIPOP* was a male born on 15/03/1949 in *Wollongong*. His hospital ID is *99999999*. He is a caucasian with tertiary qualifications, and an income of $100,000-150,000 per year earned in a professional job. He is a property owner.

He was a well man. His creatinine clearance was measured as 80 mLs/min using the *Cockcroft-Gault* algorithm. He has normal peripheral nerve motor function, normal peripheral nerve sensory function and normal auditory function with no auditory function loss. He takes no medical drugs. He is not smoking. He ceased smoking in 1994 before which he was smoking cigarettes at 1 packet per day for 20 years. He drinks wine every days at the rate of 4 drinks per day and 28 drinks per week. He had
a performance status of 0 on 02/04/2009, and a performance status of 0 on 17/10/2011. Actuarial estimates give him 35 years of remaining life.

He was diagnosed with a colon cancer (C18.7) on 03/03/1998 which was an adenocarcinoma (8140/3) with moderate differentiation (G2). Immunohistochemistry was positive for CK7. The tumour was staged at Stage IIa. Pathologic staging revealed a T3 (3.0 CM) local tumour with N0 (0/9) nodes. Image-based staging revealed no metastases (M0). The intent of treatment was cure and primary surgery was undertaken for the purposes of locoregional control using a sigmoid colectomy which achieved an R0 resection and no complications. He received no radiotherapy and no chemotherapy after the operation. When assessed on 10/05/1998, no measurable disease was found, in particular the primary had a CR and the nodes had a CR. There was no evidence of local recurrence on 06/11/2011, no evidence of regional recurrence on 06/11/2011 and no evidence of distant recurrence on 06/11/2011. When last seen on 06/11/2011 he was alive.

He was diagnosed with a base of tongue cancer (C01) on 06/03/2009 with symptoms of right otalgia, dysphagia, neck swelling and no weight loss and signs of an exophytic tongue base lesion crossing midline and extending down to the vallecula with a right level II/III firm mobile node and a left level II firm mobile node. A CT scan was undertaken of the Head & Neck because of symptoms. A FDG-PET was undertaken on 11/03/2009 which reported “An FDG PET scan was performed from vertex to proximal femora with a low dose non-contrast CT scan
for attenuation correction and localisation. SCAN FINDINGS: The known primary lesion in the right tongue base demonstrates intense FDG accumulation (maximum SUV = 8.9) with apparent extension inferiorly to just above the level of the vallecula. Moderate to intense FDG uptake was demonstrated within several enlarged lymph nodes in the right upper cervical regions (level II) with the most intense uptake localising to the largest lymph node measuring 27mm in the right submandibular region and the 22 mm lymph node more superiorly. Mildly increased FDG uptake was also seen in several level II lymph nodes in the left upper cervical region. Tracer distribution the remainder of the study was within physiologic limits (prominent uptake was seen in the left tongue/tonsillar region most likely physiological). CONCLUSION: The known primary malignancy in the right tongue base which appears to extend inferiorly to just above the level of the vallecula is intensely metabolically active. There is evidence of bilateral cervical (level II) lymph node metastases, much larger and more intense on the right. No evidence of metabolically active disease in the remainder of the study.” The maximum SUV was 8.9.

Histopathology was reported as a Basaloid squamous cell carcinoma (8083/3 with poor differentiation (G3). Immunohistochemistry was positive for CK7. The tumour was staged at Stage IVa. Image-based staging revealed a T4a tumour with a size of 55 mm, local tumour with infiltration of muscles of the tongue, and N2c with 2 nodes, one on the right measuring 27mm in level II, and one on the left measuring 22mm in level II. Image-based staging revealed a no metastases (M0).
He was eligible for inclusion on trial TROG.02.02, and also for guidelines NCCN H&N ADVANCED, BCCC OROPHARYNX, SIGN H&N and ICCC ReScan Protocol. He was entered on the ICCC ReScan Protocol.

The intent of treatment was cure. The therapies to be used consisted of no surgery, primary external beam radiotherapy, no brachytherapy, and concurrent chemotherapy. Supportive therapy consisted of a prophylactic PEG tube inserted on 02/04/2009 and removed on 22/07/2009.

The radiation prescription called for 70 GY in 35 FX treated 1 per day, 5 per week with BD compensation for treatment breaks, using photons (6MV) with IMRT using non-coplanar beams. Radiation was prescribed to a non-ICRU prescription point.

The patient underwent radiotherapy simulation in a supine position with an immobilisation mask and bolus. Field imaging utilised digitally reconstructed radiographs and a simulation CT.

Target volumes for the IMRT technique consisted of a PTV7000 with a prescription dose of 70Gy/35FX which was a 3mm expansion of the CTVp, which was based on the GTVp with a 5mm expansion, and a 3mm expansion of the CTVn, which was based on the GTVn with a 5mm expansion.
Target volumes for the IMRT technique consisted of a PTV6000 with a prescription dose of $60\text{GY}/35\text{FX}$ which was a 3mm expansion of the CTVp, which was based on the GTVp with a 5mm expansion, and a 3mm expansion of the CTVn, which was based on the GTVn with a 5mm expansion, and a 3mm expansion of the CTVn0, which was based on the UNINVOLVED LYMPH NODES with a 5mm expansion. Planning contours includes the spinal cord, right parotid gland, left parotid gland, right submandibular gland, left submandibular gland, mucosa, and mandible.

During Radiotherapy Planning, PTV dose heterogeneity ranged between -5% and +7%. For the spinal cord (SPINAL_CORD), the Organ At Risk dose constraint set to 45Gy, for the right parotid gland it was less than a mean of 26Gy, for the left parotid gland it was less than a mean of 26Gy, for the right submandibular gland it was less than a mean of 26Gy, for the left submandibular gland it was less than a mean of 26Gy, for the mucosa it was as low as reasonably achievable, and for the mandible it was as low as reasonably achievable.

The concurrent chemotherapy regime was Weekly Cisplatin given over 7 cycles that started with radiotherapy and lasted 1 week each. On day 1 of the cycle, cisplatin at a dose of $40\text{mg}/\text{m}^2$ was administered intravenously as a 1 hour infusion starting 1 hour before radiotherapy, supported with IV hydration of 500mL normal saline and an antiemetic drug. During the chemotherapy he developed febrile neutropaenia, and suffered a hospital admission from 20/05/2009 to 22/05/2009. He also developed dehydration.
Following the completion of treatment his response was assessed with a FDG-PET on 10/08/2009 which reported **CONCLUSION: The scan findings suggest good partial metabolic response with mild uptake in the anterior aspect of the primary tumour at the base of the tongue and also mild uptake in residual upper cervical lymph nodes, suggestive of residual disease. No new focus of FDG-avid disease is seen.** There was no measurable disease, and according to RECIST criteria, the primary response was scored as a **CR**, and the nodal response was scored as a **CR**.

There was no local recurrence on 06/11/2011, no regional recurrence on 06/11/2011 and no distant recurrence on 06/11/2011. He was alive on 06/11/2011. The late side effects suffered on 6/10/2011 consisted of **G1** late effects in the skin, **G0** late effects in subcutaneous tissue, **G2** late effects in mucosa, **G0** late effects in the spinal cord, **G0** late effects in larynx, and **G0** late effects in feeding.

**J.2 The CKML coding of this Clinical History**

Using the CKML structure described in Appendix I, the clinical history was translated into the CKML structure. All unused criteria have been removed.
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An FDG PET scan was performed from vertex to proximal femora with a low dose non-contrast CT scan for attenuation correction and localisation. SCAN FINDINGS: The known primary lesion in the right tongue base demonstrates intense FDG accumulation (maximum SUV = 8.9) with apparent extension inferiorly to just above the level of the vallecula. Moderate to intense FDG uptake was demonstrated within several enlarged lymph nodes in the right upper cervical region (level II) with the most intense uptake localising to the largest lymph node measuring 27mm in the right submandibular region and the 22 mm lymph node more superiorly. Mildly increased FDG uptake was also seen in several level II lymph nodes in the left upper cervical region. Tracer distribution the remainder of the study was within physiologic limits (prominent uptake was seen in the left tongue/tonsillar region most likely physiological). CONCLUSION: The known primary malignancy in the right tongue base which appears to extend inferiorly to just above the level of the vallecula is intensely metabolically active. There is evidence of bilateral cervical (level II) lymph node metastases, much larger and more intense on the right. No evidence of metabolically active disease in the remainder of the study.

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Appendix K

A CKML subset for use in a Clinical Trial Protocol with example
The “HeadSTART” trial was devised and executed under the auspices of the Trans-Tasman Radiation Oncology Group (TROG). The trial was also called by its TROG designation “TROG02.02”. This trial has closed, and was a Phase III randomised trial of concomitant radiation, cisplatin, and tirapazamine (SR259075) versus concomitant radiation and cisplatin in patients with advanced head and neck cancer. The trial was undertaken to compare the efficacy and safety of standard treatment (concurrent cisplatin chemotherapy with high dose radiotherapy) with a new agent, tirapazamine, which had shown an affinity for hypoxic areas in some tumours and also been shown to produce more radiation damage than normal in these areas. The trial sought to demonstrate a difference in overall survival. This primary endpoint is most highly prized as the patient group to be included cannot expect a great probability of cure according to previous data. See the element ¡TrialPredictedSurvivalControl¿ below for specific numbers.

Following are two documents. The first provides a handcrafted CKML instance of the completed clinical trial protocol known as TROG.02.02. Only items that relate to clinical management have been entered. Even so, the specification is lengthy.

The second item is the actual protocol document used in the CKML production.
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  <TrialPrincipalInvestigator>LESTER PETERS</TrialPrincipalInvestigator>
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Appendix L

The Trans-Tasman Radiation Oncology Group (TROG) ”HeadSTART” Clinical Trial protocol (TROG02.02)

This protocol was provided on request by Professor Lester Peters through the TROG Trials Office.
CLINICAL TRIAL PROTOCOL

COMPOUND:
SR259075

Phase III randomized trial of concomitant radiation, cisplatin, and tirapazamine (SR259075) versus concomitant radiation and cisplatin in patients with advanced head and neck cancer

STUDY No.:EFC4690

VERSION DATE: 29 April 2002

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# CLINICAL TRIAL SUMMARY

**COMPOUND:** SR259075  
**STUDY No.:** EFC4690

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<td>• Time to locoregional failure with date of randomization as the start date.</td>
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<td>• Failure-free survival. Failure is defined as death due to any cause, locoregional failure or development of distant metastasis.</td>
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<td>• Patterns of failure as the initial site of failure at the primary site, neck, distant sites or combinations of these.</td>
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<td>• Cumulative incidence of unacceptable locoregional treatment outcome as a function of time. An unacceptable outcome is defined as either locoregional failure or severe late treatment-related toxicity which may be any of the following: grade 4 skin, subcutaneous tissue, mucous membrane or bone toxicity, grade 3 or 4 spinal cord toxicity, grade 4 laryngeal toxicity requiring tracheostomy, or the need for enteral feeding persisting beyond 12 months following completion of treatment.</td>
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<td>• Change in QoL from baseline as assessed by FACT-H&amp;N scale in eligible patients at 6 months post-treatment (see 6.1.2.7 QoL Evaluation).</td>
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<td>• Toxicity and safety, determined through review of adverse events, routine symptom assessment, and laboratory determinations.</td>
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<td>• Initial response rates defined as rates of CR, PR, SD or PD eight weeks after completion of chemoradiation therapy as described in Section 6.1.2.5.</td>
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<td>• Final CR rate as defined in Section 6.1.2.5 (d).</td>
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Additional analysis will include correlation of efficacy with baseline hypoxia measurements. Measurements of hypoxia will include FAZA-PET (in selected sites) and blood levels of chemical markers.

| STUDY DESIGN | Phase III, open-label, 2-armed, randomized, controlled, multicenter. |
**STUDY POPULATION**

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<th>Subjects with previously untreated squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx. Stage III or Stage IV (excluding T1N1, T2N1 and metastatic disease). Subjects must have ambulatory ECOG performance status ( \leq 2 ) and adequate renal, hepatic, and hematologic function.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total expected number of patients:</td>
<td>550 evaluable subjects</td>
</tr>
<tr>
<td>Expected number of centers:</td>
<td>Between 50 and 80.</td>
</tr>
</tbody>
</table>

**INVESTIGATIONAL PRODUCT(S)**

<table>
<thead>
<tr>
<th>Formulation(s):</th>
<th>250 ml of Tirapazamine will be supplied as a clear yellow-orange liquid (0.7 mg/ml) in an isotonic citrate buffer with a pH between 3.7 and 4.3 in 300 ml bottles.</th>
</tr>
</thead>
</table>
| Route(s) of administration: | Tirapazamine and cisplatin: Intravenous (IV)  
Antiemetics: Oral (PO) and/or intravenous (IV)  
Antidiarrheals: Oral (PO) |
| Dose regimen: | Radiotherapy: All patients will receive conventionally fractionated radiation therapy with the macroscopic sites of disease treated to 70 Gy in 35 fractions over 7 weeks. Techniques using conformal techniques to deliver the radiation can be used. Centers not using conformal techniques have a one-time option of changing to such techniques.  
Cisplatin (Arm 1)  
Cisplatin (100 mg/m\(^2\), 1-hour infusion) immediately before radiation therapy on Day 1 of weeks 1, 4, and 7 of radiotherapy.  
Tirapazamine and cisplatin (Arm 2)  
Tirapazamine (290 mg/m\(^2\), two-hour infusion), followed after 1 hour by cisplatin (75 mg/m\(^2\), 1-hour infusion) immediately before radiation therapy on Day 1 of weeks 1, 4, and 7 of radiotherapy.  
Tirapazamine (160 mg/m\(^2\), two-hour infusion) on days 1, 3, and 5 of weeks 2 and 3 of radiotherapy. |
**EVALUATION CRITERIA**

**Efficacy Criteria:**
- The primary endpoint is overall survival.
- Secondary efficacy endpoints: time to locoregional failure, failure-free survival, patterns of failure, cumulative incidence of unacceptable locoregional treatment outcome, Quality of Life (QoL), toxicity and safety, response rate and final CR rate.
- Additional analyses will include correlation of baseline hypoxia as assessed by FAZA-PET scans (in selected centers) and tumor markers to outcome.

**Safety Criteria:**
- Safety will be determined through review of adverse events, routine symptom assessment, and laboratory determinations.

**ASSESSMENT SCHEDULE**
- See Flow Chart

**STATISTICAL CONSIDERATIONS**
- The sample size of 275 per treatment arm will provide at least 80% power under the following assumptions:
  - Survival in the control arm is 60% at 2 years and 51% at 3 years. Beyond 3 years the mortality risk (hazard rate) will be 0.05 death per patient per year.
  - The test population will experience a 31% reduction in the risk of mortality, compared to the controls. This would produce a survival rate of 70% at 2 years and 63% at 3 years. For patients surviving beyond 3 years the mortality risk (hazard rate) would be 0.0345 death per patient per year.
  - 1.5-year accrual period, with 2.5 years of follow-up after enrollment of the last patient.
  - Type I error of 0.05 with 2-sided logrank test.
  - Constant hazard rates in each treatment arm during the periods 0 - 2 years, 2 – 3 years, and 3 + years.
  - Constant accrual rate.
| STATISTICAL CONSIDERATIONS (continued) | The cutoff date for the final survival analysis will be the date of the 240th death. An interim analysis of survival will be done at the time of the analysis of locoregional failure. The level of the interim test will be determined by the proportion of the expected 240 deaths that have been observed, using an O’Brien – Fleming like alpha spending function.

An analysis of time to locoregional failure will be done with a two-sided logrank test when 150 patients have reached this endpoint. The analysis of locoregional failure has at least 85% power to detect a difference in postulated locoregional failure rates of 40% in the control arm versus 25% in the experimental arm with a two-sided test at the 0.05 level. It is assumed that among the patients who do experience locoregional failure, the yearly event probability will be 0.7.

Treatment assignment will be done by centrally stratifying for disease stage (III v IV), primary site (oropharynx/larynx v hypopharynx/oral cavity), hemoglobin (≥13.5 g/dL for men and ≥12.5 g/dL for women v otherwise). A dynamic allocation method will be used to avoid extreme imbalance of treatment assignment within a single institution.

The stratified log rank test will be used to compare the treatment groups for time-related parameters, such as time to locoregional failure and failure free survival. Categorical parameters, such as response rate, will be evaluated using the chi-squared test.

Characteristics of subjects assigned to the 2 treatment arms will be summarized. These include sex, race, age, weight, height, performance status, histology, stage of disease, measurable disease, time since diagnosis, presence of other disease conditions, and clinical laboratory tests.

