ΠΑΝΕΠΙΣΤΗΜΙΟ ΠΑΤΡΩΝ
ΣΧΟΛΕΣ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ - ΘΕΤΙΚΩΝ ΕΠΙΣΤΗΜΩΝ
ΤΜΗΜΑΤΑ ΙΑΤΡΙΚΗΣ - ΦΥΣΙΚΗΣ

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Κλινικά προσδιορισμένες σχέσεις Δόσης – Απόκρισης για τη στένωση του
οισοφάγου από ακτινοθεραπεία κεφαλής και τραχήλου

ΕΛΕΥΘΕΡΙΑ ΑΛΕΥΡΟΝΤΑ

Εξεταστική επιτροπή: Νικηφορίδης Γεώργιος
Επιβλέπων: Νικηφορίδης Γεώργιος
Παναγιωτάκης Γεώργιος
Σακελλαρόπουλος Γεώργιος

Πάτρα, Σεπτέμβρης 2008, Ελλάδα
MSc Thesis

Clinically derived Dose-Response relations for esophageal strictures from Head & Neck Radiotherapy

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ΠΕΡΙΛΗΨΗ

Κλινικά προσδιορισμένες σχέσεις Δόσης – Απόκρισης για τη στένωση του τραχηλικού οισοφάγου από ακτινοθεραπεία κεφαλής και τραχήλου

Σκοπός

Ο σκοπός αυτής της μελέτης είναι ο προσδιορισμός των παραμέτρων δόσης απόκρισης του μοντέλου σχετικής σειριακότητας αναφορικά με το κλινικό αποτέλεσμα της στένωσης του οισοφάγου μετά από ακτινοθεραπεία κεφαλής και τραχήλου. Αυτό επιτυγχάνεται με τη συσχέτιση των ξεχωριστών τρισδιάστατων κατανομών δόσης των ασθενών με τα αντίστοιχα μετακτικά αποτελέσματα από την κλινική παρακολούθηση.

Υλικά και μέθοδοι

Αυτή η μελέτη είναι βασισμένη σε 72 ασθενείς που υποβλήθηκαν σε ακτινοθεραπεία για καρκίνο κεφαλής και τραχήλου στο νοσοκομείο Καρολίνας της Στοκχόλμης Σουηδίας. Η ανάλυση έγινε για τις περιόδους 1991-2000 και 2001-2005, λόγω των διαφορετικών τεχνικών ακτινοβολίας που χρησιμοποιήθηκαν. Για κάθε ασθενή υπολογίστηκαν οι τρισδιάστατες κατανομές δόσης των ανώτερων 5εκ. του οισοφάγου και ήταν διαθέσιμα τα κλινικά αποτελέσματά της θεραπείας. Για να εκτιμηθεί η εμφάνιση της προκαλούμενης από ακτινοβολία στένωσης του οισοφάγου, χρησιμοποιήθηκαν κλινικά συμπτώματα και ακτινολογικά ευρήματα. Η διάγνωση της στένωσης έγινε 1-60 μήνες μετά την ακτινοθεραπεία. 33 ασθενείς ανέπτυξαν στένωση του οισοφάγου ενώ 39 ασθενείς δεν εκδηλώσαν κανένα σύμπτωμα. Τα δεδομένα χρησιμοποιήθηκαν σε μια διαδικασία προσαρμογής μέγιστης πιθανόφανειας (maximum likelihood fitting) ώστε να υπολογιστούν οι βέλτιστες τιμές των παράμετρων που χρησιμοποιούνται από το μοντέλο σχετικής σειριακότητας.

Αποτελέσματα

Για την περίοδο 1991-2000, η μέση και η μέγιστη τιμή της δόσης είναι 49.9 και 61.2 Gy, αντίστοιχα για την ομάδα ασθενών με στένωση, ενώ για την ομάδα έλεγχου οι αντίστοιχες τιμές είναι 46.3 και 64.8 Gy. Για την περίοδο 2001-2005 αυτές οι τιμές είναι 49.8 και 61.4 Gy για την ομάδα ασθενών με στένωση, ενώ για την ομάδα έλεγχου είναι 20.6 και 46.1 Gy, αντίστοιχα. Για την περίοδο 2001-2005 οι βέλτιστες εκτιμήσεις των παραμέτρων δόσης απόκρισης είναι $D_{50}=62.3$ Gy (52.4-87.3 Gy), $γ = 1.14$ (0.74-2.28) και $s = 0.11$ (0.01-0.33). Επίσης, βρέθηκε στατιστικά σημαντική θετική συσχέτιση των στενώσεων που προκαλούνται από την ακτινοβολία με τη βιολογικά ομοιόμορφη δόση στα 50 Gy (odds ratio (OR) = 13.0 με
95% διάστημα εμπιστοσύνης (confidence interval, CI) = 2.9-58.6). Επιπλέον, το μοντέλο σχετικής σειριακότητας φαίνεται να διαφοροποιεί καλά τις ομάδες ασθενών με και χωρίς στένωση, καθώς σύμφωνα με την ανάλυση η περιοχή κάτω από της καμπύλη ROC είναι ίση με 0.92.

Συμπεράσματα

Βρέθηκε ότι οι στενώσεις που προκαλούνται από ακτινοβολία έχουν ισχυρή συσχέτιση με τον όγκο (χαμηλή σχετική σειριακότητα). Οι εκτιμώμενες παράμετροι δόσης απόκρισης μπορούν να χρησιμοποιηθούν για να προβλέψουν τη δημιουργία στένωσης στον τραχηλικό ουσοφάγο. Σημαντικά μεγαλύτερες μέσες και μέγιστες τιμές δόσεων χαρακτηρίζουν την ομάδα των ασθενών με στένωση σε σχέση με την ομάδα των ασθενών χωρίς στένωση.
ABSTRACT

Dose-Response Parameters of Stricture in the Proximal Esophagus from Head & Neck Radiotherapy

Purpose
The purpose of this work is to determine the dose-response parameters of the relative seriality model regarding the clinical endpoint of esophageal stricture after head & neck radiotherapy. This is accomplished by associating the individual 3-dimensional dose distributions of the patients with the clinical follow-up findings.

Material and Methods
This study is based on 72 patients who received radiation treatment for head & neck cancer at Karolinska Hospital, Stockholm, Sweden. The analysis was conducted for the periods 1991-2000 and 2001-2005 because of the different irradiation techniques used. For each patient the 3D dose distribution delivered to the upper 5 cm of the esophagus (proximal esophagus) and the clinical treatment outcome were available. Clinical symptoms and radiological findings were used to assess the manifestation of radiation induced esophageal strictures. Stricture was diagnosed 1–60 months after radiotherapy. 33 patients developed esophageal stricture and 39 were symptom free. These data were introduced into a maximum likelihood fitting to calculate the best estimates of the parameters used by the relative seriality model.

Results
For the period 1991-2000, the mean and maximum doses are 49.9 and 61.2 Gy, respectively for the group of patients with stricture, whereas they are 46.3 and 64.8 Gy, respectively for the control group. For the period 2001-2005 these values are 49.8 and 61.4 Gy, respectively for the group of patients with stricture, whereas they are 20.6 and 46.1 Gy, respectively for the control group. For the period 2001-2005 the best estimates of the dose-response parameters are $D_{50}=62.3$ Gy (52.4-87.3 Gy), $\gamma = 1.14$ (0.74-2.28) and $s = 0.11$ (0.01-0.33). A statistically significant positive association of radiation induced esophageal stricture with the biologically effective uniform dose (cutoff at 50 Gy) was found (odds ratio (OR) = 13.0 with 95% confidence interval (CI) of 2.9-58.6). Furthermore, the relative seriality model seems to differentiate well the patient groups with and without stricture since in a ROC analysis it gives the area under the ROC curve = 0.92.
Conclusions
Radiation induced strictures were found to have a strong volume dependence (low relative seriality). The estimated dose-response parameters can be used to predict the development of esophageal stricture. Significantly larger mean and maximum doses characterize the group of patients with stricture compared to the group of patients without stricture.

This thesis has been done in collaboration with:
Division of Medical radiation Physics, Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweeden.
## List of abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>CTV</td>
<td>Clinical Target Volume</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DSB</td>
<td>Double-strand break</td>
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<tr>
<td>DVH</td>
<td>Dose –volume histogram</td>
</tr>
<tr>
<td>EUD</td>
<td>Equivalent uniform dose</td>
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<tr>
<td>FSU</td>
<td>Functional subunit</td>
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<tr>
<td>GT</td>
<td>Gross tumour</td>
</tr>
<tr>
<td>IMRT</td>
<td>Intensity-modulated radiation therapy</td>
</tr>
<tr>
<td>ITV</td>
<td>Internal target volume</td>
</tr>
<tr>
<td>LQ</td>
<td>Linear-quadratic model</td>
</tr>
<tr>
<td>LN</td>
<td>Lymph nodes</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NG</td>
<td>Nasogastric gastrostomy</td>
</tr>
<tr>
<td>NTCP</td>
<td>Normal tissue complication probability</td>
</tr>
<tr>
<td>PEG</td>
<td>Percutaneous endoscopic gastrostomy</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PET-CT</td>
<td>Positron emission tomography- Computed tomography</td>
</tr>
<tr>
<td>PTV</td>
<td>Planning Target Volume</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>RT</td>
<td>Radiation Therapy</td>
</tr>
<tr>
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<td>Single-strand break</td>
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Introduction

1.1 Background

1.1.1 Anatomy of Esophagus

The oesophagus transports the bolus from the pharynx into the stomach. This transport is accomplished by waves of circular muscle contractions (peristalsis) that are normally directed toward the stomach. The oesophagus is also subject to a longitudinal tension (fixed by the larynx above and the diaphragm below) that stabilizes its course and favours the passage of the bolus of food during swallowing. In the adult, the oesophagus is about 25–30 cm long. It runs through the thorax behind the trachea and in front of the spine. Below, the oesophagus penetrates the diaphragm through the oesophageal hiatus to empty directly into the stomach. The oesophagus (Figure 1) can be divided into a short cervical part, a thoracic part, and an abdominal part. In certain places the oesophagus is narrowed by oesophageal constrictions. The highest constriction is at the cricoid cartilage; it is the narrowest with a diameter of about 14 mm. In the middle the closely related aortic arch causes a constriction. The lowest constriction corresponds to the diaphragmatic hiatus and is the site of a complex closing mechanism. At this limited constriction, larger boluses can at times become wedged and cause severe pain.

The oesophagus has the mural layers characteristic of the whole gastrointestinal tract. An inner mucous membrane (tunica mucosa = mucosa) is followed by a loose areolar connective tissue layer (tunica submucosa = submucosa), in which run larger blood and lymph vessels. Outside this is a muscular layer (tunica muscularis = muscularis), which consists of an inner circular layer and an outer longitudinal layer. By alternating the contractions of the circular and longitudinal muscles segment by segment (peristalsis), this arrangement of the muscles facilitates the transport of food toward the stomach. This, then, is the effective movement of the gastrointestinal tube, coordinated by the autonomic nervous system. Outside the muscle layer is a connective tissue layer (tunica adventitia = adventitia), which anchors the oesophagus in its bed and allows some mobility.
Figure 1.1: The left picture illustrates divisions, inclinations, and constrictions of the oesophagus: 1. cervical part, 2. Thoracic part. 3. Abdominal part. Red arrows mark the inclinations; black arrows mark the physiological constrictions. The hiatus sling is part of the diaphragm. The right picture illustrates the parts of which oesophagus consists.