The incidence of adverse events will be summarized by type of event and toxicity grade. |
| DURATION OF STUDY PERIOD (per subject) | The duration of study for an individual patient will include a period for inclusion and treatment planning of up to 1 month, a 7 week treatment period followed by a minimum of 4 weeks of follow-up for chemotherapy related toxicities after the last dose of study drug(s). All subjects will be followed for disease status until locoregional disease progression, death, or the study cutoff date, whichever comes first. All subjects will be followed for QoL until three years after completion of therapy or study cut-off date. All subjects will be followed for survival, radiation toxicity and further therapy until death or the study cutoff date. The study cutoff date is defined as the date of the 240th death. |
# TABLE OF CONTENTS

1. INTRODUCTION AND RATIONALE .............................................................................. 18
   1.1 Natural history of head and neck cancer ................................................................. 18
   1.2 Locoregionally advanced disease ............................................................................ 18
   1.3 Hypoxia and head and neck cancer ......................................................................... 18
   1.4 Rationale for tirapazamine in advanced head and neck cancer ............................. 19
      1.4.1 Tirapazamine related toxicities .......................................................................... 20
   1.5 Clinical experience with tirapazamine for head and neck cancer ....................... 21
      1.5.1 Radiotherapy and single-agent tirapazamine ..................................................... 21
      1.5.2 Radiotherapy, cisplatin, and tirapazamine for head and neck cancer .............. 21
         1.5.2.1 The Peter MacCallum Phase I Trial ............................................................... 21
         1.5.2.2 The Stanford Experience ............................................................................. 22
         1.5.2.3 The TROG Randomized Phase II Trial ......................................................... 23
   1.6 Rationale for study .................................................................................................. 23
      1.6.1 Selection of a control arm ................................................................................ 24
      1.6.2 Selection of endpoints ...................................................................................... 24
         1.6.2.1 Overall survival ........................................................................................... 24
         1.6.2.2 Locoregional failure .................................................................................... 24
         1.6.2.3 Quality of life evaluation ............................................................................. 25
            1.6.2.3.1 Quality-of-life hypotheses ................................................................. 25
   1.6.2.3.1 Quality-of-life hypotheses ........................................................................... 25

2. STUDY OBJECTIVES ..................................................................................................... 26
   2.1 Primary ..................................................................................................................... 26
   2.2 Secondary ................................................................................................................. 26

3. STUDY DESIGN ............................................................................................................... 26
   3.1 Description of the protocol ..................................................................................... 26
   3.2 Interim analysis ....................................................................................................... 26
   3.3 Study committees ................................................................................................... 27
   3.4 Duration of study participation .............................................................................. 27

4. SELECTION OF PATIENTS .......................................................................................... 28
   4.1 Number of patients planned .................................................................................. 28
   4.2 Inclusion criteria ..................................................................................................... 28
   4.3 Exclusion criteria .................................................................................................... 28

5. TREATMENT .................................................................................................................... 29
   5.1 Radiotherapy .......................................................................................................... 29
      5.1.1 Central radiation QA review .......................................................................... 29
      5.1.2 Immobilization ................................................................................................ 30
      5.1.3 Standard simulation ....................................................................................... 30
      5.1.4 Standard planning .......................................................................................... 30
      5.1.5 Standard dosimetry ....................................................................................... 31
      5.1.6 Standard field verification .............................................................................. 31
      5.1.7 Conformal planning ...................................................................................... 31
      5.1.8 Conformal dosimetry .................................................................................... 31
5.1.9 Conformal treatment delivery verification ................................................................. 32
5.1.10 Fractionation ............................................................................................................ 32
5.1.11 Dose calculation and reporting ................................................................................ 32
5.1.12 QA documentation .................................................................................................. 33
5.2 Chemotherapy .............................................................................................................. 35
5.2.1 Dose modification ..................................................................................................... 37
5.2.2 Management of neutropenia ..................................................................................... 39
5.3 Post-chemoradiation neck surgery ................................................................................. 39
5.4 Investigational product ................................................................................................. 40
5.5 Method of assigning patients to treatment group .......................................................... 41
5.6 Packaging and labeling ............................................................................................... 41
5.7 Storage conditions ....................................................................................................... 42
5.8 Responsibilities for investigational product ................................................................. 42
5.9 Retrieval and/or destruction of investigational product ............................................... 42
5.10 Concomitant therapy ................................................................................................. 42
5.10.1 Not permitted concomitant therapy ...................................................................... 42
5.10.2 Permitted concomitant therapy .............................................................................. 43

6. OUTCOME ASSESSMENT ............................................................................................... 43
6.1 Efficacy ......................................................................................................................... 43
6.1.1 Clinical assessment methods .................................................................................... 43
6.1.2 Criteria of efficacy .................................................................................................... 44
6.1.2.1 Primary criteria ...................................................................................................... 44
6.1.2.2 Secondary criteria ................................................................................................. 44
6.1.2.3 Measurement of response .................................................................................... 45
6.1.2.4 Definition of measurable/non-measurable disease .............................................. 45
6.1.2.5 Definition of response ......................................................................................... 45
6.1.2.5.1 Primary site ...................................................................................................... 45
6.1.2.5.2 Neck nodal disease ......................................................................................... 46
6.1.2.5.3 Initial response assessment ............................................................................ 46
6.1.2.5.4 Final complete response rate ...................................................................... 46
6.1.2.6 Definition of locoregional failure ........................................................................ 47
6.1.2.7 Quality-of-life evaluation .................................................................................... 47
6.1.2.7.1 FACT-H&N Quality-of-life questionnaire ...................................................... 48
6.1.2.7.2 Timing of assessment .................................................................................... 48
6.2 Safety .......................................................................................................................... 48
6.3 Pharmacokinetics ........................................................................................................ 49

7. PATIENT SAFETY ........................................................................................................ 49
7.1 Adverse events monitoring ......................................................................................... 49
7.2 Laboratory tests monitoring ......................................................................................... 50
7.3 Safety instruction ......................................................................................................... 50

8. PATIENT WITHDRAWAL ............................................................................................ 51
8.1 Criteria for withdrawal from treatment ..................................................................... 51
8.2 Withdrawal from study .............................................................................................. 51
8.3 Withdrawal from follow-up ....................................................................................... 51
8.4 Consequence ................................................................................................................ 51
10.8.1.2 Treatment-emergent adverse events ................................................................. 61
10.8.1.3 Deaths and serious adverse events ................................................................. 61
10.8.1.4 Adverse events leading to treatment discontinuation ....................................... 61
10.8.2 Clinical laboratory evaluations ......................................................................... 61
10.8.3 Vital signs ........................................................................................................... 61

11. ETHICAL AND REGULATORY STANDARDS .................................................. 61
11.1 Ethical principles .................................................................................................... 61
11.2 Laws and regulations ............................................................................................. 61
11.3 Informed consent .................................................................................................. 61
11.4 Institutional Review Board/Independent Ethics Committee (IRB/IEC) ..................... 62

12. STUDY MONITORING ....................................................................................... 62
12.1 Responsibilities of the Investigator(s) .................................................................. 62
12.2 Responsibilities of the Sponsor ............................................................................ 63
12.3 Source document requirements .............................................................................. 63
12.4 Use and completion of Case Report Forms (CRFs) and additional request ............. 63

13. ADMINISTRATIVE RULES .............................................................................. 64
13.1 Curriculum vitae .................................................................................................... 64
13.2 Record retention in study sites(s) .......................................................................... 64

14. CONFIDENTIALITY ............................................................................................ 64

15. OWNERSHIP OF DATA AND USE OF THE STUDY RESULTS ...................... 64

16. INSURANCE COMPENSATION ......................................................................... 65

17. SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES ........... 65

18. PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSING OUT OF A CENTRE ....................................................... 65
18.1 Premature discontinuation of the study ................................................................. 65
18.1.1 Early stopping rules ......................................................................................... 66
18.2 Premature closeout of a centre ............................................................................. 66

19. CLINICAL STUDY REPORT ............................................................................. 66

20. PUBLICATIONS ................................................................................................. 66

21. PROTOCOL AMENDMENTS ............................................................................. 67

22. BIBLIOGRAPHIC REFERENCES ....................................................................... 68
LIST OF ABBREVIATIONS

5HT: 5-hydroxytryptophan.
AE/SAE: Adverse event/ Serious adverse event.
ALT: Alanine transaminase (SGPT).
APTT: Activated partial thromboplastin time.
AST: Aspartate aminotransferase.
BP: Blood pressure.
CI: Confidence interval.
CIB: Clinical investigator’s brochure.
CIS: Cisplatin.
CO-60: Cobalt 60.
CR: Complete Response.
CRF: Clinical report form.
CT: Computed tomography.
DNA: Desoxyribonucleic acid.
FAZA: Fluoro-azomycin-arabinoside.
FDG: Fluorodeoxyglucose.
G-CSF: Granulocyte colony stimulating factor.
GM-CSF: Granulocyte/macrophage colony stimulating factor.
GTV: Gross tumor volume.
Gy: Gray.
HF: Hyperfractionated.
HR: Heart rate.
IEC: Independent Ethics Committee.
IRB: Institutional Review Board.
LD: Longest diameter.
LRF: Locoregional failure.
m²: Square meters.
mg: Milligram.
MRI: Magnetic resonance imaging.
MV: Megavolt.
NCI: National Cancer Institute.
PD: Progressive disease.
PET: Positron emission tomography.
PR: Partial Response.
PTV: Planning target volume.
QARC: Quality Assurance Review Center.
QoL: Quality of life.
RECIST: Response Evaluation Criteria in Solid Tumors.
RT: Radiation therapy.
RTOG: Radiation Therapy Oncology Group.
SD: Stable disease.
SGOT: Serum glutamate oxaloacetate transaminase.
T: temperature.
TMC: Trial management committee.
TROG: Trans-Tasman Radiation Oncology Group.
ULN: Upper limit of normal.
WHO: World Health Organization.
1. INTRODUCTION AND RATIONALE

1.1 Natural history of head and neck cancer

Head and neck cancer occurs with an annual incidence of approximately 40,000 cases in the United States (1). Generally, about 30% of these patients will present with locally confined (T1 or T2, Stage I or Stage II) lesions. The majority of patients will present with locoregionally advanced disease (T3, T4, N1-N3, Stage III or IV). Metastatic spread to distant organs at the time of diagnosis is seen clinically in few patients. Autopsy series, however, have indicated a higher incidence of approximately 50% of patients with micrometastatic spread (2,3). Due to the firm association of this disease with tobacco and alcohol use, patients with head and neck cancer usually suffer from a variety of additional diseases related to these risk factors, e.g., advanced arteriosclerosis, obstructive lung disease and hepatic disease (4). Most importantly, they are at risk for second synchronous or metachronous malignancies in the head and neck region as well as other organs, predominantly the lung and esophagus (5).

1.2 Locoregionally advanced disease

For patients with locoregionally advanced disease (Stage III or IV), surgery and radiation have traditionally been used in sequence. Despite this aggressive bimodality treatment approach, cure is achieved in only a minority of patients (6). Most patients die of locoregional persistence or recurrence of disease. The addition of chemotherapy to the overall treatment plan has been studied intensively over the last 3 decades. Research strategies, generally, have included the use of induction (neoadjuvant) or adjuvant chemotherapy, as well as concomitant chemoradiotherapy. The primary goal of such research is to improve local control and survival. Given the anatomic location of the disease and the frequently aggressive surgical approaches used, the use of less extensive surgery (and the preservation of organ function) is an important second treatment goal. Recently reported randomized trials conducted to study the role of chemotherapy have yielded the consistent finding that concurrent administration of chemotherapy (platinum +/- 5-FU) and radiotherapy results in improved locoregional control and overall survival compared to radiotherapy alone (7,8,9,10,11,12). Conversely, sequential (usually neoadjuvant) chemotherapy has yielded only a marginal non-significant benefit (6). As of 2002, it is now widely accepted that combinations of cisplatin with radiation are the standard of care for those patients with locally advanced disease in whom surgery cannot be performed or for those patients who do not wish the radical surgery that is required (13).

1.3 Hypoxia and head and neck cancer

Radiation kills dividing cells through the creation of double stranded DNA breaks. This process is dependent on the presence of oxygen, which “fixes” free-radical-induced lesions produced by ionizing radiation.

Hypoxia in tumors limits the potential of radiation therapy to kill tumor cells (14). This has been found to happen not only in animal models but it also has been found to have an
important clinical effect. This has been best demonstrated in head and neck cancer where the disease is accessible to direct measurement of intratumor oxygen tension (15,16,17,18). The presence of hypoxia was found to be a strong prognostic factor in predicting the outcome of patients with advanced head and neck cancer after radiation therapy.

1.4 Rationale for tirapazamine in advanced head and neck cancer

Tirapazamine is a bioreductively activated, hypoxia-selective antitumor agent of the benzotriazine series. It is 35 to 450 times more cytotoxic (dependent on tumor cell line studied) to hypoxic cells than to well-oxygenated cells (19,20,21,22). Tirapazamine is bioactivated to a cytotoxic metabolite by electron transfer. This one-electron reduction product, which is an oxidizing radical anion, causes extensive single- and double-strand breaks in DNA. It may also accentuate DNA damage induced by radiation or DNA-damaging cytotoxic agents by inhibiting DNA repair (23).

Tirapazamine also results in a marked potentiation of cisplatin cytotoxicity (24). This may be the primary cause of anti-tumor efficacy, since in a number of models, the level of cytotoxicity of tirapazamine alone is quite low while the combination of tirapazamine and cisplatin increases the level of cell kill by many orders of magnitude.

The scientific rationale for and function of tirapazamine in oncology is supported by previous human experience, particularly in non-small cell lung cancer. This experience may be summarized as follows:

- In solid tumors, the combination of cisplatin and tirapazamine is efficacious compared to cisplatin alone. [Phase II (25,26) and Phase III (CATAPULT I) (27) trials]
- In man, tirapazamine can be added to radiation regimens safely, and tirapazamine is likely to contribute to the therapy of those tumors, where hypoxia has long been known to limit the effectiveness of radiation. [DRI2938 (28), EFC3344, EFC3714 (29)]

The selection of tirapazamine for development in the treatment of head and neck cancer is based on the observation that:

- It is a disease, which is known to be significantly hypoxic, and where hypoxia is known to be a marker for poor prognosis after radiation therapy (15,16,17,18,23)
- It is a disease where both cisplatin and radiation therapy have an important role in therapy, but where these active agents still do not cure a majority of selected patients. Furthermore, no second chemotherapy agent has a clearly established role.
- It is a disease where local control has an important benefit for patients because of the functional and cosmetic importance of the anatomical area.
1.4.1 Tirapazamine related toxicities

Based on the patients treated with tirapazamine plus cisplatin in 2 large randomized Phase III trials in lung cancer, 5 toxicities have been observed where the tirapazamine arm had significantly more events than the control arm (See the CIB for more details):

- **Muscle cramps:** Muscle cramps tend to occur early in the course of therapy. They are associated with the administration of treatment (median = 1 day from prior infusion), and are typically of brief duration (median = 2 days). Only 45% of patients experiencing muscle cramps during the first cycle experienced a recurrence on subsequent cycles. There was no tendency toward progressive worsening of muscle cramps upon repeat exposure. Muscle cramps is not a dose related toxicity.

- **Hearing loss:** Two distinct patterns of hearing loss (early onset and late onset) were observed in EFC2753, with some evidence to support distinct underlying pathogenesis. In the tirapazamine plus cisplatin treatment arm, the time to first occurrence of hearing loss was acute and most often occurred in the first few days of Cycle 1. This early onset hearing loss (reported within 5 days or less after 1st infusion) was acute (median occurrence = 1 day from 1st infusion) and of short duration (median = 1 day). For some tirapazamine-treated subjects with early onset hearing loss, unscheduled audiograms were performed early in the first treatment cycle. Analyses of these audiograms revealed a distinct pattern of decreased hearing threshold across all frequencies, which typically reversed at the subsequent examination (end of Cycle 2, per protocol). Hearing loss is a dose related toxicity and the frequency of this event is lower using doses lower than 390 mg/m² as was used in the randomized trials. In addition, late onset hearing loss (occurring more than 5 days after 1st infusion) was also identified. The co-administration of tirapazamine did not appear to enhance the frequency or severity of late onset-hearing loss that is associated with cisplatin.

- **Abnormal vision:** Visual adverse events were of interest during the conduct of EFC2753 because preclinical toxicology findings had identified eye lesions in the dog as a potential toxicity of tirapazamine. Because of these findings, visual adverse events were of particular interest in this study. A more frequent incidence of varied visual adverse events [blurred vision, decreased visual acuity, visual disturbance, etc.] were reported in the tirapazamine plus cisplatin treatment arm [50 (23%) of 219 subjects in the tirapazamine plus cisplatin treatment arm reported this event vs. 21 (10%) of 219 subjects in the cisplatin monotherapy treatment arm]. No evidence of late onset cumulative toxicity of this event was observed. Specific visual tests (visual acuity and color discrimination) were performed at 6-week intervals during the study to further characterize vision changes. The incidence of objective abnormalities in visual acuity and color discrimination was low overall, the same in both treatment arms, and did not appear to be related to clinical adverse events. No evidence of visual toxicity of the severity or frequency observed in the dog was seen in human subjects.

- **Nausea/vomiting:** Both nausea and vomiting were significantly more frequent in the tirapazamine arm of EFC2753 (86% and 82% compared to 69% and 46% respectively in the cisplatin monotherapy arm). No evidence of clinically significant late-onset cumulative toxicity was apparent in either treatment arm. Nausea and vomiting induced by tirapazamine, especially when given in combination with cisplatin or other emetogenic agents, should be managed prophylactically with 5HT antagonists.
Diarrhea: Diarrhea was typically of abrupt onset (median <1 day from prior infusion), and brief in duration (median <1 day), irrespective of grade and cycle of onset. High-grade episodes were reported in the context of associated incontinence, presumably related to the abrupt onset. Patients could be re-treated without necessarily experiencing a recurrence of diarrhea or worsening in severity.

1.5 Clinical experience with tirapazamine for head and neck cancer

1.5.1 Radiotherapy and single-agent tirapazamine

A Phase II trial was done to determine the tolerability of radiation therapy and concomitant tirapazamine in head and neck cancer (30). Thirty-nine patients with Stage III or IV head and neck cancer were treated with conventional RT (70 Gy in 7 weeks) and concurrent tirapazamine (159 mg/m² intravenously 3 times per week for 12 doses). 32/39 (83%) received full 12 drug doses and 32/39 received full radiation. The most frequent drug toxicities were muscle cramps and nausea/vomiting. Thirteen patients had Grade 3 or Grade 4 drug related toxicities. No excessive RT-associated acute normal tissue reactions were noted. With a median follow-up of 13 months, the 1-year and 2-year local control rate (primary site only) was 64% and 59% respectively. The authors concluded that the tirapazamine regimen was well tolerated, the toxicity with RT was acceptable, and the disease control was encouraging.

1.5.2 Radiotherapy, cisplatin, and tirapazamine for head and neck cancer

1.5.2.1 The Peter MacCallum Phase I Trial

The maximally tolerated dose of tirapazamine when combined with cisplatin and radiation in patients with T_3,4 and/or N_2,3 squamous cell carcinoma of the head and neck has been investigated by Rischin et al (31).

The starting schedule was conventionally fractionated radiotherapy (70 Gy in 7 weeks), with concomitant cisplatin 75 mg/m² and tirapazamine 290 mg/m² (prior to cisplatin) in weeks 1, 4, and 7, and tirapazamine alone 160 mg/m² 3 times a week in Weeks 2, 3, 5, and 6. PET scans for tumor hypoxia (¹⁸F misonidazole) were performed prior to and during radiotherapy. This regimen is schematically shown in Figure (1.5.2.1) 1.
Sixteen patients with predominantly oropharyngeal primaries, including 10 patients with T4 or N3 disease were treated. Febrile neutropenia occurred towards the end of radiotherapy in 3 out of 6 patients treated on the initial dose level. Another 10 patients were treated with the same doses, but weeks 5 and 6 tirapazamine doses were omitted. This resulted in less neutropenia, only 1 dose-limiting toxicity (febrile neutropenia), and 8 out of 10 patients completed treatment without any dose omissions. The acute radiation toxicities were not obviously enhanced compared to chemoradiotherapy regimens using concurrent platinum and 5-fluorouracil. Muscle cramps were troublesome in some patients during the first 2 weeks of treatment. However, the cramps had generally subsided and largely resolved by the third week of treatment, without any alteration to chemotherapy doses and irrespective of the treatment given for the cramps. Transient skin rashes due to tirapazamine were seen in 4 patients. $^{18}$F misonidazole scans detected hypoxia in 14/15 patients at baseline with only 1 patient having detectable hypoxia at the end of treatment. With a median follow-up of 2.2 years, the 2 year failure-free survival rate is 69% (SE = 12%), the 2 year local progression-free rate is 88% (SE = 8%), and the 2 year overall survival rate is 75% (SE = 11%).

The authors concluded that dose-limiting toxicity was febrile neutropenia, which could be overcome by omitting tirapazamine in weeks 5 and 6. The triple combination of tirapazamine, cisplatin, and radiotherapy resulted in remarkably good and durable clinical responses in patients with very advanced head and neck cancers.