1.1.2 Oral complications of radiotherapy

Adverse reactions to radiotherapy will depend on the volume and area being irradiated, on the total dose, on the fractioning, on the age, on the patient’s clinical conditions and on the associated treatments. A small increase on tumor dosage is enough for a significant increase on the complications incidence. Acute reactions happen during the treatment and most of the time, they are reversible. Late complications are normally irreversible, leading to permanent incapability and to a worsening of quality of life [40], and they vary on intensity, being normally classified into mild, moderate and severe [35]. Many head and neck cancer patients are submitted to high doses of radiotherapy on large areas of radiation including the oral cavity, maxilla, mandible and salivary glands. Thus, anti-cancer therapy is associated with several adverse reactions. These reactions can occur in an acute stage (during or at the weeks right after treatment) or in a chronic stage (months or years after radiotherapy). The severity
of acute oral complications will depend on the inclusion degree of these structures on the radiated area [40, 41]. [5]

**Mucositis**

Mucositis is defined as a mucosal irritation [40]. Anti-neoplastic-therapy-induced mucositis is a significant adverse reaction that may interfere on the radiotherapy process altering the tumor local control and therefore, the patient’s survival. Mucositis is believed to occur in four stages (inflammatory/vascular, epithelial, ulcerative/bacteriologic and healing). The most used scale to measure oral mucositis is the one by the WHO, which classifies mucositis into four degrees. Degree 0 is when there are no signs or symptoms. Degree 1 is when the mucosa is erythematose and painful. Degree 2 is characterized by ulcers, and the patient can eat normally. Degree 3 is when the patient has ulcers and can only drink fluids. Finally, degree 4 is when the patient cannot eat or drink [42]. Due to oral mucosa damages, patients will complain of pain, what may lead to the need of using painkillers during treatment. The pain intensifies whenever the patient tries to eat or drink [40]. Mucositis is even worse when chemotherapy is used in association with radiotherapy in cancer treatment [43]. [5]

**Candidosis**

Radiated patients are more prone to developing oral infections caused by fungi and bacteria [44]. Studies have showed that patients submitted to radiotherapy have a higher number of microbian species, such as Lactobacillus spp., Streptococcos aureus and Candida albicans [37]. Oral candidosis is a common infection in patients being treated for upper airways and digestive tract malignancies. Colonization of oral mucosa can be found in as many as 93% of these patients, whereas Candida infection can be found in 17-29% of patients submitted to radiotherapy. The increased risk for oral candidosis is likely to be the result of the drop in salivary flow as a consequence of radiotherapy [45, 46]. Besides, a possible explanation for a higher predisposition of irradiated patients to candidosis is a reduced phagocytic activity of salivary granulocytes against these micro-organisms [47]. Clinically, candidosis can be seen colonization and infection of radiated patients both in its pseudomembranous and erythematous forms. The latter can be of difficult diagnosis, and it may be confused with irradiation induced mucositis. Patients complain more of pain and / or burning sensation [45, 46]. Ramirez-Amador et al [46] verified that Candida prevalence in patients increased from 43% in the first visit to the doctor’s office to 62% during radiotherapy and finally to 75% during post-radiotherapy control visits. In the study by Redding et al. [48], 73% of patients analyzed showed colonization by Candida, whereas 27% of them had the infection. The study by Grotz et al. [49] analyzed colonization by Candida in irradiated patients. They verified that...
the maximum colonization rate happened six months after radiotherapy, and 12 months after radiotherapy the values went back to be lower than normal. Several studies have already analyzed which Candida species were involved in. Previous studies [45, 46] showed that Candida albicans was the most prevalent micro-organism. However, other species had been identified recently. C. glabrata e C. krusei micro-organisms had already been seen in patients submitted to radiotherapy [50]. Recent studies found a relation between oral candidosis and C. dubliniensis species. In this study, the authors suggest that the species C. albicans and C. dubliniensis probably act together in the infections that affect radiated patients [88, 89]. Besides, it is known that the non-albicans species distribution varies according to geographical location. Thus, in North America, the predominant species is C. glabrata. Whereas a study done in Brazil showed that the predominant species is C. tropicalis [90]. [5]

**Dysgeusia**

Dysgeusia affects patients from the second or third week of radiotherapy onwards, and it may last for several weeks or even months. It occurs because the taste buds are radiosensitive, with the degeneration of their normal histological architecture. The increase of salivary flow viscosity and the saliva biochemical alteration creates a mechanical barrier of saliva which makes it difficult the physical contact between the tongue and foodstuff. The recovery until reaching almost normal levels generally takes place around 60 to 120 days after the end of the radiation. Studies show that dysgeusia is a complaint by approximately 70% of patients submitted to radiotherapy, also implying in the loss of appetite and weight, being the most uncomfortable complication for most radiated patients [40, 43, 84]. However it is a very rare complication.[5]

**Radiation caries**

Even patients, who had not experienced tooth decay for some time, may develop radiation caries when submitted to radiotherapy [85]. The main factor for the development of such injuries is the decrease of saliva amount and its qualitative alterations [86]. Besides, radiation has a direct effect on teeth, making them more susceptible to decalcification [85]. [5]

**Osteoradionecrosis**

Osteoradionecrosis (ORN) is a bone ischemic necrosis caused by radiation, being one of the most serious consequences of radiotherapy, causing pain as well as possible substantial loss of bone structure [40, 87]. Due to anticancer therapy, bone cells and the vascularization of bone tissue may suffer irreversible injuries [85]. ORN may occur spontaneously or more commonly, after trauma (generally dental extractions). In 95% of cases ORN is associated with soft tissue necrosis and subsequent bone exposure [87] Mandibles are more affected than
maxillas and patients with their natural teeth have greater chances of developing ORN. Spontaneous bone exposure occurs approximately one year after finishing radiotherapy and the risk of developing this complication remains indefinitely [85]. Besides, studies show that approximately 60% of patients complain of pain, ranging from mild pain, controlled with drugs, to extremely painful conditions. However, the presence of these symptoms does not appear to be related to the extension of the process. ORN may also result in edema, suppuration and pathological fractures, which may occur in 15% of patients, always experienced together with pain [87],[5]

**Soft tissue necrosis**

Another possible consequence of radiotherapy is soft tissue necrosis, which may be defined as an ulcer located in the radiated tissue, without the presence of residual malignancy. The occurrence of soft tissue necrosis is related to dose, time and volume of the radiated gland, when the brachytherapy is used, the risk is higher. Soft tissue necrosis is a normally painful condition and good oral hygiene together with the use of painkillers and often times, antibiotics, are necessary to manage the condition. Since ulcerations are often seen on the tumour primary site, regular evaluations are necessary until the necrosis retreats, therefore excluding the possibility of recurrence [85]. Besides, soft tissues may suffer fibrosis after radiotherapy, becoming pale, thin and without flexibility. When fibrosis affects chewing musculature (temporal, masseter and pterygoid muscles) trismus can happen. In the most serious cases, trismus may interfere with eating and dental care [40]. [5]

**Xerostomia**

Xerostomia, or “dry mouth”, can result from some diseases or it can be an adverse reaction to some drugs [91]. Among radiated patients in the head and neck area, it is one of the most frequent complains [92] Chencharick and Mossman [84] noticed that 80% of radiated patients complain of xerostomia. However, the relation between the individual perception of dry mouth and the real values of salivary flow have not yet been completely defined [93] In some situations, there is a co-relation between reduced salivary flow and xerostomia complaint [93].However, in many cases there is not a relation between xerostomia and objective findings of salivary gland dysfunction - that is to say, patients without alterations of salivary flow may complain of mouth dryness. Patients with xerostomia complain of oral discomfort, taste loss, speech and swallowing difficulties [95] Saliva also suffers qualitative alterations resulting from radiotherapy with decrease of amylase activity, buffer capacity and pH, with consequent acidification. There are also alterations of several electrolytes such as calcium, potassium, sodium and phosphate. [94, 85] Thus, individuals who were radiated are more
susceptible to periodontal disease, rampant tooth decay and oral infections by fungus and bacteria [44]. Xerostomia treatment can be done through the use of mechanic/taste stimulants, saliva substitutes or systemic agents [97, 98]. Alternative methods, such as acupuncture, had also been mentioned as treatment options for xerostomia [99]. Generally speaking, stimulants and saliva substitutes only reduce xerostomia, without altering salivary flow. On the other hand, systemic agents besides reducing xerostomia, also decrease oral problems associated with salivary glands hypofunction, through the increase of salivary flow. Thus, the treatment of choice for radiotherapy-induced xerostomia, should be through the use of systemic agents, and pilocarpine is the most studied one among them. Besides, studies show that systemic agents, such as pilocarpine, are more effective when used during radiotherapy [96,100]. This has also been recently showed for betanechol, when the drug used concomitantly with radiotherapy is able to increase salivary flow at rest, right after the end of the radiotherapy treatment, besides decreasing the subjective complaint of dry mouth [101]. [5].

1.1.3 Incidence

Dysphagia is commonly observed in patients with head and neck carcinoma. A wide range of swallowing problems induced by the tumour itself or by any therapeutic intervention generally is considered to be problems that must be accepted. Particular emphasis, however, must be placed on the pathogenesis of such problems to improve the situation for the patient. Even though the nutritional status of the patient might be restored by tube feeding, swallowing problems generally have a considerable impact on quality of life and also might lead to social isolation. There are certain conditions that should be recognized by the physician to avoid malnutrition and unnecessary suffering. One such condition is injury to the proximal oesophagus induced by radiotherapy. Injury to the gastrointestinal tract is a well recognized complication after radiotherapy for pelvic and abdominal malignant tumours. The ileum and rectum are parts of the gastrointestinal viscera that quite frequently are damaged because of the wide use of radiotherapy for gynaecologic and urologic malignancies.[23] The incidence of gastro-intestinal irradiation injury is dependent on different factors but knowledge of the tolerance of normal tissue is limited for the majority of sites.[21] The oesophagus at the upper end of the gastrointestinal tract is reported to be fragile and radiosensitive.[27] Acute radiation esophagitis is commonly observed in connection with radiotherapy for operable breast carcinoma, inoperable carcinoma of the lung, and
oesophageal carcinoma[25, 26]. It has been suggested that there is no clear relation between acute esophagitis observed during radiotherapy and late side effects such as stricture of the esophagus [28]. The pathophysiology of the acute and late side effects on the oesophagus therefore might differ. To our knowledge there have been a few previous reports in the medical literature of oesophageal irradiation injury in patients with head and neck carcinoma. To our knowledge, uncertainty exists regarding the predisposing factors and the incidence of stricture of the oesophagus. Early signs of radiation reactions frequently are observed in some patients whereas others appear to be resistant. [1]

Oesophageal strictures can be divided grossly into two categories, according to their benign or malignant aetiology. Among the benign strictures, functional and organic origins must be distinguished: functional strictures are the consequence of increased tonicity of the muscular wall while benign organic strictures mainly result from collagen deposits and fibrous tissue formation induced by mucosal injuries of diverse origins. The severity of strictures varies from a fibrous ring of the oesophageal inlet to deep fibrosis with possible subtotal obliteration of the lumen, which occurs generally in the setting of hypopharyngeal tumours. There are numerous factors predisposing a patient to develop strictures following radiation. The most important is the total absorbed dose; doses greater than 60Gy predispose the structures to stricture formation [31]. Other factors include increased volume of irradiation in locally advanced tumours and circumferential irradiation [2]. Lee et al. reported a 21% prevalence of symptomatic strictures in a group of patients primarily treated with concurrent chemoradiation therapy for head and neck cancer. In this study, the risk factors included radiation therapy performed twice daily, primary tumours situated in the hypopharynx and female gender [32]. Although prevalence of strictures with concomitant chemotherapy has not been specifically investigated, the increased mucosal toxicity of these treatments is well known, and a higher degree of oesophageal-wall fibrosis can be expected than after radiotherapy alone. Chronic xerostomy provoked by oropharyngeal irradiation impedes acid neutralization in the oesophagus and may also predispose the patient to esophagitis [24] and development of stricture. Another evoked risk factor is prolonged enteral nutrition during radiotherapy, explained by the decreased activity of the hypopharyngeal and oesophageal musculature predisposing the area to mucosal adhesions and fibrosis [29]. Percutaneous endoscopic gastrostomy has been suggested as a factor that increases the need for dilatation when compared to nasogastric tube, because of the lack of a stent-like effect [30]. [6] Furthermore patients with PEG (percutaneous endoscopic gastrostomy) may be at increased risk of stricture formation because of the relative inactivity of upper
esophageal/hypopharyngeal musculature as compared with those patients without feeding tubes. Gillespie et al [29] reported that patients who had been without oral intake for more than 2 weeks had worse swallowing outcomes. In reviewing our patients in 2001, Mekhail et al [30] found that hypopharyngeal primary site, female sex, a T4 primary tumor classification, and treatment with chemotherapy were predictive of a need for a feeding tube (PEG or NG). They also suggested that NG (nasogastric gastrostomy) tubes decreased the need for esophageal dilation versus PEG tubes. These investigators speculated that the NG feeding tube may serve as a stent that prevents or decreases the severity of strictures. However, they did not specifically identify the presence of strictures in these patients. [7] The value of the incidence rate, which we have got from the hospital records of Radiumhemmet, for the years 1991-1998, is 2-4%.

### 1.1.4 Stages of oesophageal stricture

Esophageal strictures are graded in 3 stages, from I to III, according their severity. This grading has been made using endoscopy. The definitions of each grade are the followings:

**Grade I:** Stricture indicated moderate stricture with a fibrous membranous ring or moderate fibrosis. The stricture initially could be passed by a rigid esophagoscope (7 mm× 10 mm) and dilated. Moderate stricture causes dysphagia to solid food but not to pulp semisolids.

**Grade II:** Indicated severe stricture with severe fibrosis of the esophageal inlet. It was not possible to pass the stricture using the smallest endoscope (7 mm×10 mm) without dilation. Severe stricture causes dysphagia to solid food but not to liquids.

**Grade III:** Indicated total obliteration. In this case there is no visible communication the hypopharynx and the oesophagus. [1], [2]
Figure 1.2: Radiographs demonstrates three representative cases with radiation-induced narrowing of the proximal oesophagus. Left: moderate stricture (fibrous membranous ring or moderate fibrosis). Center: severe stricture (severe fibrosis of the oesophageal inlet). Right: total obliteration (no communication visible between the hypopharynx and oesophagus). The arrow in the graph indicates where the stricture is located in each case.

1.1.5 Diagnostic Criteria and Treatment about oesophageal stricture

Clinical symptoms that lead to suspicion of a stricture were impaired swallowing function and weight loss that was either persistent after radiotherapy or of late onset. Conventional swallow X-ray using barium contrast material was performed as the initial examination. Endoscopic examination was performed under general anaesthesia to identify the cause of deglutition disorder and to diagnose the degree of stricture. Repeated dilation using Savary dilators generally was used to dilate the oesophageal stricture. In appropriate patients this maneuver was followed by repeated dilations as an outpatient procedure using mercury bougies. In addition, rigid endoscopes were used to dilate mild strictures by placing endoscopes of different sizes, starting with a 7 mm x 10 mm endoscope and ending with a 14 mm x 16 mm endoscope. Alternatively, resection of the esophageal stricture was performed with reconstruction using a free microvascular forearm flap. [1] However this is rare due to radiotherapy, but if it happens, is done by free vascular transplant from the bowel and is happened for benign strictures.
1.1.6 Classification

The TNM classification is the internationally accepted system for staging all forms of newly detected cases of cancer and the TNM-stage is for many tumors the most significant prognostic factor [192].

TNM system is used to numerically describe the anatomical extent of cancer and is based on three components: **T**, extent of the primary tumor; **N**, absence or presence of the disease in the regional lymph nodes. The definitions of the **N** categories for all head and neck sites except nasopharynx and thyroid are the same. Midline nodes are considered ipsilateral nodes except in the thyroid. **M**, absence or presence of distant metastasis. The definitions of the **M** categories for all head and neck sites are the same. The numerical staging aids oncologists in planning treatment and evaluating treatment results. The TNM staging system considers the disease only at diagnosis and has been suggested to use the clinical state from diagnosis to death as a dynamic model of disease progression [8, 10]. The histopathology can be assessed with a *Gleason score*; the system describes a score between 2 and 10, with 2 indicating the least aggressive and 10 the most aggressive tumor [9, 10]. The definitions of **G** categories apply to all head and neck sites except of thyroid. The absence or presence of residual tumour after treatment is described by the symbol **R**. The definitions of the **R** classification apply to all head and neck sites. [10]

<table>
<thead>
<tr>
<th>T-Primary Tumour</th>
<th>G-Histopathological Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tx</strong></td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td><strong>T0</strong></td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td><strong>Tis</strong></td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td><strong>T1, T2, T3, T4</strong></td>
<td>Increasing size and/or local extend of the primary tumour</td>
</tr>
<tr>
<td><strong>N-Regional Lymph Nodes</strong></td>
<td><strong>G4</strong></td>
</tr>
<tr>
<td><strong>Nx</strong></td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td><strong>N0</strong></td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td><strong>N1, N2</strong></td>
<td>Increasing involvement of regional</td>
</tr>
</tbody>
</table>

**Table I:** This table illustrates TMS classification, histopathological grating and R classification.
<table>
<thead>
<tr>
<th>N3</th>
<th>Lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-Distant Metastasis</td>
<td>R1</td>
</tr>
<tr>
<td>Mx</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

**Table II:** this table illustrates TMS classification, histopathological grating and R classification for head and neck tumours.

<table>
<thead>
<tr>
<th>Larynx</th>
<th>Lip, Oral cavity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraglottis</td>
<td>T1</td>
<td>≤2cm</td>
</tr>
<tr>
<td>T1</td>
<td>One subsite, normal mobility</td>
<td>T2</td>
</tr>
<tr>
<td>T2</td>
<td>Mucosa of more than one adjacent subsite of supraglottis or glottis or adjacent region outside the supraglottis, without fixation</td>
<td>T3</td>
</tr>
<tr>
<td>T3</td>
<td>Cord fixation or invades postcricoid area, pre-epiglottic tissues, paraglottic space, thyroid cartilage erosion</td>
<td>T4a</td>
</tr>
<tr>
<td>T4a</td>
<td>Through thyroid cartilage, trachea, soft tissue of neck: deep/extrinsic muscle of tongue, strap muscles, thyroid esophagus</td>
<td>T4b</td>
</tr>
<tr>
<td>T4b</td>
<td>Prevertebral space, mediastinal structures, carotid artery</td>
<td>N1</td>
</tr>
<tr>
<td>Glottis</td>
<td>N2</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Limited to vocal cord(s), normal mobility</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(a) one cord</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(b) both cords</td>
<td></td>
</tr>
</tbody>
</table>

- 23 -
<table>
<thead>
<tr>
<th>Stage</th>
<th>Area of Involvement</th>
<th>T4a</th>
<th>T4b</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>Supraglottis ,subglottis,impaired cord mobility</td>
<td>Pharynx</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Cord fixation, ,paraglottic space, thyroid cartilage erosion</td>
<td>Oropharynx</td>
<td></td>
</tr>
<tr>
<td>T4a</td>
<td>Through thyroid cartilage ,trachea ,soft tissue of neck: deep/extrinsic muscle of tongue ,strap muscles, thyroid esophagus</td>
<td>≤ 2cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prevertebral space, mediastinal structures, carotid artery</td>
<td>&gt;2 to 4cm</td>
<td></td>
</tr>
<tr>
<td>Subglottis</td>
<td>T3</td>
<td>&gt;4cm</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Limited to Subglottis</td>
<td>T4a Larynx ,deep/extrinsic muscle of tongue, medial pterygoid, hard plate, mandible</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Extends to vocal cord(s) with normal/impaired mobility</td>
<td>T4b Lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base, carotid artery.</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Cord fixation</td>
<td>Hypopharynx</td>
<td></td>
</tr>
<tr>
<td>T4a</td>
<td>Through thyroid cartilage ,trachea ,soft tissue of neck: deep/extrinsic muscle of tongue ,strap muscles, thyroid esophagus</td>
<td>≤ 2cm and limited to one subsite</td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>Prevertebral space, mediastinal structures, carotid artery</td>
<td>&gt;2 to 4cm or more than one subsite</td>
<td></td>
</tr>
<tr>
<td>All sites</td>
<td>T3</td>
<td>&gt;4cm or with hemilarynx fixation</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>Ipsilateral Single≤3cm</td>
<td>T4a Thyroid/cricoids cartilage, hyoid bone, thyroid gland ,esophagus, central compartment soft tissue</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>a) Ipsilateral Single&gt;3cm to 6 cm</td>
<td>T4b Prevertebral fascia, carotid artery, mediastinal structures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) Ipsilateral multiple ≤6cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c) Bilateral ,contralateral ≤6cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>&gt;6cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oropharynx and Hypopharynx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>Ipsilateral Single ≤ 3cm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| N2   | d) Ipsilateral Single >3cm to 6 cm  
|      | e) Ipsilateral multiple ≤ 6cm  
|      | f) Bilateral, contralateral ≤ 6cm |
| N3   | >6cm |
| **Nasopharynx** |
| T1   | Nasopharynx |
| T2   | Soft tissue |
| T2a  | Oropharynx/nasal cavity without parapharyngeal extension |
| T2b  | |
| T3   | Bony structures, paranasal sinuses |
| T4   | Intracranial, cranial nerves, infratemporal fossa, hypopharynx, orbit, masticator space |
| N1   | Unilateral node(s) ≤ 6cm, above supraclavicular fossa |
| N2   | Bilateral node(s) ≤ 6cm, above supraclavicular fossa |
| N3   | a) >6cm  
|      | b) In supraclavicular fossa |

**Stage classification**

The stages of tumour have been classified as presented in the following table:

**Table III:** This table illustrates the tumor stages.

<table>
<thead>
<tr>
<th>Stage 0</th>
<th>Tis*</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T1-T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0-N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV A</td>
<td>T4</td>
<td>N0-N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Every T</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV B</td>
<td>Every T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV C</td>
<td>Every T</td>
<td>Every N</td>
<td>M1</td>
</tr>
</tbody>
</table>
*Tis = Cancer in situ: Cancer in situ is not an invasive, which means that is not breaking through the basal membrane. In other words is local.

### 1.2 Management options of head and neck tumor

Treating the patient with H&N cancer is complex. Each specific site of disease, the extent of disease, and the pathologic findings dictate the appropriate surgical procedure, radiation fields, dose and fractionation, and indications for chemotherapy. Single modality treatment with surgery or radiotherapy is generally recommended for the approximately 40% of patients who present with early-stage disease (stage I or stage II). The two modalities result in similar survival in these individuals. In contrast, for the 60% of patients with locally advanced disease at diagnosis, combined modality therapy is generally recommended. Symptoms induced by radiation therapy are recorded in protocols like RTOG or EORT.

#### 1.2.1 Head and Neck Surgery

**Resectable Versus Unresectable Disease**

A patient's cancer is deemed unresectable if H&N surgeons doubt their ability to remove all gross tumor on anatomic grounds or if they are certain local control will not be achieved after an operation (even with the addition of radiotherapy to the treatment approach). Typically, such tumors densely involve the cervical vertebrae, brachial plexus, deep muscles of the neck, or carotid artery.