1.5.2.2 The Stanford Experience

A second randomized Phase II trial comparing a cis/5FU/Radiation regimen to that of the same regimen with TPZ added is in progress directed at organ preservation at Stanford and the toxicities have been reported in an abstract (32). Tirapazamine 300-330 mg/m$^2$ day (d) 1, 22, cisplatin 100 mg/m$^2$ d1, 22 and fluorouracil 1000 mg/m$^2$/d by continuous infusion d1-5 & d22-26 are given initially, followed by the simultaneous administration of radiotherapy and tirapazamine 160-260 mg/m$^2$ d43, 45, 47, 71, 73, 75, and cisplatin 20 mg/m$^2$ d43, 45, 47, 71, 73, 75, and fluorouracil 600 mg/m$^2$/day by 96 hour continuous infusion d43-46 & d71-74. At the time of the interim analysis, 23 patients have been randomized to treatment with tirapazamine and 20 were evaluable for toxicity.
Granulocytopenia was the most frequent toxicity during the induction chemotherapy. Grade 3 or 4 granulocytopenia occurred in 8/16 patients treated at 300 mg/m² and 4/4 treated at 390 mg/m². During simultaneous chemoradiation, 1/4, 3/12, and 2/4 patients treated with 160mg/m², 220 mg/m², and 290 mg/m² developed Grade 3 granulocytopenia. The most common toxicity during simultaneous chemoradiation was mucositis, which reached Grade 3 in 9/20 and Grade 4 in 2/20. Skin reactions, weight loss, fatigue, muscle cramps and tinnitus, and other of mild toxicity were also seen. The authors concluded that the overall toxicity is comparable to the same regimen without tirapazamine.

1.5.2.3 The TROG Randomized Phase II Trial

Following the interesting results of the Phase I trial, the TROG initiated a randomized Phase II trial that was designed to select the experimental arm for their next Phase III study.

The 2 arms were the CDDP/TPZ/XRT regimen developed in the Phase I trial and a “chemoboost” regimen slightly modified from a protocol developed by Peters and colleagues at the University of Texas’ MD Anderson Cancer Center (33). The modified regimen differed from the MD Anderson protocol by administration of cisplatin as a weekly bolus rather than a continuous infusion and reduction of the 5FU dose from 400mg/m² to 360 mg/m² because of hematological toxicity. The “chemoboost” regimen was piloted at the Peter MacCallum Cancer Institute in 28 patients with locally advanced head and neck cancer including 14 patients with T4 and/or N3 disease (34). The overall complete response rate was 71% (95% CI: 51%-67%). With a median potential follow-up time of 29 months, the 2 year failure-free survival rate was estimated to be 40% (CI: 21%-59%) and the 2 year overall survival rate was estimated to be 50% (CI: 29%-71%). The initial site of relapse or progression was locoregional in 11 of the 16 patients who failed.

The TROG randomized Phase II study has currently accrued over 100 of a target of 120 patients at 11 centers in Australia and New Zealand. An interim safety analysis was performed on the first 63 patients (35). On the tirapazamine arm, Grade 3 neutropenia occurred in 30% and Grade 4 neutropenia in 3% of patients. Twelve percent of patients on this arm experienced an episode of febrile neutropenia. Thrombocytopenia of any grade was uncommon in both arms, but 2 patients on the tirapazamine arm had grade 4 thrombocytopenia. There was no statistically significant difference in mucositis between the 2 arms, but the radiation skin reaction was of longer duration in the “chemoboost” arm. While the toxicities were significant, including hematological toxicities and some of the known toxicities of tirapazamine, TROG has concluded that the regimen can be used in a multicenter trial.

1.6 Rationale for study

The approach of using concurrent radiation, tirapazamine, and cisplatin appears promising from the initial Phase I/II trials. This randomized Phase III trial will be a pivotal trial to compare this regimen with a standard regimen that is currently used for head and neck cancer.
1.6.1 Selection of a control arm

Most investigators today agree that a platin (cisplatin or carboplatin) is the most active agent to add to radiation. However, no single platin-based regimen combined with radiation therapy has emerged as an overall standard of care. Several recent randomized trials, either in progress or planned, use 3 doses of cisplatin, 100 mg/m$^2$ in weeks 1, 4, and 7 of standard radiation therapy (70 Gy in 35 fractions over 7 weeks). These include the recently reported Intergroup Phase III trial for laryngeal cancer RTOG 91-11 (11), the Intergroup trial for unresectable head and neck cancer (12) and the planned RTOG Phase III trial (KK Ang personal communication) where this regimen will be the control arm.

1.6.2 Selection of endpoints

The study is powered for the primary endpoint of overall survival. An analysis of time to locoregional failure (TLRF) is planned prior to the completion of follow-up for survival.

1.6.2.1 Overall survival

The goal of therapy in this protocol is to cure the patient. As such, overall survival is the primary endpoint. With advanced head and neck cancer, uncontrolled locoregional disease is the most common cause of death and it is therefore expected that improved locoregional control should be associated with improved overall survival. However, it is apparent that the survival gain to be expected from any realized improvement in locoregional control is quantitatively less because of deaths from distant metastatic disease, second cancers and intercurrent non-malignant medical conditions to which this patient population is prone.

1.6.2.2 Locoregional failure

Squamous cell carcinoma of the head and neck is a disease that if locally uncontrolled causes considerable morbidity and mortality. This is because the natural history of the disease is usually of local progression and regional spread in advance of life-threatening distant metastasis. A relatively small percentage of patients with head and neck cancer will manifest distant metastases. This is particularly true for head and neck cancer patients with early stage nodal disease. The vast majority of treatment failures involve a component of loco-regional disease recurrence. Depending on the exact site of disease, locally uncontrolled disease is associated with debilitating problems in eating, breathing and speaking, pain, malodor, and in the case of advanced neck disease, tumor fungation. Death usually results from inanition, aspiration pneumonia, or torrential hemorrhage.

Patients with locally uncontrolled head and neck cancer frequently become social outcasts and in need of high level palliative care. Because uncontrolled disease exacts such a heavy price, the general consensus within the head and neck community is that loco-regional control is the single most important determinant of patient well-being. This is intuitively obvious and has, therefore, not been the subject of formal QoL studies in head and neck cancer. One study, however, on 40 patients without and 8 patients with recurrent disease, reported, not surprisingly, that patients with recurrence scored badly in all domains (36).
An important concern with locoregional failure as an endpoint for clinical trials is the potential subjectivity of the endpoint, which can cause bias, and irreproducibility of the results. However, for head and neck cancer, recurrence of disease is generally not clinically silent to careful examination or symptoms. The areas at risk for locoregional failure are amenable to examination by direct inspection, fiberoptic endoscopy and palpation of accessible primary sites and the neck. For this study, these examinations will be done every 2 months the first year, every 3 months the second year and every 4 months the third year or until study cut-off. If there is a suspicion of recurrence, CT /MRI will be done as well as biopsy. Scheduled CT or MRIs will complement the clinical exams every 4 months for the first year and then every 6 months until the cut-off date. Using this rigorous follow-up, bias of the observer can be minimized. Furthermore, when there is recurrence of disease, it is usually rapidly progressive, and inter-observer differences would not significantly alter time to locoregional failure.

1.6.2.3 Quality of life evaluation

Quality of life (QoL) is an important secondary outcome of this phase III trial. It is possible that the primary hypothesis of improved overall survival may not be demonstrated with statistical significance. Such an outcome could reasonably occur due to dilution of a true treatment effect by high rates of intercurrent illness and non-cancer deaths. In this event, improved locoregional control in the experimental arm combined with improved QoL may constitute sufficient evidence of benefit for the experimental treatment to be adopted as standard. In contrast, durably inferior QoL results in the experimental arm would necessitate a careful examination of the risks and benefits before adopting the experimental arm as standard treatment, even if a survival benefit of small magnitude is shown.

1.6.2.3.1 Quality-of-life hypotheses

It is expected that baseline QoL scores will decline during treatment and recover approximately to baseline by 6 months following completion of treatment in patients achieving a complete response. Thereafter, the average QoL in both arms will decline over time as more patients relapse and develop new symptoms. As pain is a dominant symptom of recurrent head and neck cancer, pain scores would be expected to be particularly sensitive to post-treatment relapse. The hypothesis to be tested is: the difference between baseline scores and the current QoL and pain scores, measured after the acute treatment toxicities have resolved, will be more positive in the experimental arm. This is consistent with the importance of the other endpoints of survival and locoregional failure, which are not acute endpoints.
2. STUDY OBJECTIVES

2.1 Primary

The trial will compare the efficacy and safety of concomitant chemoradiation with tirapazamine, cisplatin, and radiation versus cisplatin and radiation. This trial is designed with the primary endpoint of overall survival.

2.2 Secondary

Secondary endpoints include, but are not limited to, the following (See Section 6.1.2.6):
• Time to locoregional failure.
• Failure-free survival.
• Patterns of failure.
• Cumulative incidence of unacceptable locoregional treatment outcome.
• Change in QoL from baseline.
• Toxicity and safety.
• Initial response rates at 2 months after completion of chemoradiation therapy.
• Final CR rate.
• Biological correlates of outcome eg hypoxia, tumor markers

3. STUDY DESIGN

3.1 Description of the protocol

This is a Phase III, multicenter, international, randomized open-label, 2-arm trial comparing 2 chemotherapy regimens: cisplatin (control arm) versus cisplatin and tirapazamine (experimental), each used with concomitant radiation in advanced head and neck cancer. A two-stage sequential design will be used.

3.2 Interim analysis

An interim analysis of overall survival will be done at the time of the analysis of time to locoregional failure. The cut-off date for these analyses is defined as the date of 150 locoregional failures, which is expected to be approximately 2.5 years after the start of accrual. It is estimated that approximately 85% of total expected locoregional failures during study will have occurred by the time of interim analysis. Interim analysis of locoregional failure will be at the 0.05 level of significance. A final analysis of locoregional failure will be conducted at the time of the primary analysis of overall survival. The interim survival analysis will be adjusted for type I error as specified in Section 10.7.1.2. The interim analysis will be performed by the trial statistician/s and their report will be submitted to the Trial Management Committee and the Sponsor, who will jointly be responsible for the trial decisions. Results of the interim analysis will also be provided to the Independent Data and Safety Monitoring Committee.
If at the time of interim analysis there is a statistically significant difference in overall survival in either direction (using an * level as defined in section 10.7.1.2), study accrual will be stopped, assuming the target sample size has not been reached. Patients already entered will be followed up for completion of clinical/survival data for a certain period to be determined by the Trial Management Committee. If the interim survival analysis is not significant, patients will continue to be accrued and followed till the study cut-off date defined in the protocol. Analysis of the locoregional failure endpoint will not form the basis for stopping early.

3.3 Study committees

A Trial Management Committee (TMC) including members of the Trans-Tasman Radiation Oncology Group (TROG) will supervise the conduct of the trial. Responsibility for the trial will be jointly held by the TMC and the sponsor, Sanofi-Synthelabo Research. There will be at least eight seats on the committee, the majority of whom shall be clinical investigators. TROG membership will include the principal investigators and the statistician. Sponsor representative will be limited to three members including a statistician. The TMC will choose additional representatives from participating clinicians.

An Independent Data and Safety Monitoring Committee (IDSMC) will meet periodically to review the safety of the trial. The broad responsibility of the IDSMC will be to independently monitor the conduct of the trial. Specifically it will monitor the trial’s scientific integrity, ensure patient safety and monitor adverse effects.

3.4 Duration of study participation

The duration of the study participation will include for each patient a one month inclusion and treatment planning period, followed by a 7 week treatment period, followed by a minimum of 4 weeks of follow-up for chemotherapy related toxicities after the completion of the study treatment. In addition, all patients will be followed for radiation toxicity until death or study cut-off. All subjects will be followed for disease status until locoregional progression, death, or the study cut-off date whichever comes first. All subjects will be followed for QoL until three years after completion of therapy or study cut-off date. All subjects will be followed for survival and further therapy until death or the study cut-off date.

The LRF analysis will be performed when 150 patients reach the endpoint of locoregional failure. The study cut-off date is defined as the date of the 240th death, which is expected to occur approximately 2.5 years after the enrollment of the last patient. The estimated time for accrual is 1.5 years, giving an estimated total duration of the trial of 4 years. Additional follow-up may be recommended by the trial management committee to answer significant clinical questions related to the objectives.
4. SELECTION OF PATIENTS

4.1 Number of patients planned

This study plans to enroll 550 evaluable patients.

4.2 Inclusion criteria

a) Previously untreated squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx, histologically or cytologically confirmed.
b) Stage III or IV disease (excluding T1N1, T2N1 and metastatic disease). (Appendix 1)
c) Age $\geq 18$.
d) ECOG performance status $\leq 2$. (Appendix 2)
e) Absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and hemoglobin $\geq 10$g/dL.
f) Serum bilirubin $<1.25$ times ULN and AST/ALT $<5$ times ULN. Calculated creatinine clearance (Cockcroft-Gault) $\geq 55$ mL/min. (Appendix 3)
g) Signed written consent.
h) Availability for follow-up for up to 4 years after treatment.
i) The patient is infertile or is aware of the risk of becoming pregnant or fathering children and will use adequate contraception (oral contraception, intrauterine devices, diaphragm and spermicide or male condom and spermicide) throughout therapy and for at least 3 months after therapy.
j) Life expectancy greater than 6 months.

4.3 Exclusion criteria

a) Significant intercurrent illness that will interfere with the chemotherapy or radiation therapy during the trial such as HIV infection, cardiac insufficiency, myocardial infarction within 6 months, pulmonary compromise, active alcohol abuse, active infection or febrile illness.
b) Primary cancers of the nasal and paranasal cavities and of the nasopharynx.
c) Distant metastases. (All patients will have had a chest CT; patients with abnormal liver function tests to have abdominal ultrasound or CT; patients with bone symptoms to have a bone scan and plain films.)
d) Symptomatic peripheral neuropathy $\geq$ grade 2.
e) Clinically significant sensori-neural hearing impairment which may be exacerbated by cisplatin (Audiometric abnormalities without corresponding clinical deafness will not be grounds for exclusion)
f) Significant cardiac disease resulting in an inability to tolerate the intravenous fluid load as required for administration of cisplatin.
g) Weight loss greater than 20% of normal body weight in the 3 months preceding trial entry.
h) High risk for poor compliance with therapy or follow-up as assessed by investigator.
i) Pregnant or lactating women.
j) Prior radiation therapy to greater than 30% of the bone marrow
k) Prior experimental therapy for cancer within 30 days of entering the trial.
l) Prior radiation for head and neck cancer. 
m) Prior chemotherapy for head and neck cancer. 
n) Prior cisplatin chemotherapy. 
o) Patients with prior cancers, except: those diagnosed more than five years ago with no 
evidence of disease recurrence and clinical expectation of recurrence of less than 5%; 
or successfully treated non-melanoma skin cancer; or carcinoma in situ of the cervix. 
However, any patient with previous invasive breast cancer, prostate cancer or 
melanoma is excluded.

5. TREATMENT

5.1 Radiotherapy

In both treatment arms radiotherapy will consist of a conventionally fractionated radical 
course of treatment. The dose to sites of macroscopic disease identified clinically or 
radiologically will be 70 Gy in 35 fractions over 7 weeks except for small volume nodal 
disease (under 2 cm maximum diameter on CT) where 60 Gy in 30 fractions over 6 weeks 
is sufficient. This is important in the lower neck to minimize the risk of brachial plexus 
injury. Sites of potential subclinical involvement will receive 50 Gy in 5 weeks or its 
biologic equivalent. Lymphatic pathways to be treated electively must include a minimum 
of two echelons of uninvolved nodes eg a patient with T3NO oropharyngeal cancer would 
require treatment of the upper and mid cervical nodes but not necessarily the 
supraclavicular nodes. Patients with ipsilateral N2 or N3 disease must have the entire 
opposite neck treated electively. Specifics of radiotherapy technique and reporting 
requirements are described below.

Treatment may be planned using either standard (parallel-opposed) or 3D conformal 
techniques. IMRT is not allowed on this study. An approved benchmark for either 
standard or 3D planning must be on file at the Quality Assurance Review Center (QARC). 
The benchmark material is available on the QARC website (www.QARC.org). Centers 
wishing to use only standard planning must complete the standard planning benchmark. 
Centers that have completed the 3D benchmark may use either planning method. To 
avoid bias, all phases of the radiotherapy course for each patient must be planned before 
randomization. If a site wishes to upgrade from standard planning to conformal planning, 
a 3D benchmark must be completed and approved by QARC.

Only linear accelerator based treatments (photon energy 4 MV or greater or electrons) are 
allowed on this study. Co-60 is not allowed.

5.1.1 Central radiation QA review

Diagnostic films and treatment plans will be reviewed centrally on all patients from each 
center. The treatment plan for all phases and associated documentation as set out in 
Section 5.1.12 must be submitted to QARC within a week of starting radiotherapy. After 
treatment is completed on each patient, a summary of the treatment actually delivered 
including port films for all phases must be provided and submitted to QARC within one
month of the treatment completion. QARC will compare each treatment plan to the treatment actually delivered to each patient.

5.1.2 Immobilization

Patients should be positioned supine and immobilized using either a thermoplastic mask or a vacuum formed mask. An intraoral stent or tongue depressor should be used if this will allow a greater amount of the tongue or oral cavity to be excluded from the treatment volume.

5.1.3 Standard simulation

At simulation, relevant anatomical landmarks should be identified as appropriate. For oral cavity tumors a radio-opaque seed to define the anterior margin of palpable disease should be inserted.

On the simulation film the lateral projection of the primary tumor and nodal disease should be marked by reconstructing the information available from clinical examination and CT/MRI scans. Alternatively, all gross disease can be marked on the planning CT. Fields should be shaped with custom blocks or multi-leaf collimators to achieve maximum sparing of normal tissues while achieving adequate tumor coverage. A minimum field margin of 2 cm around all gross disease and potential sites of subclinical involvement is required for the first phase of treatment. A minimum field margin of 1 cm round gross disease (as defined pre-treatment) is required for the boost. Skin fall-off should be avoided anteriorly whenever possible. Except in patients who have had an open biopsy of neck nodal disease, or in whom tumor is infiltrating the skin, no surface bolus should be used.

5.1.4 Standard planning

All patients must have a planning CT for dose calculation and to verify coverage of gross disease in the treatment volume. At a minimum, slices for isodose calculation must be obtained at the central axis of the field, through the plane of maximum tumor bulk (if this does not coincide with the central axis) and 1 cm inside the upper and lower margins of the fields. In the plane of maximum tumor bulk the isodose distribution should be overlaid on the CT image to confirm tumor coverage.