Unresectable tumors (ie, those tumors unable to be removed without imposing unacceptable morbidity) should be distinguished from those tumors in patients whose constitutional state precludes an operation (even if the cancer is readily resected with few sequelae). Additionally, a subgroup of patients will refuse surgical management, but these tumors should not be deemed unresectable. Although local and regional disease may be surgically treatable, patients with distant metastases are usually treated as though the primary tumor were unresectable. Thus, patient choice or a doctor's expectations regarding cure and morbidity will influence or determine treatment.

Patients with resectable tumors who can also be adequately treated without an operation represent a very important group. Definitive treatment with radiation therapy (RT) alone or RT combined with chemotherapy may represent an equivalent or preferable approaches to resection in these individuals. Although such patients may not undergo surgery, their tumours
should not be labelled as unresectable. Their disease is usually far less extensive than disease that truly cannot be removed.

Cervical Lymph Node Dissections
Historically, cervical lymph node dissections have been classified as “radical” or “modified radical” procedures. The less radical procedures preserved the sternocleidomastoid muscle, jugular vein, and spinal accessory nerve. The panel prefers to classify cervical lymphadenectomy differently, classifying cervical lymph node dissections as either “comprehensive” or “selective.”

A neck dissection is one that removes all lymph node groups that would be included in a classic radical neck dissection. Whether the sternocleidomastoid muscle, jugular vein, or spinal accessory nerves are preserved does not affect whether the dissection is comprehensive. Neck dissections have been developed based on an understanding of the common pathways for spread of H&N cancers to regional nodes. A supraomohyoid neck dissection is designed to remove the nodes most commonly involved with metastases from the oral cavity. A supraomohyoid neck dissection includes nodes found above the omohyoid muscle (level I, level II, level III, and the superior parts of level V). Similarly, a lateral neck dissection removes the nodes most commonly involved with metastases from the pharynx and larynx. A lateral neck dissection includes nodes in level II, level III, and level IV. H&N squamous cell cancer with no clinical nodal involvement rarely presents with nodal metastasis beyond the confines of an appropriate selective neck dissection (<10% of the time).

Many factors influence survival and locoregional tumor control in patients with H&N cancer. In most NCCN member institutions, patients with extracapsular nodal spread and/or positive surgical margins receive adjuvant chemoradiotherapy after resection. Patients with massive cancers (even if resected with a seemingly satisfying margin) or with laryngeal tumors that require preoperative tracheotomy are usually treated with postoperative radiotherapy.

1.2.2 Radiation Therapy

For over a century, physicists and clinicians have been trying to develop ways and means of delivering doses, to tumours in different anatomical sites of patients. Various types of equipment and methods of treatment delivery have been developed to meet different clinical requirements. Metallic beam modifiers were first used in the 1960s to alter the spatial
distribution of the intensity of the treatment beams. These have been an effective means of providing better coverage of dose to the tumours. Beam blocks, wedge filters, and beam compensators have been commonly used in 2-dimensional (2D) radiotherapy treatments. Practical means of delivering intensity modulated beams to achieve 3D dose conformity were not available until the mid 1990s. It was then that computer controlled linear accelerators with fully motorised multi-leaf collimators (MLC) were developed. In addition, 3D treatment planning computers with inverse planning algorithms for optimisation of dose were developed. Since then linear accelerator based IMRT treatment delivery systems that include the binary multi-leaf intensity-modulating collimator (MIMiC) [56], step-and-shoot MLC [57], dynamic MLC (sliding window) [58] and intensity modulated arc therapy (IMAT) [59] have been developed. They are commercially available for clinical implementation. Two other types of IMRT equipment, with different designs, namely Cyberknife [60] and helical tomotherapy [61] tool have also been developed and are commercially available. [55]

Radiotherapy for H&N cancer is extremely complex. Only a specially trained team consisting of a radiation oncologist, physicist, dosimetrist, and radiation technologist can achieve optimal results. In addition, modern radiotherapy equipment and techniques should be used. Anatomic, tumour, and clinical circumstances dictate the use of radiation as primary treatment or as an adjuvant to surgery in combination with chemotherapy for H&N cancer. Much variation in practice exists among various countries and even within different institutions in the same country. [123]

Figure 1.3: Exploded view of treatment head of the racetrack accelerator.
1.2.3 External Beam Three-Dimensional Conformal Radiotherapy (3-D CRT)

In conventional radiotherapy, the therapeutic dose is often limited by normal tissue tolerance [64]. Three-dimensional conformal radiotherapy has been developed to reduce the dose load to normal tissue by exactly tailoring the dose distribution to match the planning target volume (PTV). To be successful, 3-D conformal radiotherapy requires the proper definition of PTV [65]. What plays an important role to the clinical implementation of conformal treatment planning is the introduction of three-dimensional patient imaging, three-dimensional treatment planning systems, computer-controlled treatment machines equipped with multi-leaf collimators (Figure 1.4), and a continuing increase in computer power and software sophistication has allowed [63]. The importance of CT scanners development has to be noted since they can be used to obtain a detailed three-dimensional description of a patient's internal anatomy [63]. The three-dimensional information is used to create elaborate three-dimensional models of the tumour volume and any organ at risk to be protected during irradiation. Conformal radiation therapy employs carefully shaped beams to maximize the destruction of cancer cells while limiting damage to the surrounding tissue. The beam-shaping can be achieved using the backup jaws, cerrobend blocks, or a multi-leaf collimator (MLC) [66, 67]. Multi-leaf collimators were developed to shape the radiation field from the beam's-eye view (BEV). The beam's-eye-view is a computer-generated image that presents a patient's anatomy as it would appear to a viewer located at the radiation source and looking toward the isocenter of the PTV to outline the planning target volume. A multi-leaf collimator consists of a set of parallel focused opposed metal leaves; each leaf can be controlled separately in the forward or reverse direction (Figure 1.4) [67]. [3]
The use of 3D-CRT has been investigated as a treatment for several head and neck cancers, including skull base tumors. For example, Leibel et al compared 3D-CRT plans with conventional two-dimensional radiotherapy plans in 15 patients with nasopharyngeal carcinoma. They found that the 3D-CRT plans were superior to the two-dimensional plans in terms of both tumor control and reduction of normal-tissue complications. The probability of tumor control was 15% higher with 3D-CRT. Emami et al also demonstrated that 3D-CRT treatment plans were superior to conventional radiotherapy plans for patients with head and neck cancer. Moreover, Perez et al reported that acute toxicity with 3D-CRT for head and neck cancer was comparable to or less than that observed with conventional radiotherapy. Multileaf collimators significantly shorten the daily treatment time required to administer 3D-CRT. Gademann et al reported promising results with 3D-CRT in 195 patients who had tumors of the head, neck, or brain. After a median follow up of 22 months, 95% of patients treated with 3D-CRT throughout their entire course of radiotherapy were still alive, versus 86% of those who received 3D-CRT only during their final weeks of radiotherapy. As was the case in other studies, Gademann et al found that morbidity with 3D-CRT compared favorably with that of conventional radiotherapy. Latz et al described the outcomes of 13 patients whose clival chordomas were treated with 3D-CRT to a median dose of 70 Gy. After a median follow up of 32 months, 12 of the 13 patients (92.3%) were still alive. The local control rate was 69%. Only one patient developed endocrine dysfunction that required hormone replacement. No complication involving the optic pathway, cranial nerves, or brainstem was observed. [123]

### 1.2.4 Intensity Modulation Radiation Therapy (IMRT)

Intensity-modulated radiotherapy is considered as a new form of three-dimensional conformal radiotherapy. Using IMRT the intensity of radiation varies in a controlled way across the beams [68, 66]. The principal motivation for intensity- modulated radiotherapy is the fact that radiotherapy would be far greater if it were possible to deliver the radiation so that only the target regardless of its shape, receive a lethal dose, i.e. that the delivery of a high radiation dose should be confined to a spatial distribution that conforms as tightly as possible to the spatial distribution of cancer cells, while reducing the radiation dose to the radiosensitive normal tissues close to the tumour even if they lie within a concavity surrounded by the planning target volume [70, 66]. For a first approximation, the intensity is roughly

- 30 -
proportional to the target thickness along the beam as assessed from the beam's-eye view. The highest value of the beam intensity is where the target has the largest diameter while the lowest value of the intensity is where the target has the shortest diameter. Using intensity-modulated radiotherapy tumour doses can be escalated while the dose to adjacent organs at risk can be restricted below a tolerance threshold. The intensity distribution can be delivered to the patient by a variety of methods such as compensators, tomotherapy or a multi-leaf collimator (“step and shoot” or dynamic sliding window technique) [74, 75, 76, 66]. What makes the clinical implementation of intensity-modulated radiotherapy a reality are the development of inverse treatment planning algorithms [69, 70, 71, 72, 73, 77, 78, 79] and the dynamic multi-leaf collimator. In the processes of inverse treatment planning, doses to the target volumes and organ at risk are specified by applying dose-volume constrains. Various optimization algorithms have been developed to calculate the optimal intensity mutilated photon beam profiles that generate the described dose distributions. To deliver an intensity-modulated beam in the clinical routine, a dynamic multi-leaf collimator is used to sweep opposing pairs of tungsten-leaves across the field. Modulation is achieved by varying the size of the gap between the leaves as well as the length of time the gap remains open at each location in the beam. Intensity-modulated radiotherapy could be used for the whole duration of radiotherapy or as a boost. [3]

Figure 1.5: A dosimetry comparison between a 3-beam conventional 2D treatment at the left figure, a 6-beam conventional 3D conformal RT treatment in the middle and a 7-beam IMRT treatment at the right figure. The PTV is represented by the solid red line. The 100% and 70% of the prescription dose are shown by the green and red colour-washed areas. A better dose conformity to the PTV can be achieved in the IMRT treatment. [55]

In head and neck (HN) malignancies, IMRT appears to be more and more commonly used for routine treatment, especially in the U.S. Due to nasopharynx location, which is near numerous critical normal organs, that is, the brain stem and optic chiasm, IMRT is ideal in its attempt to
deliver an adequate dose to the gross tumor while sparing these surrounding normal tissues. By their location, sinonasal tumors are surrounded by critical structures, including the frontal and temporal lobes of the brain, pituitary gland and brainstem, lacrimal glands, eyes, optic nerves, and chiasm. Using conventional radiotherapy techniques, the lacrimal apparatus and the optic pathway structures (retina, optic nerves, chiasm) often received doses equal to the target prescription dose. Conventional radiation therapy for sinonasal cancer resulted in significant ocular toxicity [35, 38–39]. IMRT allows selective underdosage of organs at risk by creating concave dose distributions around the optic pathway structures together with steep cranial, lateral, and caudal gradients outside the PTV to spare the lacrimal apparatus and the central nervous system. Hypothetically, selective underdosage could decrease toxicity at unchanged target prescription doses. Comparative dose distribution studies have shown that IMRT can improve the target dose homogeneity in laryngeal and hypopharyngeal SCC while reducing the dose to normal tissues at risk [48–50]. Notwithstanding the limitations of this technique, all series of IMRT outcome have reported outstanding locoregional control rates for oropharyngeal cancer [11, 12, 43–45]. These series reported 2-year locoregional tumour control rates of 90%–98% for patient populations consisting mainly of stage III–IV tumours. [54] The promising results of IMRT can, however, be achieved only when all treatment conditions are met, for example, optimal selection and delineation of the target volumes and organs at risk, appropriate physical quality control of the irradiation, and accurate patient setup with the use of onboard imaging or more advanced imaging like CT during therapy. Because of the complexity of the various tasks, it is thus likely that these conditions will be met only in institutions having a large patient throughput. Therefore, patient referral to those institutions with experience in treating many patients with IMRT of HN cancer is recommended. [54]
1.2.5 Brachytherapy

Brachytherapy is used less often because of improved local control obtained with concurrent chemo/RT. However, brachytherapy still has a role primarily for lip cancer, cancer of the oral cavity, and oropharynx. Several European and North American medical centers have had extensive experience with brachytherapy. The success of brachytherapy techniques is partly dependent on the training, experience, and skills of the implant team.

1.2.6 Radiotherapy for Head and Neck cancer in Stockholm

In the beginning of the 1990s, dose-planning was guided by CT scanning using a TMS 3-dimensional (3-D) treatment planning system (TMS, MDS Nordion) at Radiumhemmet (Karolinska University Hospital). The technique has been changed during the year 2000. Radiation therapy became more conformal by the use of multi-leaf collimators and by increasing the number of fields.

From the data collected for this study the number of fields for some diagnoses used can be presented for the group of patients with oesophageal stricture and the group of patients without oesophageal stricture. For patients with tumour in Larynx area mostly have been used 2 fields and less often 4 or 7 for the control group, while patients of the case group have been treated mostly using 4 field or 8 less often. Patients with tumour in oropharynx have been treated using 2, 4, 5, 9 fields with the same weighting for the control group, while 2, 4, 8, 9, 11 fields for the case group also with the same weighting. For the treatment of patients with tumour diagnosed in the oral site mostly 4 fields have been used but also 2 fields for the control group, while mostly 6 fields have been used for the case group but also 4 fields. Finally for the treatment of patients with tumours diagnosed on the epipharynx site, 8 and 3 fields have been used with the same weighting for the control group, while 11 fields for the control group.

Radiation therapy using IMRT technique is made for eligible patients. In order to treat the patient by IMRT, some criteria considering age and tumour site have to be fulfilled. Furthermore it is used mostly for local tumours or when an organ at risk needs to be protected.
Figure 1.7: Image from treatment planning system, which illustrates the treatment technique. It is also illustrates the different radiation beams, the irradiated field in blue color, oesophagus in yellow color and the tumour in red color.

Figure 1.8: The figure illustrates the treatment planning system station TMS [Hellax]. [124, 125]

1.3 Dose-volume histograms

A 3-D treatment plan consists of dose distribution information over a 3-D matrix of points over the patient’s anatomy. Dose volume histograms (DVHs) summarize the information contained in the 3-D dose distribution and are extremely powerful tools for quantitative evaluation of treatment plans.
In its simplest form a DVH represents a frequency distribution of dose values within a defined volume that may be the PTV itself or a specific organ in the vicinity of the PTV. Rather than displaying the frequency, DVHs are usually displayed in the form of “per cent volume of total volume” on the ordinate against the dose on the abscissa.

Two types of DVHs are in use:
- Direct (or differential) DVH
- Cumulative (or integral) DVH

The main drawback of the DVHs is the loss of spatial information that results from the condensation of data when DVHs are calculated.

### 1.3.1 Direct Dose Volume Histogram

To create a direct DVH, the computer sums the number of voxels with an average dose within a given range and plots the resulting volume (or more frequently the percentage of the total organ volume) as a function of dose. An example of a direct DVH for a target is shown in Fig. 1.9 (a). The ideal DVH for a target volume would be a single column indicating that 100% of the volume receives the prescribed dose. For a critical structure, the DVH may contain several peaks indicating that different parts of the organ receive different doses. In Figure 1.9 (b), an example of a DVH for a rectum in the treatment of the prostate using a four-field box technique is sketched.

### 1.3.2 Cumulative Dose Volume Histogram

Traditionally, physicians have sought to answer questions such as: “How much of the target is covered by the 95% isodose line?” In 3-D treatment planning this question is equally relevant and the answer cannot be extracted directly from the direct DVH, since it would be necessary to determine the area under the curve for all dose levels above 95% of the prescription dose. For this reason, cumulative DVH displays are more popular.

- The computer calculates the volume of the target (or critical structure) that receives at least the given dose and plots this volume (or percentage volume) versus dose.

- All cumulative DVH plots start at 100% of the volume for 0 Gy, since all of the volume receives at least no dose.
For the same organs as indicated in the example of Figure 1.9, Figure 1.10 shows the corresponding cumulative DVH (both structures are now shown on the same plot). While displaying the percent volume versus dose is more popular, it is useful in some circumstances to plot the absolute volume versus dose. For example, if a CT scan does not cover the entire volume of an organ such as the lung and the un-scanned volume receives very little dose, then a DVH showing percentage volume versus dose for that organ will be biased, indicating that a larger percentage of the volume receives dose. Furthermore, in the case of some critical structures, tolerances are known for irradiation of fixed volumes specified in cm$^3$.

Figure 1.9: Differential dose volume histograms for a four field prostate treatment plan for (a) the target volume and (b) the rectum are shown. The ideal target differential DVHs would be infinitely narrow peaks at the target dose for the PTV and at 0 Gy for the critical structure.

Figure 1.10: Cumulative dose volume histograms for the same four field prostate treatment plan used in Figure 1.9. The ideal cumulative DVHs are shown on the right. [11]
1.4 Biological aspects of radiotherapy

Radiotherapy is a treatment option for malign tumours whose therapeutic agent is ionizing radiation, that is to say, the type of radiation that promotes ionization in the area in which it is applied, making it electrically unstable. Ionizing radiations are divided into the corpuscular and electromagnetic ones. Corpuscular radiations are represented by electrons, protons and neutrons; electromagnetic radiations are called photons, being represented by X rays and by gamma rays. In the clinical practice, most radiotherapy treatments are done through the use of photons [34]. Ionizing radiations act on the nuclear DNA leading to death or loss of its reproductive capacity. Since DNA content duplicates during mitosis, those cells with a high degree of mitotic activity are more radiosensitive than those with low mitotic rate. Radiation action can be direct or indirect. On the direct action, the DNA molecule is cleaved, interfering in the duplication process. On the indirect effect, water is dissociated into its two elements, H+ and OH; the latter reacts with the basis of DNA, interfering in the duplication process. Since water represents most part of cell content, the indirect effect is proportionally more important than the direct one [35]. Due to the fact of being in a continuous multiplying process; malignant cells can suffer the radiation effects. However, the multiplying ability varies according to cell type. Thus, there is a radiosensitivity scale both for tumour and normal cells. Embryonic malignancies and lymphomas are radiosensitive tumours, whereas carcinomas are moderately radiosensitive [36]. In order to express the amount of absorbed radiation by the tissues, an international unit, rad (radiation absorbed dose) was initially proposed, that is to say, the difference between the applied radiation and that which went through the tissues. Recently, this unit was replaced by Gray, defined as 1 joule per kilogram. Gy is short for Gray, thus: 1 Gy = 100 cGy =100 rad [37, 38]. Radiotherapy can be administered in short duration schemes up to extremely long schemes, lasting for several weeks. The justification for applications in small daily fractions is based on radiobiology “5 Rs”: reoxygenation, redistribution, recruitment, repopulation and regeneration.6 Most patients on radiotherapy receive a total dose of 50-70 Gy as curative dose. These doses are fractioned during a period of 5-7 weeks, once a day, 5 days a week, with a daily dose of approximately 2Gy. On the concomitant treatment, 45c Gy are used on the pre-operative stage and 55-60 Gy on the post-operative [39]. [5]
1.5 Treatment techniques and dose planning

Figure 1.11: In the anterior angled technique, which is illustrated on the right part of the figure two angled anterior fields are applied. This technique is used for small tumours without lymph node involvement. The transverse slice shows the anatomical structures of the gross tumour (GT), the oesophagus (ES) and the spinal cord (SC) that are involved in this clinical case. This is the first slice, where proximal oesophagus appears. From the sagittal view, we can see that the proximal oesophagus lies in the high dose region. In the unilateral field technique, which is illustrated at the left part of the figure, the applied fields irradiate only one side of the patient’s neck. It is applied to clinical cases where the tumour and the lymph node involvement lie laterally. In the transverse slice the internal target volume (ITV) is shown together with the anatomical structures of the normal tissues involved. Although in the sagittal view it is shown that the proximal oesophagus lie in the high dose region, the transverse view shows that the dose fall-off takes place inside the oesophagus, meaning that parts of it receive low dose.[2]
Figure 1.12: In bilateral field technique, two different treatment configurations are combined. Both of these dose plans involve lateral fields. The first configuration is applied for 23 fractions (2 Gy per fraction) though the second one follows for nine fractions. The main difference between the two configurations is the use of a protective block in the way of the beams in the second plan to protect the spinal cord. However, the dose distribution in the esophagus is approximately the same for both of the plans. Both the transverse and the sagittal views show that the proximal esophagus lies in the high dose region. [2]

All patients were set up in the supine position and immobilized in a mask (Posifix; Sinmed BV, Reeuwijk, The Netherlands). Treatment planning was performed on a three-dimensional conformal treatment planning system (TMS; Helax MDS-Nordion, Ottawa, Ontario, Canada).
The planning was based on approximately 30 computed tomography (CT) slices with a thickness of 0.5–1 cm and contiguous acquisition. This allows a slice by slice delineation of the region that is to be irradiated. In the calculation process of the treatment plan, correction for tissue inhomogeneity was performed. All patients in the study were treated on a 6-megavolt accelerator [1]. In order to record the fields and the angles have been used, the treatment protocol had been extracted from TMS for each patient.

Clinical Target Volume (CTV) consisted of the primary gross tumour (GT) and the locally involved lymph nodes (LN) [80]. A margin of 1-2 cm in all directions from known or suspected tumour was included to form the Planning Target Volume (PTV). Cervical and supraclavicular lymph nodes were included in all treatments except for early glottis cancers (T1). In bilateral treatments the posterior neck nodes were treated to 46Gy but otherwise a dose of 64Gy was delivered to the whole neck and supraclavicular nodes. Treatments were lateralized in cases of lateral primary tumour without neck nodes or with only ipsilateral spread. In hypopharyngeal and laryngeal cancers, treatment was always bilateral. Patients with small tumours in frontal localization (glottis larynx T1) were treated in a standardized way with two oblique, tilted rectangular fields without shielding. Patients with laterally located targets were planned with one frontal and one oblique posterior field. The treatment technique for a bilateral internal target volume (ITV), which included a primary tumour, bilateral lymph nodes and supraclavicular lymph nodes, consisted of two opposed coplanar or non-coplanar lateral conformal fields. In some of the cases where it was difficult to cover the supraclavicular region with the prescribed dose, the region was treated with anterior and posterior fields. The junction between the lateral fields and the anterior-posterior fields was at least 1-2 cm from the gross tumour volume (GTV). To improve the homogeneity of the dose distribution in a volume ranging from mandibula to jugulum, low weighted beam segments were added within the large fields.

The following guidelines, specified by the radiotherapists, were followed in treatment planning:

- Doses of preferably 65-/70Gy should be given to the GTV and similar doses (60-70 Gy) should be delivered to the lymph nodes apart from the posterior nodes, which should receive 46Gy.
- The dose to the spinal cord must not be higher than 50Gy.
- The treatment for head and neck includes PTVa and PTVb. PTVa includes CTV and lymph nodes and is also limited to 46Gy. However PTVb receives dose of 65-
70Gy. PTVb includes only PTVb, which means that only the CTV does not include lymph nodes (Bilateral lymph nodes).