For the first phase of treatment (on cord) fields should be planned where possible to avoid splitting any nodal disease. For the second phase, if the location of nodal disease permits, oblique off cord fields are recommended to cover all gross disease. If this is not possible abutting electron fields should be used to treat extensions of nodal disease posterior to the mid-vertebral plane. The energy of the electron beam must be determined by the thickness of nodal disease to ensure adequate coverage but at the same time avoiding too high a dose to the spinal cord. In the event that immobilization is inadequate due to weight loss or significant regression of the node(s) during treatment a second planning CT scan is required.
5.1.5 Standard dosimetry

The prescription point for parallel opposing fields is in the midplane of the central axis (ICRU 50). Missing tissue compensation should be used if available to provide dose homogeneity within the PTV. The dose variation within 1.5 cm of gross disease should not exceed +7% and –5% of the prescription point dose. Where an electron beam abuts a photon beam overlying gross disease a small volume hot spot of up to 120% is permissible. For electron fields the dose will be specified as the peak dose (D max) with energy chosen to deliver at least 90% to sites of gross disease. The nominal tumor dose to gross disease as defined clinically or radiologically shall be 70 Gy except for small volume nodal disease (under 2 cm diameter) where a minimum dose of 60 Gy shall be specified. Sites of potential subclinical involvement shall be treated to 50 Gy. In the lower neck this (subclinical disease) dose will be specified at a depth of 2 cm.

If the junction plane between lateral and anterior neck fields provides a margin of less than 1 cm below all gross nodal disease, the subclinical dose should be increased to 60 Gy within a buffer zone adjacent to gross disease. Likewise clinically impalpable but radiologically suspicious (not definitely involved) nodes should be boosted to 60 Gy. The dose to the spinal cord shall not exceed 40 Gy from the direct beams and shall not exceed 45 Gy from all dose contributions. If the location of gross disease mandates a higher cord dose to achieve adequate coverage of gross disease, a cord dose of up to 48 Gy is permitted. Point doses to the spinal cord within the cone down volume must be calculated.

5.1.6 Standard field verification

Portal films should be taken weekly. At least one portal film for each field (or hard copy of real time portal images) must be submitted for QA audit.

5.1.7 Conformal planning

A planning CT covering the entire volume of interest is required with slice separation of no more than 5 mm through sites of imagable disease and 10 mm elsewhere. The planning CT should be fused with diagnostic images whenever possible. The gross tumor volume (GTV) must be marked on all slices where imagable disease is present. Two planning target volumes (PTVs) must be marked: PTV1 to cover the GTV (primary and involved nodal regions) and potential areas of local extension or lymphatic spread with a minimum 1.5 cm margin, and PTV2 to cover the GTV (primary and involved lymph node regions) with a minimum 0.5 cm margin in all planes. In cases where small volume neck disease is present, a third PTV3 will be marked to cover this disease with a minimum 0.5 cm margin. Parotid and/or submandibular gland sparing techniques are encouraged to the extent that coverage of the PTV is not compromised.

5.1.8 Conformal dosimetry

The dose to PTV1 will be 50 Gy, to the PTV2 70 Gy, and to PTV3 60 Gy all in 2 Gy fractions. The dose variation within PTV2 and PTV3 should not exceed +7% and –5% of the prescription point dose. The maximum spinal cord dose shall not exceed 45 Gy from
all fields. If the location of gross disease mandates a higher cord dose to achieve adequate coverage of gross disease, a cord dose of up to 48 Gy is permitted. Point doses to the spinal cord must be calculated for all relevant fields. Composite isodose distributions and dose volume histograms for PTV1, PTV2, PTV3 and the spinal cord shall be submitted.

5.1.9 Conformal treatment delivery verification

Isocenter verification on orthogonal films plus BEV and REV (Section 5.1.13) are required.

5.1.10 Fractionation

For both arms of the trial, conventional once daily fractionation, 5 fractions per week are specified. In the event of public holidays, missing treatment(s) should be made up in the same way as for treatment interruptions (see below). Every effort must be made to avoid protraction of treatment beyond 7 weeks. Treatment interruptions should be avoided unless there is severe acute toxicity which cannot be managed conservatively. In the event of a treatment interruption for any other reason, the missing dose fraction(s) should be made up by treatment on a weekend or by giving a second treatment on one or more of the remaining treatment days with a minimum 6-hour interfraction interval provided that no more than 6 fractions are given in any one week. The reason for any treatment interruption must be documented. Chemotherapy scheduling will be adjusted to conform to any break in radiotherapy. (Section 5.2.1)

5.1.11 Dose calculation and reporting

**Prescription point**
The monitor units required to deliver the prescribed dose to the prescription point shall be calculated and submitted.

**Dose uniformity**
For standard treatment plans the maximum and minimum doses within 1.5 cm of gross disease shall be reported. For conformal plans, the maximum and minimum doses in the PTV shall be calculated and reported as per ICRU 50. These may be extracted from isodose distributions, calculated separately or derived from DVHs.

**Reference point**
The dose reference point calculated on this study is the isocenter. The total dose to this point shall be calculated and reported.

**Critical organs**
The maximum dose to the spinal cord shall be calculated, recorded in the treatment records, and submitted with the QA documentation. For patients treated with volume-based techniques, the appropriate dose volume histograms shall be submitted. This includes the parotids for patients treated with parotid sparing techniques.

**Isodose distribution**
An isodose plot of dose distribution in the central transverse plane through the target volume shall be submitted. In addition, dose distributions 1 cm inside the upper and lower margins of the fields shall also be submitted. The prescription point and the outlines of the planning target volume and critical organs shall be shown. Isodose values must be clearly labeled. The effects of shielding blocks shall be included and corrections for heterogeneity shall be shown.

For volume based treatment planning, a hard copy isodose distribution for the total dose plan in the axial, sagittal, and coronal planes, which includes the isocenter of the planning target volume (PTV) must be submitted (central axis, two superior and two inferior planes). These dose distributions must include the following:

A sufficient number of isodose contours should be shown to determine that the dose distribution conforms to the protocol guidelines. These isodoses should be superimposed over treatment planning CT or MR images. However, if such hard copy presents difficulty, similar plots without the gray scale image are acceptable if enough critical contours are identified to verify the dose distribution to target volumes and critical normal structures. Specifically, include those volumes for which there are dose volume histograms.

5.1.12 QA documentation

Note: Black and white copies of color documentation are not acceptable.

Within one week of the start of radiotherapy, the following data shall be submitted for rapid review for patients using standard planning techniques:

- Copies of the planning CT and the diagnostic imaging utilized in defining the gross target volume.
- Copies of simulator films and/or digitally reconstructed radiographs (DRRs) for each field. It is required that the lateral projection of all gross disease be drawn on the simulator films.
- Copies of verification (portal) films for each field.
- Photographs of the patient in the treatment position, with the fields marked on the skin or on the immobilization device and visible in the photograph.
- The RT-1 Dosimetry Summary Form, one for each target volume.
- Copies of worksheets and/or printouts used for calculations of monitor settings to give the prescribed dose, and doses to all normal structures.
- Copies of isodose distributions for all phases of treatment to demonstrate that the dose variation is within specification. The treatment volumes and the prescription point must be clearly shown.

If 3D-conformal treatment planning is utilized, submit the following for rapid review:

- Copies of the planning CT and the diagnostic imaging utilized in defining the gross target volume.
- Digitally reconstructed radiographs of each treatment portal.
RT-3D Dosimetry Summary Form, which includes a complete description of each portal, including energy, gantry, couch and collimator position, wedge description (if used), and equivalent field size.

One set of orthogonal anterior/posterior and lateral films for isocenter localization for each group of concurrently treated beams. If portals being submitted contain an orthogonal set, this is sufficient.

Photographs of the patient in the treatment position, with the fields marked on the skin or on the immobilization device and visible in the photograph.

BEVs of portals showing collimator, beam aperture, target volume and critical structures.

A room’s eye view (REV), i.e., a composite illustration of all the fields and their angles, if available from your planning system. Otherwise submit an overview diagram or illustration of the patient with all beams and their orientation indicated.

Copies of the isodose distributions for the total dose plan in the axial, sagittal and coronal planes, which includes the isocenter(s) of each planning target volume. The target volume isocenter and the prescription point (if different) must be clearly indicated.

Dose volume histograms for the entire treatment course for PTV 2 and critical structures within the treatment volume as required in 5.1.11.

Within one month of the completion of radiotherapy, the following data shall be submitted.

Copies of additional simulation and verification (portal) films for any field modifications or re-planning done subsequent to the initial reporting of data for rapid review.

A copy of the patient's radiotherapy record including prescription, and the daily and cumulative doses to all required areas and specified dose points.

Copies of calculations and isodoses performed subsequent to the submission of the rapid review data.

An RT-1 Dosimetry Summary Form or RT-3D Dosimetry Summary Form if changes have been made subsequent to submission of rapid review data.

The RT-2 Radiotherapy Total Dose Record Form

These data should be forwarded to:
Quality Assurance Review Center
825 Chalkstone Avenue
Providence, Rhode Island 02908-4735

Questions regarding the dose calculations or documentation should be directed to:
Protocol Dosimetrist
Telephone 401-456-6500
FAX 401-456-6550

Email: physics@qarc.org

Definitions of Deviations in Protocol Performance:
**Prescription dose**
Minor Deviation: The dose per fraction or total dose to the prescription point differs from that in the protocol by between 6% and 10%. For the spinal cord, any dose greater than 48 and less than or equal to 50 Gy.
Major Deviation: The dose per fraction or total dose to the prescription point differs from that in the protocol by more than 10%. Any spinal cord dose greater then 50 Gy.

**Dose uniformity**
Minor Deviation: the variation of dose to areas of gross disease exceeds +7% or –5% of the dose to the planning target volume.
Major deviation: Variation in dose to areas of gross disease exceeds +/- 20%.

**Volume**
Minor Deviation: Margins less than specified or unnecessary irradiation of normal tissue.
Major Deviation: Geographic miss of any part of the GTV

**Treatment Prolongation**
Minor Deviation: Greater than 7 weeks less than/equal to 8 weeks
Major Deviation: Greater than 8 weeks.

### 5.2 Chemotherapy

**Arm 1**
– Cisplatin 100 mg/m^2^ will be given as a 1-hour infusion immediately before radiotherapy on day 1 of weeks 1, 4, and 7 of radiotherapy. Hydration will be required with each dose of cisplatin with the standard hydration schedule used at each institution. Standard antiemetic regimens for cisplatin should be used, which would generally include a 5-HT3 antagonist and dexamethasone.

**Arm 2**
– Tirapazamine will be given at a dose of 290 mg/m^2^ via a 2 hour intravenous infusion followed after a 1 hour interval by cisplatin 75 mg/m^2^ as a 1 hour infusion immediately before radiotherapy on day 1 of weeks 1, 4, and 7.

Tirapazamine alone at a dose of 160 mg/m^2^ will be given as a 2 hour infusion on days 1, 3, and 5 of weeks 2 and 3, with radiotherapy given not earlier than 30 minutes and not later than 2 hours after the end of the infusion. Hydration will be required with each dose of cisplatin with the standard hydration schedule used at each institution. A possible schedule for hydration with cisplatin and tirapazamine is outlined in Appendix 4. For cisplatin and tirapazamine doses, an antiemetic regimen including a 5-HT3 antagonist and dexamethasone is required. The antiemetic regimen for delayed emesis should include dexamethasone. In Weeks 2 and 3 a 5-HT3 antagonist and 4 mg dexamethasone intravenously prior to each tirapazamine dose is generally adequate to control nausea and vomiting. Diarrhea of short duration frequently occurs during or immediately following the tirapazamine infusion, particularly after the higher dose given prior to cisplatin. Treatment of muscle cramps is symptomatic with analgesics and muscle relaxants such as benzodiazepines.
For patients with a calculated body surface area >2.0 m\(^2\) but \(\leq 2.2\) m\(^2\) the Investigator may cap the dose at 2.0 m\(^2\). For patients with a calculated body surface area >2.2 m\(^2\), the Investigator must cap the dose at 2.2 m\(^2\).
5.2.1 Dose modification

The schedules for dose reductions are presented in the following tables:

*Cisplatin (Arm1) or combined cisplatin/tirapazamine (Arm 2) in Weeks 4 and 7*

<table>
<thead>
<tr>
<th>Hematological toxicity</th>
<th>Cisplatin</th>
<th>Tirapazamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>On treatment day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil ≥ 1.0 x 10^9/L And Platelets ≥ 100 x 10^9/L</td>
<td>Full dose when scheduled</td>
<td>Full dose when scheduled</td>
</tr>
<tr>
<td>On treatment day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil ≥ 0.5 and &lt; 1.0 x 10^9/L And/or Platelets &gt; 25 and &lt; 100 x 10^9/L</td>
<td>1) Delay by up to 4 days.</td>
<td>1) Delay by up to 4 days.</td>
</tr>
<tr>
<td></td>
<td>2) AND then: Administer the full dose if Neutrophil ≥1.0 x 10^9/L and/or Platelets ≥100 x 10^9/L</td>
<td>2) AND then: Administer the full dose if Neutrophil ≥1.0 x 10^9/L and/or Platelets ≥100 x 10^9/L</td>
</tr>
<tr>
<td></td>
<td>Or Omit that dose if after 4 days any of those counts remain under those limits and administer the next planned dose without dose reduction</td>
<td>Or Omit that dose if after 4 days any of those counts remain under those limits and administer the next planned dose without dose reduction</td>
</tr>
<tr>
<td>On treatment day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil &lt; 0.5 x 10^9/L And/or Platelets &lt; 25 x 10^9/L</td>
<td>1) Delay by up to 4 days.</td>
<td>1) Delay by up to 4 days.</td>
</tr>
<tr>
<td></td>
<td>2) AND then: Administer the dose with 25% dose reduction if Neutrophils ≥1.0 x 10^9/L and/or Platelets ≥100 x 10^9/L</td>
<td>2) AND then: Administer the full dose if Neutrophils ≥1.0 x 10^9/L and/or Platelets ≥100 x 10^9/L</td>
</tr>
<tr>
<td></td>
<td>Or Omit that dose if after 4 days any of those counts remain under those limits and administer the next planned dose without dose reduction</td>
<td>Or Omit that dose if after 4 days any of those counts remain under those limits and administer the next planned dose without dose reduction</td>
</tr>
<tr>
<td>Nadir</td>
<td>Administer the next dose with 25% dose reduction if Neutrophils ≥1.0 x 10^9/L and/or Platelets ≥100 x 10^9/L</td>
<td>Administer the next dose as a full dose if Neutrophils ≥1.0 x 10^9/L and/or Platelets ≥100 x 10^9/L</td>
</tr>
</tbody>
</table>
If chemotherapy is delayed by up to 4 days in Week 4, then the Week 7 dose should be no earlier than 20 days later.

### Renal Toxicity

<table>
<thead>
<tr>
<th>Creatinine Clearance calculated using the Cockcroft Gault formula</th>
<th>Cisplatin</th>
<th>Tirapazamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50 mL/min</td>
<td>No modification</td>
<td>No modification</td>
</tr>
<tr>
<td>40-50 mL/min</td>
<td><strong>Administer it but reduce</strong> dose to 50 mg/m² (applies to both arms)</td>
<td>No modification</td>
</tr>
<tr>
<td>&lt; 40 mL/min</td>
<td><strong>Omit</strong> that dose.</td>
<td>No modification</td>
</tr>
</tbody>
</table>

### Peripheral neuropathy (CTC)

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin</th>
<th>Tirapazamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; Grade 2</td>
<td><strong>Omit</strong> that dose.</td>
<td>No modification</td>
</tr>
</tbody>
</table>

### Ototoxicity (CTC)

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin</th>
<th>Tirapazamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ Grade 2, not acutely reversible</td>
<td><strong>Omit AND restart</strong> if condition improves to &lt;Grade 2</td>
<td>No modification</td>
</tr>
<tr>
<td>Acute reversible hearing loss</td>
<td><strong>No modification</strong></td>
<td>In case of hearing loss ≥Grade 2 the dose should be reduced by 25% in Weeks 4 and 7 but not in Weeks 2 and 3 when a lower dose of tirapazamine is administered.</td>
</tr>
</tbody>
</table>

### Other non-hematological toxicities * (CTC)

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin</th>
<th>Tirapazamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0-2</td>
<td>No modification</td>
<td>No modification</td>
</tr>
<tr>
<td>Grade 3-4 (excluding nausea/vomiting, alopecia and acute radiation related toxicities)</td>
<td>Hold chemotherapy until symptoms improve to ≤Grade 2. If symptoms persist &gt;2 weeks contact Medical Monitor or withdraw patient. Restart if Grade &lt; 2. Subsequent doses may be reduced by 25% at the discretion of the Investigator.</td>
<td></td>
</tr>
</tbody>
</table>

* If the toxicity is clearly due to one of the chemotherapy drugs, then only the dose of that drug should be reduced.

### Tirapazamine toxicity

The dose limiting toxicity in the Phase I trial has been neutropenia, which only occurred in the last 2-3 weeks of treatment. Muscle cramps, diarrhea, and rashes do not generally require dose reductions or omission of doses. Cramps and skin rashes do not appear to be dose related. Cramps are most troublesome in the first 2 weeks, and then appear to subside despite continuing treatment with tirapazamine. Tirapazamine doses may be reduced by 25% following severe tirapazamine related toxicity, at the discretion of the Investigator. Hearing loss after tirapazamine has generally been seen at doses higher than are being used in this trial. If acute reversible hearing loss (≥ Grade 2) occurs, then a 25% dose reduction of tirapazamine would be required for weeks 4 and 7, but not in weeks 2 and 3 when a lower dose of tirapazamine is administered.
Nausea and vomiting predominantly occur following combined tirapazamine/cisplatin doses, and in general should not result in a dose reduction. Grade 3 or 4 non-hematologic toxicity (apart from toxicities mentioned above) that is due to the chemotherapy may require a dose delay for cisplatin/tirapazamine doses or a dose omission for tirapazamine alone doses. Subsequent doses may be reduced by 25% at the discretion of the Investigator.

**Delays**

- If radiotherapy is interrupted then chemotherapy will also be delayed. When radiotherapy is reintroduced, chemotherapy should not be given on days when two fractions of radiation are given.
- Combined cisplatin and tirapazamine doses on the experimental arm may be delayed for up to 4 days if required (longer if radiotherapy has also been delayed). If severe chemotherapy toxicity persists for more than 2 weeks the chemotherapy drug related to that toxicity should be definitively discontinued.
- If cisplatin has been terminated due to toxicity, tirapazamine may still be given in weeks 4 and 7. Tirapazamine alone doses in weeks 2 and 3 that cannot be given on the scheduled day due to toxicity will be omitted rather than delayed, unless radiotherapy had to be delayed as well.
- If radiotherapy is interrupted, missed doses of radiotherapy should be made up. If chemotherapy is delayed or ceased due to toxicity then radiotherapy should continue to be given according to protocol.
- No chemotherapy will be administered after completion of radiotherapy.

Chemotherapy toxicity will be graded according to the Common Toxicity Criteria (CTC Version 2.0 Publish Date: April 30, 1999) (Appendix 7).

**5.2.2 Management of neutropenia**

The dose limiting toxicity in the Phase I trial has been neutropenia, which only occurred in the last 2-3 weeks of treatment. Preliminary analysis of the first 50 patients in the randomized phase II trial showed that 30% percent of the patients on the tirapazamine arm had Grade 3 neutropenia and 3% had grade 4 neutropenia. 12% of the patients on the tirapazamine arm had febrile neutropenia. Although the neutropenia is often mild, it occurs when the acute mucous membrane and skin toxicities are at a maximum and when the patients are at a high risk of aspiration pneumonia. During the period when the patients are at greatest risk of febrile neutropenia (weeks 5-7) patients on both arms should check their temperatures twice a day and notify their physician of temperatures greater than 38°C. Patients who develop febrile neutropenia must be managed carefully and aggressively with fever work-up including blood cultures and chest x-ray and intravenous antibiotics.

**5.3 Post-chemoradiation neck surgery**

Two months following completion of chemoradiotherapy, patients will have an evaluation described under assessments (6.1).
Provided there has been a complete response at the primary site, there are 3 management strategies for residual resectable neck masses that can be adopted on this trial. Each institution must elect at the outset which of these 3 policies it wishes to adopt for this trial, and consistently apply the policy. The 3 policy options are:

1) If there is a residual mass in the neck either clinically or radiologically, a planned selective neck dissection will be performed.

2) If the neck mass is regressing, it will be kept under surveillance at monthly intervals up to a further 6 months (8 months following end of treatment) with surgery being allowed at any time if the mass ceases regressing.

3) Planned neck dissection will be undertaken in all patients with baseline N2 (> 3 cm) or N3 disease irrespective of response in the neck, provided there has been a CR at the primary site. If bilateral neck dissections are planned, they should be done as separate procedures. Institutions adopting this option must declare if they will use policy 1 or 2 for residual neck masses from nodes initially ≤ 3 cm.

With policies 1 and 2, no neck dissection will take place if there has been a clinical and radiological CR in the neck at the 2-month evaluation. Regardless of the policy adopted for the management of the neck, any surgical intervention requires that residual nodal disease be deemed completely resectable.

Patients who are thought to be in clinical CR at the primary site but have a minor residual imaging abnormality will be assumed to be in CR for the purposes of deciding about neck surgery. When there is considerable edema at the 2-month evaluation, e.g. laryngeal cancer, that makes the clinical and imaging determination of CR at the primary site difficult, sites that have adopted policies 1 and 3, may revert to policy 2 for these patients. This will allow more time to clarify the response at the primary site prior to any neck dissection.

5.4 Investigational product

Tirapazamine will be supplied by Sanofi-Synthelabo. 250ml of Tirapazamine will be supplied as a clear yellow-orange liquid (0.7 mg/ml) in an isotonic citrate buffer with a pH between 3.7 and 4.3 in 300 ml bottles. Tirapazamine is supplied in solution form that will not need dilution. The total dose of tirapazamine for each subject scheduled to receive this drug should be transferred from the supplied bottles into a chemotherapy bag/bottle and must be administered via infusion pump for the stated time interval. Tirapazamine will not be administered with a diluent unless specifically stated.

The dose of tirapazamine (TPZ) will be calculated as follows:

$$\frac{BSA (m^2) \times TPZ \text{ dose (mg} / \text{m}^2)}{0.7 \text{ mg} / \text{mL}} = TPZ \text{ volume (mL)}$$

Thus, for a subject with a BSA (body surface area) = 1.85 m² treated at a tirapazamine dose of 290 mg/m², the volume of tirapazamine to be administered would be 766 ml.
Volumes of the bottles may fluctuate slightly. However, when the entire bottle containing the expected 250 ml of solution is planned to be used, one can assume the volume is correct and the actual volume does not need to be measured. The possible excess is less than 3.5%. Note that the subject's weight and BSA must be re-evaluated prior to each treatment cycle, with corresponding adjustment of dose as appropriate.

Information on expiration dates of tirapazamine will be supplied on a lot-by-lot basis. The Sponsor will notify the Investigator of any lots that are about to expire, and replacement supplies will be shipped. All cancer chemotherapeutic agents should be handled with utmost care during preparation and administration. To avoid any form of physical contact with the drug by the health care provider, gowns, gloves, and masks should be worn when appropriate. As a parenteral agent, tirapazamine should be prepared in a vertical-flow biologic safety cabinet. Refer to hospital guidelines for any additional precautions that may apply.

Cisplatin will be handled in accordance with standard procedures for these cytotoxics at the institution.

5.5 Method of assigning patients to treatment group

Randomization will only be done after all phases of radiation planning have been completed. At sites where PET-FDG scans are being performed prior to treatment, the results must be reviewed before randomization. Randomization should take place as close as possible but not more than 2 weeks prior to the anticipated start of treatment. Treatment assignment will be done centrally, by stratifying for disease stage (III v IV), primary site (oropharynx/larynx v hypopharynx/oral cavity), and hemoglobin (≥13.5 g/dL for men and ≥12.5 g/dL for women v otherwise). A dynamic allocation method will be used to avoid extreme imbalance of treatment assignment within an institution.

5.6 Packaging and labeling

250mL of tirapazamine 0.7 mg/mL solution is supplied in 300mL bottles.

Tirapazamine bottles are individually labelled with a booklet label, with text in all languages of the participating countries, and a separate label containing variable information (product batch number).

Four bottles are packaged in a labelled and sealed outer box, with a foam insert to hold the bottles in place, and either an absorbent pad (placed under the bottles) or absorbent sachets (placed alongside) in case of breakage. Each outer box is sealed in a polythene bag.

Outer cartons are labelled with booklet labels, a label “4x” to indicate that 4 bottles are in the carton and a label which details batch number and expiry date.
5.7 Storage conditions

Information on expiration dates of tirapazamine will be supplied on a lot-by-lot basis. The Sponsor will notify the Investigator of any lots that are about to expire, and replacement supplies will be shipped.

Tirapazamine must be stored between 15° C and 30° C in the light proof packaging provided. During administration to subjects Tirapazamine must be protected from light, though it is not necessary to protect infusion lines. As an investigational agent, tirapazamine must be kept in a secure area and may be supplied only to subjects treated under the direction of the Investigator and in accordance with this protocol.

Cisplatin will be stored in accordance with standard procedures for these cytotoxics at the institution.

5.8 Responsibilities for investigational product

The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense Investigational Product will be responsible for ensuring that the Investigational Product used in the study is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

All Investigational Product shall be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of Investigational Product issued and returned is maintained.

Under no circumstances will the Investigator supply Investigational Product to a third party, allow the Investigational Product to be used other than as directed by this protocol, or dispose of Investigational Product in any other manner.

5.9 Retrieval and/or destruction of investigational product

- All partially used treatments should be destroyed at the site. A detailed treatment log of the destroyed supplies will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.
- At the end of the trial or upon for expiration.
- The Investigator will destroy the unused Investigational Product after written authorization by the Sponsor or Sponsor's representative.

5.10 Concomitant therapy

5.10.1 Not permitted concomitant therapy

Concomitant therapy with agents known to have anticancer activity (including systemic retinoids) is not permitted during the treatment phase of the study. Erythropoietin is not allowed while the patient is on study.
Subjects may not participate in any other protocols using investigational treatment(s) or procedure(s) while participating in the treatment phase of this trial, except those that may be directly related to this trial and approved by the Trial Management Committee.

5.10.2 Permitted concomitant therapy

Medications used for the treatment of pre-existing illnesses or new symptoms and illnesses are permitted unless they are not permitted (refer to the Section 5.10.1). G-CSF and GM-CSF are allowed for use during or after an episode of febrile neutropenia, but their use must be recorded. However, G-CSF or GM-CSF must stop 24 hours before any chemotherapy is administered. G-CSF should not be used prophylactically. The unexpected finding has been reported that G-CSF had a negative impact on local control and survival in a study that first randomized patients to receiving either hyper fractionated (HF) accelerated radiochemotherapy or hyper-fractionated accelerated radiotherapy in advanced H&N cancer followed by a second randomization to evaluate the prophylactic use of G-CSF.

6. OUTCOME ASSESSMENT

6.1 Efficacy

6.1.1 Clinical assessment methods

The secondary endpoints require the determination of disease status at the end of the treatment phase and sequentially thereafter. It is highly important to have objective definitions and measures of clinical status since there is a concern that bias can be introduced with the proposed definition of loco-regional failure.

Clinical follow-up examinations will be performed by members of a qualified head and neck cancer team nominated by each institution. Physical examination will include direct inspection and palpation of accessible sites and fiberoptic endoscopy. The neck will be examined by palpation. Imaging will be done at defined times (specified below) or at any time there is clinical suspicion of recurrence or progression. Biopsy or cytological confirmation of recurrent disease should be obtained whenever possible.

Imaging (CT or MRI depending on which was done prior to treatment) of primary site and neck will be performed at 2 months after treatment and prior to any surgery. Patients with a clinical and radiological CR in the neck will not undergo neck dissection, unless the treating center has adopted a policy of routine neck dissection in all patients with baseline N2 (>3 cm) or N3 disease (Section 5.3). Radiological CR requires that any residual nodal tissue is <1cm in maximum diameter and of homogeneous (non-necrotic) appearance. For centers with PET capability, there must be no residual metabolic activity on ¹⁸F-FDG scanning.

Following the 2-month assessment, patients will be reviewed for disease status and toxicity assessments at least every 2 months the first year, every 3 months the second year and every 4 months the third year. Imaging will be repeated every 4 months for the first
year and then every 6 months or until study cut-off. Please see flow chart for other assessments.

6.1.2 Criteria of efficacy

6.1.2.1 Primary criteria

The trial will compare the efficacy and safety of concomitant chemoradiation with tirapazamine, cisplatin, and radiation versus cisplatin and radiation. The primary endpoint will be overall survival.

6.1.2.2 Secondary criteria

Secondary endpoints include the following:

- Time to locoregional failure with date of randomization as the start date. Locoregional failure is defined in this study as the presence of persistent progressive or recurrent disease above the clavicles (see Section 6.1.2.6).
- Failure-free survival. Failure is defined as death due to any cause, locoregional failure or development of distant metastasis.
- Patterns of failure as the initial site of failure at the primary site, neck, distant sites or combinations of these.
- Cumulative incidence of unacceptable locoregional treatment outcome as a function of time. An unacceptable outcome is defined as either locoregional failure or severe late (>90 days from the start of treatment) treatment-related toxicity which may be any of the following: grade 4 skin, subcutaneous tissue, mucous membrane or bone toxicity, grade 3 or 4 spinal cord toxicity, grade 4 laryngeal toxicity requiring tracheostomy, or the need for enteral feeding persisting beyond 12 months following completion of treatment.
- Change in QoL from baseline as assessed by FACT-H&N scale in eligible patients at 6 months post-treatment (see 6.1.2.7 QoL Evaluation).
- Toxicity and safety, determined through review of adverse events, routine symptom assessment, and laboratory determinations.
- Initial response rates defined as rates of CR, PR, SD or PD 2 months after completion of chemoradiation therapy as described in Section 6.1.2.5.
- Final CR rate as defined in Section 6.1.2.5 (d).

Additional analysis to include correlation of efficacy with baseline hypoxia measurements including F-AZA-PET (at selected sites) and blood levels of chemical markers for hypoxia as directed by the Trial Management Committee. For example, correlation of hypoxia has been studied with the serum markers, osteopontin (37) and PAI-1. Unstained slides of tumor biopsies will be collected for immunohistochemical analysis for prognostic markers such as Ki-67, HIF1α and p53.
6.1.2.3 Measurement of response

The initial response will be determined after all protocol treatment has been finished, whether or not all of the planned treatment is achieved. This evaluation will be performed 8 weeks after completion of chemoradiation therapy.

The RECIST (Response Evaluation Criteria in Solid Tumors) criteria, as modified below, will be followed for assessment of tumor response (38). These criteria are a revised version of the World Health Organization (WHO) criteria originally published in 1979. The RECIST criteria were developed by a consensus group (including the WHO, NCI Canada, NCI U.S., cooperative oncology groups and industry). The RECIST criteria require confirmation of responses with a second study. This trial does not conform to the usual chemotherapy trial with repeated doses of chemotherapy where confirmation makes sense. In this trial, response will only be measured after a discrete period of concomitant therapy. A confirmatory study after the concomitant therapy would not be appropriate since the initial assessment will occur 8 weeks after the completion of chemoradiotherapy.

6.1.2.4 Definition of measurable/non-measurable disease

The following definitions of measurable and non-measurable disease will be used:

- **Measurable disease**: lesions that can accurately be measured in at least one dimension as ≥2.0 cm with conventional techniques or as ≥1.0 cm with spiral CT scan. The longest diameter (LD) will be recorded.
- **Non-measurable disease**: all other lesions, including those with a longest diameter <2.0 cm with conventional techniques or as <1.0 cm with spiral CT scan.

6.1.2.5 Definition of response

Responses will be recorded separately for the primary site and the neck.

6.1.2.5.1 Primary site

RECIST criteria will be modified to take into account clinical (which must include fiberoptic examination for sites not amenable to direct inspection) and radiologic findings.

- **Complete Response (CR)**: Complete disappearance of the primary tumor. A CR requires that there is no evidence of disease (other than an equivocal imaging abnormality at the primary site) by both clinical and radiologic criteria.
- **Partial Response (PR)**: Decrease by 30% or greater in the LD of the primary lesion in reference to the baseline LD by both clinical and radiological criteria; or decrease by 30% or greater in the LD of the primary lesion by radiologic criteria associated with definite regression by fiberoptic endoscopy in sites not amenable to direct clinical measurement; or decrease by 30% or greater in the LD of the primary lesion by direct clinical measurement in a lesion that is not measurable radiologically; or definite regression by fiberoptic endoscopy in a lesion that is not measurable either clinically or radiologically.
• **Stable disease (SD):** Failure to observe CR or PR as described above, in the absence of progressive disease.

• **Progressive Disease (PD):** At least a 20% increase in the LD of the primary lesion measured clinically or radiologically in reference to the smallest LD recorded since initiation of treatment; or definite evidence of progression by clinical (including fiberoptic) examination for non-measurable lesions.

### 6.1.2.5.2 Neck nodal disease

When assessing initial disease status, nodes which are not palpable but which may be noted on CT/MRI scans with diameters of < 1 cm should not be considered a site of disease unless there is other evidence of involvement e.g., necrotic center.

• **Complete Response (CR):** Complete disappearance of all tumor lesions. When assessing the response of initially involved nodes, all of which regress completely clinically but persist on CT/MRI with a diameter < 1 cm and without central necrosis, a CR should be scored.

• **Partial Response (PR):** Decrease by 30% or greater in the sum of LD of all nodal lesions in reference to the baseline sum LD, both clinically and radiologically. No nodal lesions should have progressed and no new nodal lesions should have appeared.

• **Stable disease (SD):** Failure to observe CR or PR as described above, in the absence of any progressive or new lesions.

• **Progressive Disease (PD):** At least a 20% increase in the sum of LD of all nodal lesions in reference to the smallest sum LD recorded, either clinically or radiologically, since initiation of treatment and/or the appearance of any new nodal lesions.

### 6.1.2.5.3 Initial response assessment

Response to treatment (CR, PR, SD, or PD) will be assessed only at 8 weeks post-treatment, prior to any neck dissection. Subsequent evaluations will be based solely on whether or not locoregional failure has occurred.

Patients who are clinically in CR but have a residual imaging abnormality at the primary site will be classified as ‘response pending’. Documentation of stable imaging appearance on 2 consecutive CTs at least 4 months apart without any clinical evidence of recurrence will result in classification of their response at 8 weeks as CR.

### 6.1.2.5.4 Final complete response rate

It is recognized that response rates in the neck at 8 weeks will underestimate the true pathologic CR rate. This will be estimated retrospectively as the proportion of patients who ever achieve CR without surgery or have negative pathology at planned neck dissection with primary disease controlled.
6.1.2.6 Definition of locoregional failure

Locoregional failure is defined for this study as the occurrence of persistent, progressive, or recurrent disease above the clavicles. Patients with persistent primary disease at the two-month post-treatment assessment will be regarded as having failed at the time of that assessment. Because a planned neck dissection for persistent (but not progressive) resectable nodal masses is part of the treatment “package”, pathologic evidence of residual tumor in the neck dissection specimen will not be regarded as a locoregional failure. Patients with residual neck masses who do not undergo neck surgery will be deemed as having failed only at the time of progression. Patients who undergo neck dissection for residual disease, which is found to be unresectable, will be deemed to fail at the time of surgery. Date of progression or recurrence is defined as the date of a measurable event, either clinical, radiological or pathological. Clinically or radiologically manifest tumor recurrence should be confirmed by biopsy or cytology whenever possible.

Patients with a clinical CR at the primary site who have a residual imaging abnormality at the primary site will undergo further imaging 4 months later and will be deemed to have locoregional failure in the primary site only if the imaging abnormality progresses. Some patients with laryngeal primaries may be unassessable at the 2-month post-treatment evaluation because of edema of the larynx. Such patients should be continued to be followed clinically and radiographically. These patients will be classified as locoregional failure only if and when progression is documented. In the absence of a target lesion biopsy is not recommended. For unusual clinical scenarios not covered above, a ruling of the occurrence of locoregional failure will be submitted to the principal investigators who will make a decision without knowing the treatment arm.

Patients with distant metastasis will continued to be followed for locoregional failure status.

Second primary cancers

A newly diagnosed cancer arising in any site involved by or adjacent to the index cancer must be designated as a local recurrence (e.g. epiglottis and base of tongue). A second primary neoplasm can only be declared when the second lesion is in a non-adjacent subsite (e.g., soft palate and glottic larynx) or is contralateral to an index cancer, which did not approach the midline (e.g., right and left tonsil).

6.1.2.7 Quality-of-life evaluation

To maximize the ability of a questionnaire to discriminate between groups of patients and to respond to changes in QoL between patients, it is necessary to choose a disease-specific instrument that measures the concerns of patients with head and neck cancer (39). To maximize the reliability and internal validity of the QoL results, participants must complete their own questionnaires without family input. To maximize the validity and generalization of QoL results, all eligible patients should participate in the QoL component of the study. Thus, the questionnaire must be available in the multiple languages in use at the participating centres. For QoL results to be interpretable, a standard questionnaire with known validity and reliability must be used.
QoL assessment is mandatory in all patients, excluding only those who meet the following criteria:

1) Inability to comprehend at least one of the following languages: (English, Dutch, French, German, Italian, Norwegian, Spanish, Swedish, Portuguese, Hungarian, Russian, Chinese, Polish)
2) Inability to comprehend QoL questions due to cognitive or psychiatric deficits.
3) In blind or illiterate patients the FACT-H&N should be administered verbally.

Whenever possible, all QoL assessments should take place during the scheduled clinic visits, and prior to the physician's assessment.

6.1.2.7.1 FACT-H&N Quality-of-life questionnaire

For this study, the FACT-H&N has been chosen. The FACT-H&N, developed by Dr. David Cella and colleagues in the United States (40), comprises a core questionnaire called FACT-G, and a disease-specific subscale. It was designed for descriptive, discriminative and evaluative use (41). The core questionnaire and head and neck modules have been tested for reliability and validity (41, 42, 43). Clinical trials have shown improvements in scores with time from treatment, which is a preliminary indicator of responsiveness (43, 44, 45). The minimal important difference, a measure of the clinical significance of a small change in questionnaire scores over time, has been measured and corresponds to a 5-10% difference in score (46). Patients typically complete the questionnaire in 10-15 minutes (47).