The dose was delivered by a fractionation schedule of 2Gy per fraction, five fractions per week. These treatment techniques were used routinely at Radiumhemmet, Karolinska Hospital during the period of the study. DVHs were calculated for the upper part of the oesophagus, which is the most relevant to the clinical findings. In the cases of bilateral ITV, the treatment volume was treated to a dose of 46Gy in 23 fractions over 4.5 weeks. The volume anterior to the spinal cord was then boosted to 64Gy in nine supplementary fractions. The absorbed dose to the spinal cord did not exceed its (routinely used) tolerance dose of 50 Gy. For patients with lateral ITV or small frontal ITV (larynx, stage I), the complete ITV was covered with 64Gy and the dose to the spinal cord still did not exceed 50Gy. In vivo dosimetry was performed according to the ordinary routine on all fields in every fraction. The results of the dose measurements from this study were within accepted limits (± 2.9% deviation between the calculated and the delivered dose per field). A better agreement between the planned and the delivered dose could be achieved through the methods of Lind [81], Lind et al. [82] and Löf [83]. In cases where eye lens were located close to the treated volume, the absorbed dose to these organs at risk was determined by means of Thermo Luminescence Dosimetry (TLD, Harshaw QS 5500).[2].

1.6 Volume effect

The volume effect as defined by Hall and Giaccia et al 2006; Steel et al 2002 [102, 103] is the dependence of radiation damage to normal tissues on the volume of the tissue irradiated or as defined by Hopewell and Trott et al 2000 [104] is the relationship between the radiation doses causing the same probability of normal tissue complication and the irradiated volume of the investigated tissue. The volume effect phenomenon has been widely studied to improve the understanding [12]. Calculating the probability of causing injury to normal tissues is much more complicated than for tumours since it is dependent on the internal structure and organization of the functional subunits of the irradiated organ. [2]

There several types of volume effect existing in clinical practice considering the type of tissue and the endpoint [105]. The factors contributing to the effect are the following:

- **Reduced tolerance due to more intense complications.** A patient can tolerate injury in a small volume better than the same damage in a larger volume, where consequences are more dangerous and healing is slower. Therefore, increasing the
volume is a reason of making the injury more incapacitating to the host, even if the radiosensitivity of the target cells or FSUs is unchanged and so the severity of radiation response per unit volume, being independent on the treated volume.

- **Increased probability of complications.** In normal tissues, where FSUs are arranged in series, like spinal cord, the loss of one subunit results in organ injury regardless on the state of the other subunits in the series. This way, the probability of complication increases with increase in the number of exposed FSUs.

- **Increased heterogeneity of dose.** When a large volume is treated there are large gradients in dose distribution. Such a situation may lead to serious consequences including producing a marked change in incidence of complication when the dose-response curve is steep. The so called double trouble effect implies that an increased dose in part of the volume will receive an increased total dose and an increased dose per fraction and also often an increased dose rate.

- **Reduction in organ "reserve".** A volume effect relates to decreasing of the organ's functional reserve in direct proportion to the irradiated volume. In such a tissue (for example lung) the total dose required to cure most local tumors would be sufficient to eliminate the functional integrity in the treatment volume [105],[12]

### 1.6.1 Functional organisation of normal tissue

The fundamental effect of ionizing radiation on a tissue is caused by the slowing down secondary electrons that induce DNA damage responsible for the associated cell kill. But the tolerance of a tissue to radiation is dependent on the clonogenic cells' ability to maintain organ functions. The function of an organ depends upon the way the cells are organized into functional subunits (FSUs). Concerning the tolerance doses, there are two types of functional subunits:

1. **Structurally defined FSU**, where survival of an organ depends upon the survival of at least one clonogenic cell within it (kidney).

2. **Structural undefined FSU**, where cells are not aggregated into a structurally defined FSUs (skin). The size of structurally undefined FSU is defined by the maximum area or volume that can be repopulated by one stem cell to maintain organ function [105, 17]. [12]
### 1.7 Radiobiological models

Most of the radiobiological models that have been developed to describe the dose-response behaviour of different normal tissues and tumours\[111\] are characterized by the some common features such as those that follow:

- Cell survival after irradiation is binomial and obeys binomial or Poisson statistics.
- Response of an organ is determined by the death or survival of its target cells (functional subunits for normal tissues and clonogens for tumours).
- All the target cells respond identically.
- Isoeffect relationships are independent of the level of response.
- Equal effects are obtained from equal dose fractions if sufficiently separated in time.

There are basically two levels where the response of clinical structures to radiation can be mathematically modelled. Microscopically, considering cellular survival, and macroscopically studying organ response.

The radiobiological model that is used presently most extensively for describing the dose-response relation for tumours and normal tissues is the linear-quadratic-Poisson model, which also accounts for the fractionation scheme applied:

\[
P(D) = \exp \left\{ -N_0 e^{-\left( \frac{D}{D_{50}} \right) \cdot (e^\gamma - \ln \ln 2)} \right\} = \exp \left\{ -e^{e\gamma - \alpha d - \beta nd^2} \right\} \tag{1}
\]

where \( P(D) \) is the probability to control the tumour or induce a certain injury to an organ that is irradiated uniformly with a dose \( D \), \( d = D/n \) is the dose per fraction and \( n \) is the number of fractions. \( D_{50} \) is the dose which gives a response probability of 50% and \( \gamma \) is the maximum normalized value of the dose-response gradient. \( \alpha \) and \( \beta \) are the fractionation parameters of the model and account for the early and late effects expected [112, 113, 114]. Both \( D_{50} \) and \( \gamma \) depend on \( N_0 \), the initial number of the clonogenic cells for tumours or the initial number of functional subunits for healthy tissues. Parameters \( D_{50} \) and \( \gamma \) (or \( \alpha \) and \( \beta \)) are specific for every organ and specific for the kind of injury (endpoint) considered and can be calculated only from clinical data.
The radiation induced normal tissue complications have been described in terms of inactivation of functional subunits (FSU). The structural organization of FSUs can be categorized in the three following types: 1) critical element, 2) integral response, and 3) graded response. The critical element type is a serial organization of the FSUs, in which a complication appears when any of the FSUs is inactivated (such tissues are the spinal cord and the nerves). Another recommended FSU structure has been described in terms of serial organization, parallel and more generally, a combination of these two. The type of FSU infrastructure of a tissue plays an important role in the expression of a clinical effect since it is related to the volume dependence (or effect) of the tissue. The volume effect describes how the tolerance dose increases with decreasing partial volume of normal tissues being irradiated.

Calculating the probability of causing injury to normal tissues is quite different than for tumours since it is dependent on the internal structure and organization of the irradiated organ. To determine how damage to functional units leads to complications it is important to understand how organs are functionally structured in parallel and serial subunits. Many researchers have provided expressions for the probability of complications in which the volume effect is accounted for.

1.7.1 NTCP modelling

Of the radiobiological models that are based on cell survival functions, the relative seriality model, the \( k \) – model, the critical element model and the critical volume model are briefly presented here.

1.7.2 Relative seriality model (s model)

In this model the volume effect is treated by a combination of both serial and parallel FSU organizations. Normal tissue complication probability \( P_s \) is expressed as [112, 115, 116, 117, 118, 119, 120]:

\[
P_s(D,V) = \left[ 1 - \left( 1 - P_s(D, V_{\text{ref}}) \right)^{V/V_{\text{ref}}} \right]^{1/s}
\]

(2)

For a heterogeneous dose distribution the response of normal tissues is given by
\[ P_i(\bar{D},\bar{V}) = \left[ 1 - \prod_{i=1}^{M} \left( 1 - P(D_i, V_{\text{ref}})^\gamma \right)^{\Delta v_i} \right]^{1/s} \]  \tag{3}

where \( \Delta v_i = \Delta V_i / V_{\text{ref}} \) is the fractional irradiated subvolume of an organ compared to the reference volume, \( V_{\text{ref}} \) for which the values of \( D_{50} \) and \( \gamma \) were calculated and \( s \) is the relative seriality parameter that characterize the internal organization of the organ. \( P(D_i, V_{\text{ref}}) \) is the probability of response of the organ having reference volume and being irradiated to dose \( D_i \) as described by equation (1) and \( M \) is the total number of voxels in the organ.

Organs with serial infrastructure have small volume dependence since every subunit is vital for organ function. For organs with parallel infrastructure a strong volume dependence can be expected since the organ can maintain most of its function even when a large portion of its subunits are damaged. A relative seriality close to zero (\( s = 0 \)) corresponds to a parallel organ like lung or liver, whereas \( s = 1 \) corresponds to a closely serial organ with minimal volume dependence like esophagus and spinal cord.

The concept of reference volume is treated differently for normal tissues and tumours. Usually, the whole volume of the healthy organ is considered as reference volume and that is because the volume of an organ is related to the functional needs of the individual human being. In the case of tumours, reference volume is related to the characteristics of the clinical material from which the parameters \( D_{50} \) and \( \gamma \) were calculated.

Figure 1 illustrates the volumes for the dose calculation (upper part of the figure) and the model specific organization of the FSUs in the lower part as they are applied in a clinical case of cervix cancer. Each organ in the body of a patient is divided to a number of voxels, each of which has certain fractional volume \( \Delta v_i \). At the planning process, a certain dose \( D_i \) is attributed to each voxel and a certain relative seriality value \( s \) to each organ depending on the endpoint considered. This way, it is assumed that a uniform dose is given to the voxel whose response probability is calculated by equation (1), though the response of the whole organ is given by equations (2) and (3) where all its voxels are taken into account.
1.7.3 The k model

The k model is also using the Poisson survival function and it is expressed as follows [112, 117]:

\[
P_i \left( D, V \right) = \exp \left\{ -e^{\gamma} + k \ln \left( V/V_{ref} \right) - (D/D_{so})(e^{\gamma} - \ln \ln 2) \right\}
\]

(4)

The biological parameters of this model are: \( D_{so} \), \( \gamma \) and \( k \). The last parameter accounts for the volume effect of the organ and it is equal to one for uniform tumours whereas it generally has a negative value of normal tissues. This model handles the decreased risk of causing injury when a smaller volume of normal tissue is irradiated in a radiobiologically comparable way to the decreased control probability when a larger effective clonogen number \( \gamma \) is assumed for a tumour.[33]

1.8 The biologically effective uniform dose (\( \overline{D} \))

As it is defined at Lind et al 1999, Mavroidis et al 2000, the biologically effective uniform dose \( \overline{D} \) is the uniform dose that causes exactly the same total tumour control or normal tissue complication probability as a given non-uniform dose distribution on a complex patient case.

The notation \( \overline{D} \) indicates that the quantity has been averaged over both the dosimetric (dose distribution) and the biological (dose response relations) information of the complex patient.

The general expression of \( \overline{D} \) is defined for a given tumour or tissue from its dose–response relation without dependence on the radiobiological model used and it is then given by

\[ P(\overline{D}) \equiv P(D(\overline{r})). \]

The \( \overline{D} \) is based on the mean value theorem, which assumes that if one function \( f(x) \) is monotonic in the interval \([a, b]\), then there exists a value \( a \leq \xi \leq b \) such that

\[
\prod_{x=a}^{b} f(x) \Delta x = f(\xi) \sum_{x=a}^{b} \Delta x
\]

For organs with parallel infrastructure or tumours \( \zeta \) is located in the interval \([a, (a+b)/2]\) though for serially organized tissues \( \zeta \in [(a+b)/2, b] \). For a case of a target volume consisting
of different well-defined gross tumour (GT) and positive lymph node (LN) volumes, the biologically effective uniform dose $\overline{D}$ can be derived from the following expression,

$$P_B = P_{GT}(\overline{D}) \cdot P_{LN}(\overline{D}) = P_{GT}(D(\overline{r})) \cdot P_{LN}(D(\overline{r}))$$

where $D(\overline{r})$ denotes the real dose distribution. The expression presented is more general since it can deal with cases where multiple targets with different biological parameters are involved or even with cases where the radiosensitivity of a tumour varies over its volume (e.g. in the presence of hypoxic cells).