The FACT instruments are self-administered multi-item indices using category-rating scales. FACT-G consists of 27 questions in 4 domains: physical (7 questions), social/family (7 questions), emotional (6 questions), and functional (7 questions). The 38-item FACT-H&N also includes an 11-item head and neck cancer specific subscale. Each response is rated from 0-4 on a Likert index, considering the past 7 days.

Items H&N8 and H&N9 are currently not scored. For all other items, scores are calculated separately for each domain. Scores range from 0 to 28 for physical, social, and functional domains and from 0 to 24 for the emotional dimension. An unweighted summary score is calculated for the FACT-G and the total FACT-H&N. The maximum score of 144 (27 + 9 = 36 items scored between 0 and 4) reflects the best possible quality of life. Because pain is often a dominant symptom of recurrent head and neck cancer, item GP4 of FACT-G (I have pain) will also be analyzed as a single item pain index. Analgesic use will therefore also be assessed at the time of each QoL assessment.

6.1.2.7.2 Timing of assessment

Quality of life and pain will be assessed at the following time points: at baseline (prior to treatment), 2 months post treatment, 6 months post-treatment, 12 months post-treatment, 24 months post-treatment and 36 months post-treatment.

6.2 Safety

Toxicity and safety will be determined through review of adverse events, routine symptom assessment, and laboratory determinations.
6.3 Pharmacokinetics

Not applicable.

7. PATIENT SAFETY

7.1 Adverse events monitoring

Definitions:

An Adverse Event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A Serious Adverse Event is any untoward medical occurrence that at any dose:
• Results in death or
• Is life-threatening or

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

• Requires in-patient hospitalization or prolongation of existing hospitalization or
• Results in persistent or significant disability/incapacity or
• Is a congenital anomaly/birth defect.
• Is a medically important event

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

These should also usually be considered serious.

Note: Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions or symptomatic ALT increase * 10 ULN that do not result in hospitalization, or development of drug dependency or drug abuse.

Adverse Events
All Adverse Events regardless of seriousness or relationship to study drug, including those occurring during the wash-out period (where applicable), are to be recorded on the corresponding page(s) included in the Case Report Form. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, maximal intensity, action taken with respect to study drug, corrective therapy given, outcome and his/her opinion as to whether there is a reasonable possibility that the Adverse Event was caused by the study drug.
**Serious Adverse Events**

In the case of a Serious Adverse Event the Investigator must immediately:

- **SEND** (within 1 working day, preferably by fax) the signed and dated corresponding page(s) in the Case Report Form to the representative of the Monitoring Team whose name and address and fax number appear on the protocol;
- **ATTACH** the photocopy of all examinations carried out and the dates on which these examinations were performed. For laboratory results, include the laboratory normal ranges.

**Follow-up**

- The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up on the outcome of any Adverse Events (clinical signs, laboratory values or other, etc.) until the return to normal or until consolidation of the patient conditions.
- In the case of any Serious Adverse Event, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the study and that additional investigations may be requested by the Monitoring Team.
- In case of any Serious Adverse Event brought to the attention of the Investigator at any time after cessation of study treatment and considered by him/her caused by the study drug with a reasonable possibility, this should be reported to the Monitoring Team.

**Grading adverse events:**

Acute radiation and all chemotherapy toxicities will be graded using CTC Version 2.0 (Appendix 7). In the case of toxicities within the irradiated volume occurring from the 2-month follow-up visit onwards, the RTOG Late Radiation Toxicity scale (Appendix 8), modified to include pharyngeal toxicity and ototoxicity, will be used. An exception relates to acute mucositis, which must be graded according to the CTC criteria until it has resolved to grade 1.

**7.2 Laboratory tests monitoring**

See Study Procedures (Section 9) the tests needed.

**7.3 Safety instruction**

The following events, should they meet the criteria of seriousness, are not to be considered as SAE:

- any non fatal event secondary to documented cancer progression. These events are collected elsewhere in the CRF since they do not impact the endpoints of the study. The cases of death related to cancer progression are reported as SAEs as usual.
- any event that is included in the cancer management such as hospitalization for insertion of a central venous catheter device or an enteral feeding tube.
8. PATIENT WITHDRAWAL

8.1 Criteria for withdrawal from treatment

Protocol treatment should be discontinued if it is considered to be in the best interest of the patient. Reasons for treatment discontinuation include:
1) Patient request
2) Patient non-compliance with the protocol
3) Life threatening or other unacceptable drug-related toxicity
4) Progressive disease
5) Physician decision in view of patient’s other medical conditions.

When treatment is discontinued, the reason(s) for discontinuation should be documented in the patient’s medical record and CRF, and follow-up should be maintained and reported. When discontinued from protocol treatment, patients will still be followed as defined in the protocol.

8.2 Withdrawal from study

The patients may withdraw from the study if they decide to do so, at any time and irrespective of reason, or this may be the Investigator’s decision.

8.3 Withdrawal from follow-up

For patients considered lost to follow-up, the CRF must be filled in up to the last visit performed. The Investigator should make every effort to re-contact and to identify the reason why the patient failed to attend the visit and to determine his/her health status.

8.4 Consequence

Patients who have been withdrawn from the study cannot be re-included in the study. Their inclusion and treatment number must not be re-used.

9. STUDY PROCEDURES

9.1 Screening and baseline procedures

Baseline evaluations including radiological exams and fiberoptic endoscopy must be performed not longer than four weeks prior to initiation of treatment. Baseline evaluations must include:
- A detailed medical and surgical history, including age, gender, ethnic origin, medication list, performance status
- The cancer history of the patient including: cancer diagnosis (site and histopathology), current status, prior chemotherapy, prior cancer surgery, prior radiation.
- A complete physical examination including fiberoptic endoscopy carried out by one of the investigators. PE must include: body systems described on the CRF, height, weight, BSA, vital signs (BP/HR/T)
• Biopsy if not already performed  
• Mandatory radiologic assessment (head and neck CT or MRI and chest CT)  
• Consultation from radiation and medical oncology (required) and surgery (recommended).  
• Further diagnostic procedures as clinically indicated e.g. panendoscopy.  
• Laboratory screening including:  
  - Hematology: hemoglobin, WBC with differential count, absolute Neutrophil count (ANC), and platelets  
  - Biochemistry: sodium, potassium, chloride, bicarbonate, calcium, magnesium, urea, glucose, creatinine, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, and total bilirubin  
  - Creatinine clearance  
  - Serum Pregnancy Test: women of childbearing potential are required to have a serum beta-HCG pregnancy test.  
• Audiogram  
• Baseline QoL measurements  

An extra plasma/serum sample will be collected for hypoxia marker studies. When available, unstained slides of the tumor biopsy should be collected. Please send 10 slides when available but a minimum of 2.  

At selected sites with PET scanning capabilities, baseline FDG-PET scan and F-AZA-PET scanning will be done for metabolic activity and hypoxia determination.  

Instruction for extra sample collection for hypoxia and biological markers:  

• Blood sample will be drawn before study treatment administration, during the study treatment period (week 5 or 6), at 2 months and 8 months following completion of the treatment. Blood samples will be collected on Becton-Dickinson 5 ml EDTA tubes.  
• Immediately after sample collection, the tubes will be centrifuged at 1500 g for 10 minutes at room temperature. The plasma will be collected with sterile pipettes, transferred into properly labelled polypropylene tubes (Sarstedt 60.558 Polypropylene screw-cap 5ml tube) and deep-frozen at -20°C.  
• The day of sampling must be recorded in the CRF.  
• One properly labelled, freeze-resistant, box will be provided per centre for storage plasma aliquots at -20°C.  
• Labeling:  
  The tubes will be identified with pre-printed stickers. Each sticker will bear the following:  
  - Protocol number: EFC4690  
  - Drug code: SR259075  
  - Sample number: P0 to Pn  
  - Subject number  
  - Centre n°:  

The following will be printed on the label affixed to the freeze-resistant box.  
  - Protocol number: EFC 4690
Shipment of the samples:
At the end of the study, or before if required, the samples bearing the mention "To be kept at -20°C on carbon ice packs. Biological samples" will be sent to:

Barbara Knight
Sanofi-Synthelabo Research
9 Great Valley Parkway
Malvern, PA 19355 - U.S.A.
Phone: 1.610.889-6071 or (610)889-6056 (to leave message)
Fax: 1.610.889-6356
Email: barbara.knight@sanofi-synthelabo.com

Contact Mrs. Knight prior to shipment with date of shipment and airbill number. No sample should be sent later in the week than Tuesday after 4 PM and not on the event of any public holiday.

Unstained slides from pre-treatment tumor biopsy (when available) should be labelled and sent with the submission form to:

Barbara Knight
Sanofi-Synthelabo Research
9 Great Valley Parkway
Malvern, PA 19355 - U.S.A.
Phone: 1.610.889-6071 or (610)889-6056 (to leave message)
Fax: 1.610.889-6356
Email: barbara.knight@sanofi-synthelabo.com

9.2 Inclusion procedure
During the screening process, it will be determined if patients qualify for the study by the inclusion and exclusion criteria. If significant clinical changes occur prior to the initiation of therapy, a reassessment should occur.

All patient with their own teeth require a dental evaluation.

9.3 Description by type of visit

9.3.1 Concomitant chemoradiation therapy period
Please see flow chart for details of assessments. Concurrent chemotherapy and radiation is frequently associated with significant acute severe toxicity that requires as standard of care frequent follow-up during treatment and immediate post-treatment period.
Biochemistry assessment will be done weeks 1, 4 and 7. Weekly hematology assessments will be done. In weeks 5-7 hematology assessment will be done twice weekly. Hematology assessment will include: hemoglobin, WBC, absolute neutrophil count (ANC), and platelets. Biochemistry assessment will include sodium, potassium, chloride, bicarbonate, calcium, magnesium, urea, glucose, creatinine, total protein, albumin, SGOT (AST), SGPT (ALT), alkaline phosphatase, and total bilirubin. Toxicity assessment will be performed weekly.

Toxicity assessment will be done at two weeks after radiation is completed. Patients with severe acute toxicities will require weekly follow-up.

9.3.2 Four-weeks follow-up visit

The patient will have a follow-up visit 4 weeks after the last radiation therapy. Please see flow chart for details of assessments.

9.3.3 Follow-up visits

Following the 2-month assessment, patients will be reviewed for disease status and toxicity assessments at least every 2 months the first year, every 3 months the second year and every 4 months the third year. Imaging will be repeated every 4 months for the first year and then every 6 months. Please see flow chart for other assessments.

9.4 Definition of source data

Source data is defined as all information in original records of clinical findings, observations, or other activities of the clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are the original documents, data and records. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes and reports, radiologic films and reports, memoranda, subject’s quality of life assessments, and pharmacy dispensing records.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical and analytical plans

This protocol contains a general description of the statistical design and of the analyses that will be done to compare Arms 1 (cisplatin + radiotherapy) and 2 (cisplatin + tirapazamine + radiotherapy) for the primary endpoint of overall survival. Methods are also described for the analysis of secondary efficacy endpoints and safety.
10.2 Determination of sample size

The sample size of 275 per treatment arm will provide at least 80% power for the survival comparison under the following assumptions:

- Survival in the control arm is 60% at 2 years and 51% at 3 years. Beyond 3 years, the mortality risk (hazard rate) will be 0.05 death per patient per year.
- The test population will experience a 31% reduction in the risk of mortality, compared to the controls. This would produce a survival rate of 70% at 2 years and 63% at 3 years. For patients surviving beyond 3 years, the mortality risk would be 0.0345 patients per year.
- 1.5 year accrual period, with 2.5 years of follow-up after enrollment of the last patient.
- Type I error of 0.05 with 2-sided log rank test.
- Constant hazard rates in each treatment arm during the periods 0 - 2 years, 2 – 3 years, and 3 + years.
- Constant accrual rate.

The control arm specifications and the difference this trial is powered to detect are based on a review of similar trials in this disease (Section 1.5).

The cutoff date for patients included in the final survival analysis is planned to be the date of the 240th death.

An analysis of time to locoregional failure will be done with a two-sided logrank test when 150 patients have reached this endpoint. The logrank test will be stratified for the factors disease stage (III v IV), primary site (oropharynx/larynx v hypopharynx/oral cavity), and hemoglobin (≥13.5 g/dL for men or ≥12.5 g/dL for women v otherwise). The analysis of locoregional failure has at least 85% power to detect a difference in postulated locoregional failure rates of 40% in the control arm versus 25% in the experimental arm with a two-sided test at the 0.05 level. It is assumed that among the patients who do experience locoregional failure, the yearly event probability will be 0.7. Under trial assumptions the analysis of locoregional failure will occur approximately 2.5 years after the start of the study.

10.3 Study patient description

All randomized patients with previously untreated squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx will be considered in the intent-to-treat population.

All patients who receive at least one dose of the assigned study treatment will be included in the safety analysis.

10.3.1 Disposition of patients

The numbers of patients who are randomized will be shown by treatment arm. The number of post-randomization discontinuations will be displayed by treatment arm and reason for stopping treatment. Follow-up status after discontinuation will be summarized.
10.3.2 Protocol deviations

Listings of patients with identified protocol deviations will be provided. Major protocol deviations include, but are not limited to,

- Violation of inclusion/exclusion criteria.
- Receipt of chemotherapy or radiotherapy regimens not specified in the protocol.
- Failure to follow dose modification procedure in the protocol.
- Receipt of concomitant anti-cancer treatment prohibited by the protocol.
- Missing data in key efficacy or safety parameters.

10.4 Data analysis considerations

10.4.1 Dataset analyzed

10.4.1.1 Treatment group considered for statistical analysis

Two treatment groups are in this study: Cisplatin + Radiotherapy (Arm 1) versus Cisplatin + Tirapazamine + Radiotherapy (Arm 2).

10.4.1.2 Populations to be analyzed

Primary statistical analysis will be done following intent to treat principles (see Section 10.3.).

All patients who receive assigned study treatment will be included in the safety analysis.

10.4.2 General Statistical Approach

The log rank test, stratified for the factors of disease stage (III v IV), primary site (oropharynx/larynx v hypopharynx/oral cavity), and hemoglobin (≥13.5 g/dL for men or ≥12.5 g/dL for women v otherwise) will be used to compare the treatment groups for time-related parameters, such as survival, time to locoregional failure and failure free survival. Categorical parameters, such as response rate, will be evaluated using the chi-squared test. Repeated measurement data, like QoL will be compared by change from the baseline at fixed time points. The primary QoL outcome will be a comparison of change from baseline in FACT H&N score at the 6-month assessment between control and experimental groups using Student’s t-test.

Characteristics of subjects assigned to the two treatment arms will be summarized. These include sex, race, age, weight, height, performance status, histology, stage of disease, and measurable disease by RECIST criteria, time since diagnosis, presence of other disease conditions, and clinical laboratory tests.
10.4.3 General conventions

10.4.3.1 General rules for data handling of missing, unused or inconsistency data

In general there will be no imputation of missing data. In the time to event analyses missing data due to reasons other than the defined event will be considered censored. For the repeatedly measured variables, the amount of missing data will be described for each treatment arm.

10.4.3.2 Other specific conventions

N/A

10.5 Demographic and baseline characteristics

Demographic and baseline characteristics will be summarized by treatment arm. Continuous variables (such as age, weight, etc.) will be summarized using the mean, standard deviation, minimum, and maximum. Qualitative characteristics (such as race, disease stage, etc.) will be summarized by counts and percents.

10.5.1 Patient demographic characteristics, medical history and diagnoses

Patient demographic characteristics include country, age, weight, sex, race, and performance status. Medical history will include all information collected in the relevant CRF. Diagnosis information will include primary site, disease stage, and laboratory tests.

10.5.2 Previous medications

Patients should not receive any prior treatment for the indicated disease before entering the study. The numbers of patients violating this criterion will be displayed.

10.5.3 Baseline efficacy/activity data

Baseline QoL data will be summarized by treatment arm.

10.5.4 Baseline safety parameters

Baseline laboratory data will be summarized by treatment arm.

10.6 Study drug and concomitant therapy

10.6.1 Study treatment

Exposure to tirapazamine, cisplatin and radiation will be summarized for each treatment arm.
10.6.1.1 Extent of exposure

The number of cycles administered, total cumulative dose, duration of dosing, and dose intensity for cisplatin and tirapazamine will be summarized by treatment arm.

10.6.1.2 Measurement of treatment compliance

N/A

10.6.2 Concomitant medication/therapy

Concomitant medications will be coded to drug class, and the percentage of patients using drugs from each class will be summarized by treatment arm.

10.7 Efficacy / activity analysis

10.7.1 Primary efficacy variable(s)

10.7.1.1 Description of the primary variable(s)

Overall survival measured from the date of randomization to the date of death from any cause will be the primary endpoint. Overall survival will be censored by the cutoff date or the date of last follow-up for patients lost to follow-up.

Time to locoregional failure measured from the date of randomization to the date of locoregional failure is a secondary endpoint. Locoregional failure is defined as the presence of persistent, progressive or recurrent disease above the clavicle (see Section 6.1.2.6) Time to locoregional failure will be censored by the cutoff date, the date of last follow-up for patients lost to follow-up, or death.

Safety will be assessed through review of adverse events, routine symptom assessment, and laboratory determinations.

10.7.1.2 Primary analysis

The log rank test, stratifying for the factors disease stage (III vs IV), primary site (oropharynx/larynx vs hypopharynx/oral cavity), and hemoglobin ($\geq 13.5$ g/dL for men or $\geq 12.5$ g/dL for women vs otherwise), will be used for the primary analysis of overall survival. The cut-off date for patients included in the final analysis will be the date of the 240th death.

Analysis of time to locoregional failure will be done when 150 events have been observed, and results for this parameter may be reported prior to completion of follow-up for survival. Testing will use the stratified logrank test, will be two-sided, and will be done at the 0.05 level.

An interim analysis of survival will be done at the same time as the analysis of time to locoregional failure, using a two-sided logrank test, stratifying for the factors disease stage...
(III v IV), primary site (oropharynx/larynx v hypopharynx/oral cavity), and hemoglobin (≥13.5 g/dL for men or ≥12.5 g/dL for women v otherwise).

The interim test for overall survival will be done at a level determined by the O’Brien – Fleming alpha spending function \([2 - 2 \times \Phi(Z_{\alpha/2}/\sqrt{t^*})]\), where \(\Phi\) is the cumulative distribution function for the standard normal, and \(t^*\) is the proportion of deaths out of 240 that will be observed at the cutoff date for the locoregional failure analysis.\] (48). This spending function requires highly significant early differences in order to stop early and requires minimal adjustment of the level of the final test.

**10.7.1.2.1 Handling of dropouts or missing data**

Patients who are lost to follow up before reaching the primary endpoint will be censored in the primary analysis.

**10.7.1.2.2 Data transformation before analysis, if any**

Not applicable.

**10.7.1.2.3 Main statistical model and adjustment for covariates**

Not applicable.

**10.7.1.2.4 Multiple comparisons/multiplicity**

Analyses of overall survival will include an interim test conducted at the time of the analysis of locoregional failure. The level of this test will depend upon the proportion of the expected number of 240 deaths that have been observed (Section 10.7.1.2). Using an alpha-spending approach, the level of the final statistical test will be adjusted appropriately to maintain an overall type I error of 0.05.

**10.7.1.3 Other Analyses for primary variable(s)**

Not applicable.

**10.7.2 Secondary / other efficacy variables**

**10.7.2.1 Description of secondary variables**

Secondary endpoints include, but are not limited to, the following:

- Time to locoregional failure with date of randomization as the start date. Locoregional failure is defined as the presence of persistent, progressive, or recurrent disease above the clavicles (Section 6.1.2.6.)
- Failure-free survival. Failure is defined as death due to any cause, locoregional failure or development of metastatic disease. Failure-free survival will be censored by the cutoff date or the date of last follow-up for patients lost to follow-up.
• Patterns of failure as the initial site of failure at the primary site, neck, distant sites or combinations of these.
• Cumulative incidence of unacceptable locoregional treatment outcome as a function of time. An unacceptable outcome is defined as either locoregional failure or severe late (>90 days from the start of treatment) treatment-related toxicity which may be any of the following: grade 4 skin, subcutaneous tissue, mucous membrane or bone toxicity, grade 3 or 4 spinal cord toxicity, grade 4 laryngeal toxicity requiring tracheostomy, or the need for enteral feeding persisting for 12 months or more following completion of treatment. The date of unacceptable outcome based on enteral feeding will be recorded as 12 months after completion of treatment. Death will be a competing event and the cut-off date or date of last follow-up for patients lost to follow-up will be censoring events.
• Change in QoL from baseline as assessed by FACT-H&N scale in eligible patients at 6 months post-treatment (see 6.1.2.7 QoL Evaluation).
• Toxicity and safety, determined by through review of adverse events, routine symptom assessment, and laboratory determinations.
• Initial response rates defined as rates of CR, PR, SD or PD 2 months after completion of chemoradiation therapy which is described in (Section 6.1.2.5).
• Final CR rate as defined in section 6.1.2.5 (d)
• Additional analysis to include correlation of efficacy with baseline hypoxia measurements including F-AZA-PET (at selected sites) and blood levels of chemical markers for hypoxia as directed by the Trial Management Committee. For example, correlation of hypoxia has been studied with the serum markers, osteopontin and PAI-1. Unstained slides of tumor biopsies will be collected for immunohistochemical analysis for prognostic markers such as Ki-67, HIF1α and p53.

10.7.2.2 Statistical analysis of secondary variables

Approaches as described in (Section 10.4.2) will be used to analyze secondary parameters.

10.8 Safety analysis

Safety analysis will include all patients who receive at least one day of treatment. Patients who receive cisplatin but not tirapazamine will be included in the cisplatin arm1. Any patient receiving tirapazamine will be included in the cisplatin + tirapazamine arm 2.

Safety analyses for patients receiving only radiotherapy will be presented separately.

10.8.1 Adverse events

10.8.1.1 Definitions

Adverse events are recorded by episode. For each occurrence of an AE, the onset date, resolution date, maximum grade, and action taken are recorded.
10.8.1.2 Treatment-emergent adverse events

An AE is considered treatment emergent if the onset date is on or after the first day of the first cycle of study treatment. Treatment-emergent adverse events are summarized by body system and preferred term, showing the incidence and maximum grade by patient and by cycle for each treatment arm.

10.8.1.3 Deaths and serious adverse events

All deaths and the causes of death will be listed by treatment arm. Serious adverse events will be summarized and compared by treatment arm.

10.8.1.4 Adverse events leading to treatment discontinuation

Adverse events leading to treatment discontinuation will be listed, and the numbers of patients discontinuing due to an adverse event will be compared between the two treatment groups.

10.8.2 Clinical laboratory evaluations

Clinical laboratory data will be graded according to the NCI common toxicity criteria version 2.0 (April 30, 1999). The numbers of patients with any abnormality and with grade 3,4 abnormalities will be compared between the treatment arms.

10.8.3 Vital signs

A listing of vital signs will be created with abnormal values flagged.

11. ETHICAL AND REGULATORY STANDARDS

11.1 Ethical principles

This trial complies with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH, GCP guideline.

11.2 Laws and regulations

This protocol also complies with the laws and regulations of the country(ies) in which the study is performed, as well as any applicable guidelines.

11.3 Informed consent

The Investigator, (according to applicable regulatory requirements), or a person designated by the Investigator, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval / favorable opinion by the Ethics Committee (IRB /IEC ).
Prior to a patient’s participation in the clinical trial, the Informed Consent Form should be signed and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion.

The Informed Consent Form used by the Investigator for obtaining the patient’s informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval / favorable opinion.

11.4 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The Investigator must submit this protocol to the appropriate Ethics Committee (IRB/IEC), and is required to forward to the Sponsor a copy of the written and dated approval / favorable opinion signed by the Chairman with Ethics Committee (IRB/IEC) composition.

The study (study number, Protocol title and version number), the documents reviewed (protocol, Informed Consent Form, Investigator’s Brochure, etc.) and the date of the review should be clearly stated on the written (IRB/IEC) approval / favorable opinion.

Investigational Product will not be released at the study site and the trial will not start until a copy of this written and dated approval / favorable opinion has been received by the Sponsor.

During the clinical trial, any amendment or modification to the protocol should be sent to the Ethics Committee (IRB/IEC). It should also be informed of any event likely to affect the safety of patients or the continued conduct of the study, in particular any change in safety and all updates to the Investigator’s Brochure will be sent to the Ethics Committee (IRB/IEC).

If requested, a progress report is sent to the Ethics Committee (IRB/IEC) annually and a summary of the trial’s outcome at the end of the clinical trial.

12. STUDY MONITORING

12.1 Responsibilities of the Investigator(s)

The Investigator(s) undertake(s) to perform the study in accordance with this protocol, Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with the Investigational Product schedule, visit schedule and procedures required by the protocol. The Investigator agrees to provide all information requested in the Case Report Form in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents to Sponsor representatives.
12.2 Responsibilities of the Sponsor

The Sponsor of this study is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the study as regards ethics, protocol compliance, integrity and validity of the data recorded on the Case Report Forms. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.

At regular intervals during the study, the centre will be contacted, through site visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and patient compliance to protocol requirements and any emergent problems. During monitoring visits, the following points will be scrutinized with the Investigator: patient informed consent, patient recruitment and follow-up, study drug allocation, patient compliance with the Investigational Product, Investigational Product accountability, concomitant therapy use, Adverse Event documentation and reporting, and quality of data. Sections of Case Report Forms may be collected on a visit-by-visit basis.

12.3 Source document requirements

According to the guidelines on Good Clinical Practice, the Monitoring Team must check the Case Report Form entries against the source documents, except for the pre-identified source data directly recorded in the Case Report Form. The Informed Consent Form will include a statement by which the patient allows the Sponsor’s duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to source data which supports the data on the Case Report Forms (e.g. patient’s medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

12.4 Use and completion of Case Report Forms (CRFs) and additional request

It is the responsibility of the Investigator to maintain adequate and accurate CRFs designed by the Sponsor to record all observations and other data pertinent to the clinical investigation. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data; a black ballpoint pen should be used to ensure the clarity of reproduced copy of all CRFs.

Should a correction be made, the information to be modified must not be overwritten. The corrected information will be transcribed by the authorized person next to the previous value, initialed and dated.

The computerized handling of the data by the Sponsor after receipt of the CRFs may generate additional requests [Discrepancy Resolution Form (DRF)] to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be appended to the CRFs held by the Investigator and the Sponsor.
13. ADMINISTRATIVE RULES

13.1 Curriculum vitae

An updated copy of the curriculum vitae limited to the experience, qualification and training for each Investigator and Sub-Investigator (and completed FDA 1572 form and Financial Disclosure Form study under an IND) will be provided to the Sponsor prior to the beginning of the study.

13.2 Record retention in study sites(s)

The Investigator must maintain all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator must retain the study documentation until at least two years after the last approval of the marketing application, or if the application is not approved, at least two years after the formal discontinuation of clinical development of the Investigational Product.

However, applicable regulatory requirements should be taken into account in case of a longer period required.

A study site must notify the Sponsor before destroying any data or records.

14. CONFIDENTIALITY

All materials, information (oral or written) and unpublished documentation provided to the Investigators (or any company/institution acting on their behalf), inclusive of this protocol, the patient Case Report Forms and the Investigator's Brochure, are the exclusive property of the Sponsor and may not be given or disclosed, either in part or in whole, by the Investigator or by any person under his/her authority to any third party without the prior express consent of the Sponsor.

However, the submission of this protocol and other necessary documentation to the Ethics Committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Investigator shall consider all information, results, discoveries, records accumulated, acquired, or deduced in the course of the study, other than that information to be disclosed by law, as confidential and shall not disclose any such results, discoveries, records to any third party without the Sponsor’s prior written consent.

15. OWNERSHIP OF DATA AND USE OF THE STUDY RESULTS

The Sponsor retains exclusive ownership of all data, results, reports, findings, discoveries and any other information collected during this study. Therefore, the Sponsor reserves the
right to use the data from the present study, either in the form of Case Report Forms (or copies of these), or in the form of a report, with or without comments and with or without analysis, in order to submit them to the Health Authorities of any country.

Furthermore, in the event that the study generates patentable results, the Investigator (or entity acting on his/her behalf according to local requirements) shall refrain from filing patent application(s) on such results, which will be filed by the Sponsor or its designees in its own name and at its expense.

16. INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy which covers the liability of the Investigator and his/her coworkers and which is in accordance with local laws and requirements. Specific statements will be contained in an appendix where needed.

An insurance certificate will be provided to the Investigator in countries requiring this document.

17. SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by the Sponsor and inspection by applicable regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

As soon as the Investigator is notified of a future inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate at this inspection. The confidentiality of the data verified and the anonymity of the patients should be respected during these inspections.

18. PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSEOUT OF A CENTRE

18.1 Premature discontinuation of the study

The Trial Management Committee (TMC) may discontinue the study if information on the Investigational Product causes doubt as to the benefit/risk ratio, or if a demonstrably superior treatment becomes available.
18.1.1 Early stopping rules

If, after accrual of 50 patients on each arm of the study, there are 5 or more treatment-related deaths on either arm, accrual will be suspended pending detailed review of the data. If no apparent correctable causes are found, then the TMC will consider early termination of the trial. (This rule is based on specifying 3% as the maximum acceptable treatment-related death rate in this group of patients, and determining that if 3% is the true rate, then the probability of observing 5 or more deaths is ≤0.05)

The overall toxicity data will be periodically reviewed by the Independent Data and Safety Monitoring Committee, which may recommend to the TMC suspension of the trial at any time.

18.2 Premature closeout of a centre

The TMC may closeout a centre if the Center’s conduct of the trial is not in accordance with the procedures defined in the approved protocol or trial agreement (e.g., low rate of recruiting, protocol deviations, or failure to ensure the quality of the data collected).

An Investigator may withdraw at any time in which case he/she must notify the Sponsor of his/her decision and give the reason in writing.

In all cases, Ethics Committee(s) (IRB/IEC) and Health Authorities should be informed.

19. CLINICAL STUDY REPORT

The Sponsor will be responsible for preparing a Clinical Study Report.

20. PUBLICATIONS

It is the policy of the Sponsor to encourage the presentation and/or publication of the results of their studies, using only clean, checked and validated data in order to ensure the accuracy of the results.

The analysis for publication will be performed by the TROG statistician in collaboration with the trial statistician. The manuscript[s] for any publication[s] will be written by TROG personnel with appropriate contributions by Sanofi-Synthelabo [but with no right of veto] and collaborating clinical investigators. The Trial Management Committee will be overall responsible for presentations and/or publications. The Trial Management Committee must send a copy of the manuscript or abstract to the Sponsor for review at least forty-five (45) days before submission, and, if necessary, delay publication or communication for a limited time, not to exceed 90 days, in order to protect the confidentiality or proprietary nature of any information contained therein.
Authorship of publications will be guided by the Vancouver Agreement (49). The Sponsor may request that the Sponsor’s name and/or names of one or several of its employees appear or not appear in such publications.

All study participants (Investigators and Committee members) give full authority to the Trial Management Committee for primary presentation and/or primary publication of results. No other publication is allowed before the primary publication. Any subsequent presentation or publication by a study participant must be approved by the Trial Management Committee and make reference to the study and the primary publication.

### 21. PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this protocol.

No changes or amendments to this protocol may be made by the Investigator or by the Sponsor after the protocol has been agreed to and signed by both parties unless such change(s) or amendment(s) has/have been fully discussed and agreed upon by the Investigator and the Sponsor. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this protocol.

Amendments are required to be approved by the Trial management committee and the TROG Scientific Committee. Any amendment to the protocol requires written approval / favorable opinion by the Ethics Committee (IRB/IEC) prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the Informed Consent Form. The Investigator must receive an IRB/IEC approval / favorable opinion concerning the revised Informed Consent Form prior to implementation of the change.
Appendix M

A CKML subset for use in a Clinical Trial Report with example
The Trans-Tasman Radiation Oncology Group’s “HeadSTART” trial protocol comparing Radiotherapy with Cis-platinum with Radiotherapy with Cis-platinum and Tirapazamine is provided in Appendix L. The trial has been completed and was published in the Journal of Clinical Oncology in 2010.¹

The following pages of this Appendix consist of the handcrafted CKML specification for this report. The specification consists of the previous trial protocol with additional elements added to detail numbers of patients included and randomised, as well as numbers receiving treatment and the characteristics of the randomised groups (see TrialArmSummary tags). Towards the end of the specification, the outcome of the trial is inserted in the sections headed by the tags OutcomeAnalysis, MultivariateAnalysis, CancerOutcome and TrialOutcome.

The second document is a copy of the trial report so that numbers can be compared and verified.

¹Tirapazamine, Cisplatin, and Radiation Versus Cisplatin and Radiation for Advanced Squamous Cell Carcinoma of the Head and Neck (TROG 02.02, HeadSTART): A Phase III Trial of the Trans-Tasman Radiation Oncology Group
J Clin Oncol 28:2989-2995 2010
Phase III randomized trial of concomitant radiation, cisplatin, and tirapazamine (SR259075) versus concomitant radiation and cisplatin in patients with advanced head and neck cancer.

Outcome Analysis:
- Overall Survival
- Time to Locoregional Failure
- Failure Free Survival
- Pattern of Initial Failure Site
- Severe Treatment Related Toxicity
- Unacceptable Locoregional Treatment Outcome
- Quality of Life
- Toxicity
- Initial Response Rate
- Final Complete Response

Trial Patients: 550

Trial Power: 80%

Trial Type 1 Error: 0.05; 2-Sided Log Rank

Trial Predicted Survival Control:
- 60% at 2 years
- 51% at 3 years

Trial Predicted Survival Experimental:
- 70% at 2 years
- 63% at 3 years

Trial Centres: 80

Inclusion Criteria:
Demographics:
- Age: 18 years or older

Biological Milieu:
- Renal Function:
  - Creatinine Clearance: 55 mL/min or more
    - Creatinine Clearance Algorithm: Cockcroft-Gault

- Hepatic Function:
  - Serum Bilirubin: 1.25 x UPPER LIMIT NORMAL
  - Serum AST: 5 x UPPER LIMIT NORMAL
  - Serum ALT: 5 x UPPER LIMIT NORMAL

- Blood Function:
  - Neutrophil Count Absolute: 1.5 x 10^9/L or more
  - Platelet Count: 100 x 10^9/L or more
  - Haemoglobin: 10 g/dL or more

Psychological Milieu:
- Follow Up Reliability: YES

Exclusion Criteria:
Biological Milieu:
- Anatomy

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Article below removed for copyright reasons.

Please refer to the citation:

Appendix N

A CKML subset for use in a Clinical Practice Guideline with example
There are several bodies that have a tradition for publishing best practice guidelines. The National Comprehensive Cancer Network (NCCN) in the USA, the Scottish Intercollegiate Guideline Network (SIGN) in the UK and the British Columbia Cancer Agency (BCCA) have published guidelines for over a decade. Their approaches to guidelines are different.

The BCCA publishes their guidelines which dictate their approach to cancer management within their own service. As such, their guidelines describe a unified common approach by a defined group of clinicians to the defined problem in a single institution. The BCCA is the sole cancer treatment organisation for British Columbia. The BCCA protocols are descriptions of practice in one institution.

The NCCN is a consortium of academic centres in the USA who seek to advise the rest of the USA on what they consider is standard and non-experimental treatment. Guidelines from the USA are usually characterised by presenting the range of options acceptable in a particular circumstance. The NCCN protocols are descriptions of the boundaries of acceptable practice for a large medical community.

The SIGN is a professional collaboration of Scottish clinicians that seeks to educate decision making. Clinicians are advised about the evidence of what works and how robust that evidence is. The SIGN protocols are descriptions of the evidence underlying medical practice anywhere.

These differences lead to guidelines with different styles. The patient described in Appendix J has an locally advanced cancer of the base of tongue which is a specific anatomical part of the oropharynx. Described below is a paraphrase of each individual
guideline which is then interpreted into CKML structure defined in Appendix I.
N.1 BCCA Guideline

The BCCA Guideline can be applied to cancers of the "Base of the tongue (posterior third of the tongue)". It states that "Advanced tumours T3 T4 N0 N1 N2 N3 should be considered for a twice daily radiotherapy schedule or concurrent chemotherapy with radiotherapy if the patient is fit." Therefore when selecting management for a fit patient with a locally advanced base of tongue cancer, this guideline advises that a single daily radiotherapy schedule and concurrent chemotherapy is appropriate.
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N.2 NCCN Guideline

The NCCN guideline (ORPH-1) is also applied to cancers of the oropharynx and is more complicated. The relevant features that apply to the patient described in Appendix J are boxed in blue. As this patient was staged as T4aN2cM0, the first page clearly points to further management specified on page ORPH-4. This page provides a selection of therapies which might be called ‘standard’ including the first preferred option of “concurrent systemic therapy/RT cisplatin”. This selection is based on Category 1 evidence. This completes the specification for the initial treatment. The path of assessing the primary site and neck disease for a complete response was followed with this patient. These observations being negative, the patient was observed.

The specification for the radiotherapy is provided in the page ORPH-A. This part of the guideline calls for IMRT as the preferred technique and advised a particular radiation dose to the visible cancer, and another to the at-risk areas (uninvolved nodal stations).

The specification for the chemotherapy, i.e., concurrent cisplatin chemotherapy is provided page CHEM-A, reveals that "cisplatin alone" is an acceptable regime.