The mathematical expression of the $\overline{D}$ concept can be solved numerically. Analytical solutions can be found by making some assumptions, which lead to formulae that are approximations. To apply this expression of $\overline{D}$, the values of $P_B$ of the complex clinical case at hand can be calculated for a range of uniform doses using the radiobiological parameters of the structures involved. $P_B$ denotes the response probability of a tumour and B denotes benefit though I refer to injury. From these data the curve $P_B$/uniform dose can be produced and the $\overline{D}$ values of the $P_B$ points that are calculated from the dose distributions of different treatment plans can be found.

The advantages of the $\overline{D}$ concept and its differences from other reporting means that have been used have to be specified. In clinical practice the mean dose of the dose distribution delivered to the tumour or the ITV and its standard deviation are mainly used to compare the effectiveness of different plans in terms of tumour control. However, these data neither take into account the biological characteristics of the targets nor do they provide a common dose-scaling basis for comparison of different plans. This is because different plans deliver generally different mean dose to the ITV at the same control rate and the effect of the treatment to the rest of the involved organs is harder to compare using this scale. [62]

**MATERIALS AND METHODS**

2.1 Study bases

In this study there were included 33 patients who had developed esophageal stricture and 39 symptom free patients. For these 33 patients, esophageal stricture was diagnosed at the department of Otolaryngology at Karolinska Hospital, Stockholm, Sweden. The rest 39 patients did not refer any swallowing problems, so they were used as a reference group. For the data collection the medical records were reviewed. Each patient included in the control
group received a questionnaire by mail, by which they were asked whether they had any swallowing problems or not. Each patient included in the control group is alive and has agreed to participate in the study. It was not possible to restore the dose plans for every patient, because some tapes were broken or data were missing from the system. Those patients have been excluded from the study. The total number of the patients included in the study is 72 and each of them has been treated for head and neck carcinoma during the period 1991-2005. All patients have received external radiotherapy at the department of Oncology, Radiumhemmet, and the prescribed total dose used was either 64Gy or 68Gy, depending on the case. The analyses were made in two subgroups according to the treatment time, one that includes patients who have been treated during 1991-2000 and one that includes patients who have been treated during 2001-2005, and the total group, because of the different irradiation techniques used. The irradiation technique changed during the year 2000 and due to this fact the two subgroups were made according to the treatment time. During the period 1991-2000, 44 patients were included in the study, 19 of which developed oesophageal stricture (case), while 25 were symptom free (control group). The subgroup 2001-2005 consists of 28 patients, 20 of them as a case group and 8 patients as control group.

The study was not anonymous according to the need of following up the patients and in order to relate the symptoms to the treatment techniques, dose and treatment volume. Therefore the patients were coded to allow additional information which is related to the investigated variables. However the study was approved by ethical comity.

### 2.2 Hospital records

Information concerning the prescribed dose, the fractionation, the treatment period, and the tumour stage were retrieved from the hospital records. To evaluate the dose plans the treatment plans for each patient were retrieved. The dose planning data for each patient that were treated in Radiumhemmet between 1991-2005 were made in the treatment planning system Helax-TMS by MDS Nordion, and stored on tapes, which have been restored in order to collect the data needed for this research. The data collected for each treatment were images of 5cm of oesophagus, 2 cm and the whole part of oesophagus which included in the slices we had for every patient, including position, dose distribution, and differential DVHs. We do not have the dose volume histograms for the whole oesophagus because the CT scanning for Head and Neck tumours does not always include CT images of the whole oesophagus. The whole esophagus and also the first 5cm and 2cm of the organ were delineated in each CT
image of each patient. This area of the esophagus has been chosen because the esophageal strictures are formed to the upper esophagus and also because the irradiation techniques that are used are such, that the lower part receives considerably lower dose. The beginning of esophagus was defined anatomically to be 2cm below the vocal cords at the point that the cricoid cartilage appears. The CT slices have 1cm or 0.5 cm distance from each other. In some treatment plans we met both slice distances of 1cm and 0.5cm.Slice distances depends on the needs of the treatment planning.
Figure 2.1: it illustrates the CT scanning for a Head and Neck patient, as it is demonstrated in the treatment planning system Helax-TMS. In this treatment technique, the applied fields irradiate only one side of the patient’s neck. In this picture the targets are delineated with the red contour, while oesophagus is delineated with the yellow contour. Big part of the proximal oesophagus lies inside the field, which means that it is located in the high dose region. The red line shows that this slice has been selected and we can see this slice in the upper right part of the figure. The right box shows the selected slice, while the left one the preceding slice; in this case the selected slice is the last one. Each of the horizontal lines denotes the position of each slice. In this picture, there are slices of both 1cm and 0.5cm. However, in the oesophagus area there are only 1cm distance slices.
Figure 2.2: It illustrates the CT scanning for a Head and Neck patient, as it is demonstrated in the treatment planning system Helax-TMS. In this picture the field used is delineated with red colour, while the whole oesophagus is denoted with the yellow contour. 5.5cm of the oesophagus lies in the field, which means that the proximal oesophagus lies in a high dose region. The red line shows that this slice has been selected and we can see it on the upper left part of the figure. The right box shows the previous slice. Both of these slices correspond to the thoracic part and we can clearly see the lugs, the heart, the spinal cord, some blood vessels and the oesophagus outlined with a yellow contour. Each of the horizontal lines denotes the position of each slice, which in this case has 0.5cm distance.
2.3 Follow up

After the final treatment the patients were seen every 1–3 months by the surgeon and oncologist, respectively, for 5 years. All patients had a nursing visit for weight control every second week during and after radiotherapy at the ward for head and neck carcinoma patients in the Department of Otolaryngology for a period of 3 months. Weight was taken at each visit. In case of a 5% weight loss compared with the weight before radiotherapy, the patient was referred to a physician for nutritional support. [1]

2.4 Dose-Volume Histograms

In order to compare the DVH (Dose Volume histograms) for the patients that develop esophageal stricture after radiation therapy with the patients that had not such symptom, first of all we extracted the dose (in step of 0.2Gy) in relation with the absolute volume. The treatment planning system calculated differential DVHs, which were exported in a text file together with other personal information and statistical information about the dose and the volume for each patient, for all the defined structures. Afterwards cumulative dose volume histograms of the 2cm and 5cm of oesophagus were assessed for each patient. The cumulative volume was normalized to the total volume of the each part of the oesophagus. Finally the mean percentage DVHs was calculated for each patient group. The area under a percentage volume DVH is 100 times the mean dose. [3]

2.5 Different treatment techniques concerning the treatment time
Figure 2.3: The above pictures illustrate the isodose curves in a CT slice for head and neck treatment, using two different techniques. Every color denotes areas which receive different percentages of the total dose: the yellow curve includes the area that receives 35-65Gy, the green curve includes the area that receives 65-85Gy, the brown curve includes the area that receives 85-95Gy, the blue curve denotes the area that receives 95-105Gy, the purple curve includes the area that receives 105-115Gy and the red curve includes the area that receives 115-160Gy. In both of the above pictures esophagus is delineated with dark red contour and is located in a high dose area.
During the year 2000 the treatment technique in Radiumhemmet was changed. After 2000, treatments have been planned using smaller fields and keeping Larynx out of the field as much as possible. However, by keeping Larynx out of the field, esophagus is also protected. The usual treatment technique includes two phases; at the first phase the total prescribed dose is 46Gy to the isocenter, while at the second phase the total prescribed dose is 18Gy and is given as a boost. At that part of the therapy spinal cord was tried to be protected. After 2000, Larynx was always out of the field during the second part of the therapy, which includes the boost of 18Gy. The only exceptions are cases, at which the tumor is located at the Larynx area. That means that both Larynx and esophagus are always in the field. In head and neck cases, when the tumor is located in any other area, esophagus receives only a percentage of the dose of 46Gy, which is given in the first phase of the therapy. The change to the technique was made due to the change to PTV, which leads to smaller volume and optimization of the conformal therapy due to the increase of dose to the target volume while sparing dose to the normal tissue. As an example, Larynx is excluded from the lower part of treatment technique by the use of block. Another difference between the treatment techniques before and after 2000 is that, before 2000 the field orientation was lateral, while after 2000 anterior posterior.

2.6 Methods for evaluation

2.6.1 The relative seriality model

This model was developed to better account for the functional organization of FSUs, cf. Kallman et al 1992 [17]. For a heterogeneous dose distribution, the response of normal tissues is given by the expression:

\[ P_1(\bar{D}) = \left[ 1 - \prod_{i=1}^{M} \left( 1 - e^{-\eta \gamma \left( D_{50} / \sigma_i \right)} \right) \right]^{1/\alpha} \]

- Where \( P_1(\bar{D}) \) (I denotes injury) is the probability of inducing a certain injury to an organ that is irradiated with a dose distribution \( \bar{D} \):
- \( D_{50} \) is the dose which gives a response probability of 50%
- \( \gamma \) is the maximum normalized value of the dose-response gradient.

Both \( D_{50} \) and \( \gamma \) depend on the initial number of functional subunits for healthy tissues.
\( \Delta v_i (= \Delta V_i/V_{ref}) \) is the fractional subvolume of an organ that is irradiated compared to the volume of the reference length for which the values of \( D_{50} \) and \( \gamma \) were calculated.

- \( s \) is the relative seriality parameter that characterizes the internal organization of the organ.
- \( M \) is the total number of subvolumes in the organ.

The linear-quadratic-Poisson model is the radiobiological model for cell kill that was used in this work in order to describe the dose-response relation of oesophagus regarding the endpoint of radiation-induced stricture [13, 14, 15, 16, 17, 18]. That model also accounts for the fractionation scheme applied. The estimated radiobiological parameters refer usually to a certain dose per fraction. For this reason, the dose distributions delivered to the patients have to be converted to an equivalent fractionation regime that delivers that dose per fraction. The linear-quadratic model is applied often to account for those fractionation effects. The application of the proper fractionation correction may have a significant effect on the calculated dose distribution. For instance, when different treatment configurations are applied in different fractions then the fractionation correction has to be applied separately to each one of them before calculating the combined dose distribution [1]. Each oesophageal dose distribution was corrected to a 2Gy per fraction using the linear-quadratic model [19]. Thus, each dose step in the dose volume histograms was corrected separately. The a/b value assumed in the linear-quadratic model correction was 3Gy [106]. However, a sensitivity test was performed and the calculation was repeated using a/b values up to 8Gy even though there is no evidence in the literature indicating a deviation from the value of 3Gy. The radiation sensitivity was assumed to be homogeneous throughout the oesophageal volume. Different approaches in treating the concept of reference volume for the normal tissues have been reported. Usually, the whole volume of the healthy organ is considered as reference volume, because the volume of an organ is related to the functional needs of the individual human being. In this study, the upper 5 cm of the proximal oesophagus has been used as the reference length on the grounds that the oesophageal strictures are formed in this region. Moreover, the techniques applied deliver high dose only to this part of the organ, with the rest of it receiving significantly reduced dose. The use of shorter oesophageal length would become critical in terms of migration of epithelia cells from adjacent (marginal) mucosa as the dose at the margins would not be trivial in such a case.
2.6.2 Maximum likelihood fitting of the response model to clinical data

For the fitting of the parameters the maximum likelihood method was used, which determines the best estimates of the parameters by maximizing the likelihood to reproduce the given pattern of observations. The fitting calculations were performed through the use of a minimization package, MINOS. For the present calculations the parameter space was restricted to positive values. To find the global maximum of the logarithm of the likelihood function avoiding eventual local maxima, the calculations were performed by changing both the initial values (starting points) and the allowed range of the parameters. [2]