---

1 NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement. All recommendations are category 2A unless otherwise noted.
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The SIGN guideline is also applied to cancers of the oropharynx. Similarly to the NCCN guideline, all stages of the disease are covered by the guideline. In the final section (13.2.2), there are a series of statements with associated levels of recommendation.
Appendix O

Clinical Practice Guideline for advanced oropharynx cancer - British Columbia Cancer Agency (Canada)

This guideline is available on-line.¹

¹http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/HeadNeck/Management/Oropharynx.htm
Oropharynx

Anatomical Sites of the Oropharynx are:

- Base of the tongue (posterior third of the tongue), vallecula, and anterior surface of the epiglottis
- Posterior wall of the oropharynx
- Soft palate and uvula
- Tonsils and faucial pillars

1. **Base of the tongue (posterior third of the tongue), Vallecula and Anterior surface of the epiglottis and Posterior wall of the oropharynx**

   Early tumours T1 T2 N0 are treated by external beam irradiation including the adjacent lymph node bearing areas bilaterally. Localized accessible tumours of the lateral base of tongue may be suitable for a radioactive implant boost.

   Advanced tumours T3 T4 N0 N1 N2 N3 should be considered for a twice daily radiotherapy schedule or concurrent chemotherapy with radiotherapy if the patient is fit.

   Surgical resection with appropriate reconstruction followed by postoperative irradiation may be indicated for advanced disease. Resection of an extensive base of tongue carcinoma may require a total glossectomy and a total laryngectomy to prevent tracheal aspiration. Radiotherapy alone is used if the patient is in poor condition.

2. **Soft Palate and Uvula**

   Radiotherapy is the treatment of choice for most cancers. Some localized superficial lesions of the soft palate and uvula may be suitable for a gold seed or iodine implant, or local excision. The remainder and those with lymph node metastases are treated by external beam irradiation.

3. **Tonsils and Faucial Pillars**

   Early tumours are treated by external beam irradiation. Well localized lesions are usually treated with a unilateral technique to spare the contralateral salivary glands. Larger tumours may be suitable for a twice daily radiotherapy schedule or radiation with concurrent chemotherapy.

   More advanced tumours should be considered for combined treatment with surgery and radiotherapy. If the patient is not fit for surgery or is unsuitable but still suitable for radical treatment, accelerated radiotherapy with concurrent boost or concurrent chemotherapy with radiotherapy can be employed. Radiotherapy alone is used if the patient is in poor condition.
Appendix P

Clinical Practice Guideline for advanced oropharynx cancer - Scottish Intercollegiate Guidelines Network (UK)

The complete oropharynx cancer treatment guideline is available on-line

[http://www.sign.ac.uk/pdf/sign90.pdf](http://www.sign.ac.uk/pdf/sign90.pdf)
13 Oropharyngeal cancer

Oropharyngeal tumours may arise from the base of tongue, vallecula, tonsil and tonsillar fossa, posterior wall and the inferior surface of the soft palate and uvula. The choice of therapeutic option for patients with cancer of the oropharynx should be determined by the tumour’s site and extent, the patient’s general condition and preference and availability of local expertise. It is important to consider the treatment related morbidity, and likely cosmetic and functional outcome of treatment as well as tumour control when making decisions about treatment.

13.1 EARLY OROPHARYNGEAL CANCER (STAGE I AND II)

No RCTs were identified comparing surgical treatment with non-surgical treatment in early oropharyngeal cancer.

There is no difference in local control, five-year cause specific and five-year absolute survival when surgery with or without radiotherapy is compared to radiotherapy with or without neck dissection in patients with tonsillar and base of tongue carcinoma.\(^{425}\) The risk of severe and fatal complications is lower in patients treated with primary radiotherapy.\(^{425}\)

No evidence comparing functional outcome following surgery or radiotherapy was identified. There is no evidence to support the routine use of concurrent chemotherapy with radiotherapy in early oropharyngeal cancer.

If appropriate expertise is available it may be possible to treat patients with small oropharyngeal tumours with a combination of external beam radiotherapy and interstitial brachytherapy.\(^{242,243,426}\)

Although the incidence of occult metastases in the lymph nodes of the neck of patients with oropharyngeal cancer is high (> 50%),\(^{68,150-152}\) there is no randomised controlled evidence showing that prophylactic treatment of the neck improves survival. Occult metastases predominate in levels II, III and IV,\(^{150-152,154}\) although distribution varies with the anatomical site of the tumour within the oropharynx. If the primary is in the base of tongue 17% of patients may have level V nodal involvement, and 35% may have bilateral involved nodes.\(^{154}\) Only 3% of patients with early carcinoma of the tonsil develop contralateral nodal metastases after ipsilateral radiation to the primary tumour and neck.\(^{427}\)

No RCTs comparing selective neck dissection to modified radical neck dissection in patients with clinically N0 oropharyngeal cancers were identified.

Neck recurrence rates following selective procedures in patients with clinically N0 neck compare favourably with those achieved by more extensive neck dissection.\(^{150,178,428}\) Radiotherapy and surgery are equally effective for prophylactic treatment of patients with N0 neck.\(^{182,429}\)

- Management of early oropharyngeal cancer should be individualised for each patient.
- Decisions regarding the choice of primary treatment modality should be made in consultation with the patient and should take into account the anatomical location of the tumour and availability of local expertise.

**Patients with early oropharyngeal cancer may be treated by:**

- primary resection, with reconstruction as appropriate, and neck dissection (selective neck dissection encompassing nodal levels II-IV, or II-V if base of tongue)
- external beam radiotherapy encompassing the primary tumour and neck nodes (levels II-IV, or levels II-V if base of tongue).

**Patients with small accessible tumours may be treated by a combination of external beam radiotherapy and brachytherapy in centres with appropriate expertise.**

**In patients with well-lateralised tumours prophylactic treatment of the ipsilateral neck only is required.**

**Bilateral treatment of the neck is recommended when the incidence of occult disease in the contralateral neck is high (tumour is encroaching on base of tongue or soft palate).**
Radiotherapy delivered postoperatively to the primary site and/or neck in patients at high risk of locoregional recurrence may improve locoregional control\textsuperscript{178,195,289-292} and survival\textsuperscript{289,292} (see section 7.3).

The administration of cisplatin chemotherapy concurrently with postoperative irradiation results in significantly better locoregional control\textsuperscript{307,308} and survival\textsuperscript{307} than with radiotherapy alone, particularly in those patients with extracapsular spread and/or positive surgical margins.

**D** Postoperative radiotherapy should be considered for patients with clinical and pathological features that indicate a high risk of recurrence.

**A** Administration of cisplatin chemotherapy concurrently with postoperative radiotherapy should be considered, particularly in patients with extracapsular spread and/or positive surgical margins.

### 13.2 Locally Advanced Oropharyngeal Cancer (Stage III and IV)

No good quality RCTs were identified comparing radiotherapy or chemoradiotherapy with surgery and postoperative radiotherapy in patients with locally advanced head and neck cancer.

Local control and overall survival are comparable in patients treated with primary radiotherapy followed by neck dissection and those receiving primary surgery followed by postoperative irradiation.\textsuperscript{425} The risk of severe and fatal complications is lower in patients treated by primary radiotherapy.\textsuperscript{425}

No evidence was identified comparing functional outcome in patients following either surgery or radiotherapy.

If external beam radiotherapy is used as the primary modality of treatment, concurrent administration of chemotherapy results in a 23\% reduction in the risk of death at five years when compared with radiotherapy alone.\textsuperscript{298}

Administration of cetuximab concurrently with radiotherapy in advanced oropharyngeal cancer results in significantly improved locoregional control, progression-free survival compared with radiotherapy alone (see section 8.2).\textsuperscript{226}

Accelerated radiotherapy or hyperfractionated radiotherapy with increased total dose results in improved locoregional control compared with conventionally fractionated radiotherapy alone (see section 6.3).

There are no RCTs comparing surgery with radiotherapy (with or without chemotherapy) in the treatment of patients with oropharyngeal cancer and node positive neck. In node positive oropharyngeal cancer, levels II, III and IV are most commonly involved. Level V is positive in 6\%-11\% of patients.\textsuperscript{151,152,165,184} Levels I and V are only involved if there are positive nodes at other levels.\textsuperscript{151,152}

There is currently insufficient evidence to support the use of selective neck dissection in patients with oropharyngeal cancer and advanced nodal disease.\textsuperscript{314}

In patients with a small primary tumour, it is possible to resect advanced nodal disease prior to treating the primary with definitive radiotherapy whilst delivering postoperative adjuvant radiotherapy to the neck without compromising cancer control (see section 5.2.4).\textsuperscript{207,208,424}

Nodal size predicts response to radiotherapy and it may be possible to treat a single node < 3 cm with radiotherapy or chemoradiotherapy alone.\textsuperscript{196,198}

Patients with N2 and N3 disease are better treated by a combination of surgery and chemoradiotherapy (or radiotherapy in those unable to tolerate chemotherapy) rather than by either modality alone (see sections 5.2.4 and 8.1).
In patients with N2 or N3 oropharyngeal tumours with clinically detectable residual disease after chemoradiotherapy, there is evidence of improved overall survival if a neck dissection is performed. It is unclear from current evidence whether it is safe to omit neck dissection for patients with N2 and N3 disease who have a complete clinical response to chemoradiotherapy. After definitive radiotherapy it may be possible to dissect nodal levels II-IV only and omit levels I and V if there is no clinical or radiological sign of residual disease at these levels.

The administration of cisplatin chemotherapy concurrently with postoperative irradiation results in significantly better locoregional control and survival than with radiotherapy alone particularly in those patients with extracapsular nodal spread and/or positive surgical margins.

- The decision regarding the choice of primary treatment modality in advanced oropharyngeal cancer should be made in consultation with the patient and be dependent on local expertise.
- In patients where surgical resection is possible, the likelihood of obtaining adequate surgical margins with acceptable morbidity, functional outcome and quality of life must be taken into account.

**Patients with advanced oropharyngeal cancer may be treated by:**
- primary surgery (if a clear surgical margin can be obtained)
- an organ preservation approach.

### 13.2.1 PRIMARY SURGERY

- Resection of the primary tumour should be followed by reconstruction as necessary.

**Patients treated by primary surgery who have a clinically node positive neck should have a modified radical neck dissection.**

- Ipsilateral neck dissection may be performed if the tumour is well lateralised.
- Prophylactic treatment of the contralateral neck should be considered, especially when tumours encroach on the midline.

**Postoperative chemoradiotherapy to the primary site and neck should be considered for patients treated by primary surgery who show high risk pathological features.**

**Administration of cisplatin chemotherapy concurrently with postoperative radiotherapy should be considered, particularly in patients with extracapsular spread and/or positive surgical margins.**
13.2.2 ORGAN PRESERVATION THERAPY

A Radiotherapy should be administered with concurrent cisplatin chemotherapy.

D The primary tumour and neck node levels (II-V) should be treated bilaterally.

A In patients medically unsuitable for chemotherapy, concurrent administration of cetuximab with radiotherapy should be considered.

A Where radiotherapy is being used as a single modality without concurrent chemotherapy or cetuximab, a modified fractionation schedule should be considered.

D ▪ Patients with N1 disease should be treated with chemoradiotherapy followed by neck dissection where there is clinical evidence of residual disease following completion of therapy.
▪ Patients with N2 and N3 nodal disease should be treated with chemoradiotherapy followed by planned neck dissection.

D In patients with a small primary tumour, locally advanced nodal disease may be resected prior to treating the primary with definitive chemoradiotherapy and the neck with adjuvant chemoradiotherapy.

☑ Salvage surgery should be available if an initial organ preservation approach is pursued.
Appendix Q

Clinical Practice Guideline for advanced oropharynx cancer - National Comprehensive Cancer Network (USA)

The complete oropharynx cancer treatment guideline is available on-line after registration with the NCCN. [1]

CLINICAL STAGING

- T1-2, N0-1 → See Treatment of Primary and Neck (ORPH-2)
- T3-4a, N0-1 → See Treatment of Primary and Neck (ORPH-3)
- Any T, N2-3 → See Treatment of Primary and Neck (ORPH-4)
- T4b, N any, or unresectable nodal disease → See Treatment of Very Advanced Head and Neck Cancer (ADV-1)

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

---

a Immunohistochemical staining for p16 is recommended. Although not used to guide treatment, HPV testing is valuable prognostically. The results of HPV testing should not change management decisions except in the context of a clinical trial.

b Anatomical imaging is also recommended.
NCCN Guidelines™ Version 2.2011
Cancer of the Oropharynx

Base of tongue/tonsil/posterior pharyngeal wall/soft palate

**CLINICAL STAGING**

- Concurrent systemic therapy/RT\(^{c,e}\) cisplatin (category 1) preferred
  - or
  - Induction chemotherapy\(^e\) followed by RT or chemo/RT (category 2B)\(^h\)

- Surgery:\(^d\) primary and neck
  - N1 N2a-b
  - N3
  - or
  - Excision of primary, ipsilateral or bilateral neck dissection\(^d\)

- Any T, N2-3
  - N2c
  - or
  - Excision of primary and bilateral neck dissection\(^d\)

**TREATMENT OF PRIMARY AND NECK**

- Residual tumor in neck
  - Post-treatment evaluation\(^l\)

- Complete clinical response of neck
  - Salvage surgery + neck dissection as indicated\(^d\)

**ADJUVANT TREATMENT**

- Negative
  - Observe

- Positive
  - Neck dissection\(^d\)

**Follow-up (See FOLL-A)**

- Recurrent or Persistent Disease (See ADV-2)

- RT\(^c\) or Consider chemo/RT\(^{c,e}\)

**Notes**
- All recommendations are category 2A unless otherwise indicated.
- Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

\(^c\)See Principles of Radiation Therapy (ORPH-A).
\(^d\)See Principles of Surgery (SURG-A).
\(^e\)See Principles of Systemic Therapy (CHEM-A).
\(^f\)Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism (See Discussion).
\(^h\)See Discussion on induction chemotherapy.
\(^l\)See Post Chemoradiation or RT Neck Evaluation (SURG-A 6 of 6).
Principles of Radiation Therapy

**Definitive RT**

- Conventional fractionation: 66-74 Gy (2.0 Gy/fraction; daily Monday-Friday) in 7 weeks
- Altered fractionation:
  - 6 fractions/week accelerated; 66-74 Gy to gross disease, 44-64 Gy to subclinical disease.
  - Concomitant boost accelerated RT: 72 Gy/6 weeks (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
  - Hyperfractionation: 81.6 Gy/7 weeks (1.2 Gy/fraction, twice daily)

**Postoperative RT**

- Preferred interval between resection and postoperative RT is ≤ 6 weeks.
- Primary: 60-66 Gy (2.0 Gy/fraction)
- Neck:
  - Involved nodal stations: 60-66 Gy (2.0 Gy/fraction)
  - Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)

Postoperative chemoradiation
- Concurrent single agent cisplatin at 100 mg/m² every 3 wks x 3 doses is recommended. 3-5

Concurrent chemoradiation
- Conventional fractionation: 2
  - Primary and gross adenopathy: 70 Gy (2.0 Gy/fraction)
  - Neck
    - Uninvolved nodal stations: 44-64 Gy (1.6-2.0 Gy/fraction)

IMRT is a preferred technique for cancers of the oropharynx in order to minimize dose to critical structures.

---

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Target delineation and optimal dose distribution require experience in head and neck imaging, and a thorough understanding of patterns of disease spread. Standards for target definition, dose specification, fractionation (with and without concurrent chemotherapy), and normal tissue constraints are still evolving. IMRT, 3D, and 2D conformal techniques may be used as appropriate depending on the stage, tumor location, physician training/experience, and available physics support. Close interplay exists between radiation technology, techniques, fractionation, and chemotherapy options resulting in a large number of combinations that may impact toxicity or tumor control. Close cooperation and interdisciplinary management are critical to treatment planning and radiation targeting, especially in the postoperative setting or after induction chemotherapy.9

Intensity-Modulated Radiotherapy (IMRT)

IMRT has been shown to be useful in reducing long-term toxicity in oropharyngeal, paranasal sinus, and nasopharyngeal cancers by reducing the dose to salivary glands, temporal lobes, auditory structures (including cochlea), and optic structures. The application of IMRT to other sites (eg, oral cavity, larynx, hypopharynx, salivary glands) is evolving and may be used at the discretion of treating physicians.10,11

IMRT and Fractionation10,11

A number of ways exist to integrate IMRT, target volume dosing, and fractionation. The Simultaneous Integrated Boost (SIB) technique uses differential “dose painting” (66-74 Gy to gross disease; 50-60 Gy to subclinical disease) for each fraction of treatment throughout the entire course of radiation.4 SIB is commonly used in conventional (5 fractions/week) and the “6 fractions/week accelerated” schedule.5 The Sequential (SEQ) IMRT technique typically delivers the initial (lower dose) phase (weeks 1-5) followed by the high-dose boost volume phase (weeks 6-7) using 2-3 separate dose plans, and is commonly applied in standard fractionation and hyperfractionation. The Concomitant Boost Accelerated schedule may utilize a “Modified SEQ” dose plan by delivering the dose to the subclinical targets once a day for 6 weeks, and a separate boost dose plan as a second daily fraction for the last 12 treatment days.6

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
## PRINCIPLES OF SYSTEMIC THERAPY

**Squamous Cell Cancers**

- **Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic larynx, Supraglottic larynx, Ethmoid Sinus, Maxillary Sinus, Occult Primary:**
  - **Primary Systemic Therapy + concurrent RT**
    - Cisplatin alone\(^1,2\) (preferred) (category 1)
    - Cetuximab\(^9\) (category 1)
    - 5-FU/hydroxyurea\(^4\)
    - Cisplatin/paclitaxel\(^4\)
    - Cisplatin/infusional 5-FU\(^5\)
    - Carboplatin/infusional 5-FU\(^6\)
    - Carboplatin/paclitaxel\(^7\) (category 2B)

- **Postoperative Chemoradiation**
  - Cisplatin alone\(^8-11\) (category 1 for high risk)

- **Induction/Sequential chemotherapy**
  - Docetaxel/cisplatin/5-FU\(^12-14\) (category 1 if induction is chosen)
  - Following induction, agents to be used with concurrent chemoradiation typically include weekly platinumums, weekly taxanes, or cetuximab.\(^15\)

**Nasopharynx**

- **Chemoradiation followed by adjuvant chemotherapy**
  - Cisplatin + RT followed by Cisplatin/5-FU\(^16,17\) (category 1)

- **Recurrent, Unresectable, or Metastatic (incurable)**
  - **Combination therapy**
    - Cisplatin or carboplatin + 5-FU + cetuximab (non-nasopharyngeal)\(^18\) (category 1)
    - Cisplatin or carboplatin + docetaxel\(^19\) or paclitaxel\(^20\)
    - Cisplatin/cetuximab (non-nasopharyngeal)\(^21\)
    - Cisplatin + 5-FU\(^20,22\)

- **Single agents**
  - Cisplatin
  - Carboplatin
  - Paclitaxel
  - Docetaxel
  - 5-FU
  - Methotrexate
  - Ifosfamide
  - Bleomycin
  - Gemcitabine\(^23\) (nasopharyngeal)
  - Cetuximab (non-nasopharyngeal)\(^24\)

*Induction chemotherapy should only be done in a tertiary setting.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.