2.6.3 Evaluation of the goodness of fit of the dose-response parameters

The goodness of fit was estimated by applying three independent statistical methods. According to the method described by Jackson et al. [107] and Eadie et al. [108], given \( D_{50}, \gamma \) and \( s \) from the maximization result, the average of the log-likelihood function and its variance are calculated assuming a Gaussian distribution for the log-likelihood function. The expected mean value and standard deviation are then compared to the optimum value of the log likelihood function found by the maximization process. Subsequently, the probability of achieving a worse fit regarding the estimated pattern of complications is calculated. A high probability (close to 1) would mean that a very good agreement between the two distributions (predictions, clinical results) has been reached and the fit can be considered as optimal. [2]

The \( x^2 \) test

The Pearson’s \( x^2 \) test is a statistic that characterizes the dispersion of the observed frequencies from the expected frequencies. The numerator of the \( x^2 \) formula is a measure of the spread of the observations whereas the denominator is a good measure of the expected spread. The \( x^2 \) value although referred to as a measure of goodness of fit actually represents a measure of lack of fit and it should thus be as low as possible. This means that the smaller the \( x^2 \) or the reduced \( x^2 \) values (taking into account the number of degrees of freedom, DF, that is the number of data points in the particular dataset reduced by the number of parameters in the respective model), the better the overall fit of the model or the better the dose response curve agrees with the experimental data, when the volume effect has been removed. [12] In this work, the goodness of fit is assessed by comparing the two different treatment techniques used in the two different treatment periods. Each patient subgroup covers a different dose range of the dose-response curve. By applying the \( x^2 \) test to the different pairs of...
results\textsuperscript{10}(observed against expected) the probability that a random sample of data points drawn from the assumed probability distribution would yield a value of $\chi^2$ as large or larger than the observed value in a given experiment with $n$ degrees of freedom. If the probability is reasonably large (close to 1), that means that the predicted distribution describes correctly the spread of the data points. If the probability is small, either the predicted distribution is not a good estimate of the parent distribution or the data sample is not representative of the parent distribution. \cite{2}

ROC curves

Another approach to test the fitting was to perform a validation based on the analysis of receiver operating characteristic (ROC) curves \cite{109, 100}, which are plots of the true positive rate against the false positive rate for different possible cut-offs of a diagnostic or predictive test. The individual probabilities of observing an oesophageal stricture were calculated using the dose distribution delivered to each patient and the model parameters derived from the maximum likelihood fitting. The patients were ordered by their calculated probabilities and a series of trial cut-offs, $P_{\text{cut}}$ was examined. By comparing the number of observed complications above $P_{\text{cut}}$ with the number of predicted complications, the true positive ratio (TPR, the ratio of observed positive incidences above $P_{\text{cut}}$ to the total number of positive incidences) and the false positive ratio (FPR, the ratio of observed incidence-free patients above $P_{\text{cut}}$ to the total number of incidence-free patients) were determined. TPR and FPR were plotted against each other in the form of a ROC curve. The area under the curve measures discrimination, which is the ability of the test to correctly classify those with and without the disease. For perfect classification of the observed against the predicted complication results, the area under the curve is 1. Random assignment of complication results leads to a ROC area of 0.5. An evaluation of the parameter errors was done by calculating their 68\% and 95\% confidence intervals. These were obtained by calculating the three-dimensional 68\% and 95\% joint confidence regions of the parameters $D_{50}$, $\gamma$ and $s$, i.e. the region in the $D_{50}$-$\gamma$-$s$ hyper-volume, in which it is estimated that there is 68\% and 95\% probability of finding the true values of the three parameters respectively. The $D_{50}$-$\gamma$-$s$ hyper-volume was found by varying the parameters around their optimum values. In order to study the impact of the parameter uncertainties on the dose-response curve, a bundle of dose-response curves was calculated using parameter values from the calculated confidence intervals. The described procedure represents a first step in quantifying the uncertainty of the dose-response curve, due to the uncertainties in $D_{50}$, $\gamma$ and $s$, imposed by the fitting procedure.
2.7 The biologically effective uniform dose, \( \bar{D} \)

The biologically effective uniform dose was defined by Mavroidis et al 2001 [62], as the uniform dose that causes exactly the same tumour control or normal tissue complication probability as the real dose distribution.

\[
\bar{D} = \frac{\gamma y - \ln(-\ln(P(\bar{D})))}{\gamma y - \ln(\ln(2))}
\]

In this work, this concept is used to find the uniform dose that is as biologically effective as the dose distribution, \( \bar{D} \) delivered to each patient in the study population. For each patient the effectiveness of the applied dose distribution is calculated by the relative seriality model and the set of parameters estimated by the maximum likelihood method. [2, 62]

Table IV: the following table demonstrates the clinical characteristics of the study population.

1991-2005

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<thead>
<tr>
<th>Clinical characteristic</th>
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<th>patients without oesophageal stricture</th>
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<td>Females</td>
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<td>15</td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
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<td>16-92</td>
<td>33-92</td>
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<tr>
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<tr>
<td>Mean dose –Gy(SD)</td>
<td>42.44(12.8)</td>
<td>49.9(8.7)</td>
<td>35.0(16.9)</td>
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**Prescribed dose at isocenter -Gy(%)**

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**No. of fractions**

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**Diagnoses(%)**

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<tr>
<td>Treatment period (d)</td>
<td>45.5</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>Diagnoses(%)</td>
<td>Larynx</td>
<td>35.5</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Oropharynx</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Hypopharynx</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Epipharynx</td>
<td>9</td>
<td>12</td>
</tr>
</tbody>
</table>

Results

Table IV illustrates the clinical characteristics of the eligible patients for the study. These clinical characteristics show how the case and the control group are matched together. From the 25 patients who developed esophageal stricture after radiation therapy during the period 1991-2000, 14 were males and 10 were females, while from the 19 symptom free patients, who received radiation therapy during the same period, 10 were males and 9 were females. During the treatment period 2001-2005, 8 patients developed esophageal stricture, from which 6 were males and 2 were females, whereas from the 20 control patients, 14 were males and 6 were females. Another important factor for the matching of the two groups is the age of the patients included in each group. The range of the ages for case group, for the treatment period 1991-2000, is 16-78 years and the mean age of these patients is 59.3 years, while for the control group of the same period the range of the ages is 43-92 years and the mean age of this group of patients is 66.2 years. For the treatment period 2001-2005 the corresponding range of patients ages and mean ages are 53-92 years and 69.6 years for the case group and 33-72 years and 59.2 years for the control group. For both treatment periods the follow up time is assumed to be 2 years. It is important to refer the mean volume of 5 cm of esophagus as it is calculated from the TMS. For the treatment period 1991-2000 the value of the mean volume...
of 5cm of esophagus is 7.1(SD: 1.7) and 7.6(SD: 2.2) for the case and the control group respectively.

3.1 Dose distributions

All the dosimetric results of this work are based on the differential DVHs, collected from the treatment plans. This section will deal with the analysis of the DVHs from 5cm of oesophagus for the two subgroups considering the treatment time and the subgroups considering the tumour diagnose.

3.1.1 Subgroups considering treatment time

The mean cumulative DVHs of the proximal oesophagus were obtained for the three different treatment periods made for this study. The following figures illustrates the mean cumulative dose volume histograms of proximal oesophagus for patients, who developed esophageal stricture and patients who were symptom free. There are DVHs for the total group of 72 patients and the two subgroups which include patients, who were treated during the periods 1991-2000 and 2001-2005. The hypothesis to make these two subgroups was that the treatment technique had been changed during the year 2000 and that could have an effect to the dose distributions in oesophagus. The dose volume histograms corresponding to the treatment period of 1991-2000 does not show any significant difference to the dose distribution between patients with or without the symptoms. On the other hand there is a significant difference to the dose distributions for patients, who have been treated during 2001-2005. The DVHs for total group are the mean DVHs of the subgroups, so we can see some difference between the DVHs of symptom and symptom free patients.
Figure 3.1: Cumulative DVHs for patients that develop stricture (blue line) and symptom free patients (purple line) for the treatment period 1991-2005.

Figure 3.2: Cumulative DVHs for patients that develop stricture (blue line) and symptom free patients (purple line) for the treatment period 1991-2000.
Figure 3.3: Cumulative DVHs for patients that develop stricture (blue line) and symptom free patients (purple line) patients for the treatment period 2001-2005.

As it is presented at the table IV the mean and maximum doses for the period 1991-2000 are 49.9 (SD: 9.1) and 61.2Gy, respectively for the group of patients with stricture, while they are 45.9(SD: 14.3) and 64.8Gy for the control group. These values, for the patients who have been treated during the period 2001-2005 are 49.8(SD: 7.7) and 61.4Gy, respectively for the group of patients with stricture, whereas they are 21.4(SD: 15.6) and 46.1Gy, respectively for the control group. The treatment has been done in two phases; during the initial phase 46Gy has been delivered in 23 fractionations of 2Gy/fraction, while 18Gy - 22Gy has been delivered as a boost in 9 or 11 fractions of 2Gy/fraction. In total 2 patients from the case group and none from the control group, that has been treated during 1991-2000 received 68Gy, while the rest 23 from the case group and 19 from the control group received 64Gy. Based on the patients group, that has been treated during 2001-2005 ,2 patients from the case group and 5 from the control group received 68Gy ,1 patient from the control group received 66Gy and 1 also patient from the control group received 60.3Gy. The rest 23 patients ,which belong to the case group and 12 which belong to the control group ,received 64Gy. The mean value of the treatment period for each patient, that has been treated during 1991-2000, is 45days and 46days ,respectively for the case and control group, while for the treatment period 2001-2005 is 50days and 43days, respectively for the case and control group.
3.1.2 Subgroups considering tumour diagnose

The total group, made by considering patients who have been treated during the whole treatment time, 1991-2005, was further divided into smaller groups based on the tumour diagnose. Table illustrates the percentages of patients distribution based on their diagnoses for the 33 patients, who developed oesophageal stricture after the radiation therapy and the 39 patients, who were symptom free. From those 33 patients which developed the symptom, 24% has been diagnosed tumour in Larynx and from the 39 patients that were symptom free, 47% has been diagnosed tumour in Larynx. The distribution of the patients percentages, which have been diagnosed with tumour in oropharynx are 28% and 16%, for the case and the control group, respectively. Furthermore, 8% of the case group and none from the control group, have been diagnosed with tumour in hypopharynx, while 12% of patients from the case group and 5% of patients from control group, have been diagnosed with tumour in epipharynx. Diagnoses as oral tumour had the 12% of the case group and 5% of the control group. Finally patients with tumours in other areas of head and neck, belongs to the subgroup which is called others. This subgroup includes 8% of patients which develop stricture after radiation therapy and 16%, which were symptom free. The following DVHs illustrates the distribution of dose into the volume for each subgroup, made based on different diagnoses, using the absolute number of patients, included in each group.
Figure 3.4: The above figure illustrates Cumulative DVHs for patients that develop stricture and symptom free patients. These patients have been diagnosed with tumours located in larynx, oropharynx and oral area have been treated during the treatment period 1991-2005.

The above figures illustrate the distribution of dose to the volume for the three main subgroups of diagnoses, which includes patients who have been diagnosed with tumour to the larynx, oropharynx and oral. From the DVHs of patient with diagnose larynx we can see, that for high doses both case and control group received almost the same dose, while for lower doses, patients who developed stricture received less dose than the symptom free group. On the other hand, in the DVHs of patients with oropharynx and larynx as diagnose, there is a significant difference between the dose received from the case and control group. The DVHs for the rest diagnoses chosen for this study are not presented, due to the small number of patients they include.

3.2 Dose-response parameters

For the period 2001-2005 the dose response parameters have been calculated correcting each step of the DVHs with the linear-quadratic model assuming the value fo the ratio a/b value of 3 Gy. The analysis was carried out for the upper 5 cm of the proximal oesophagus and the best estimates of the dose-response parameters are $D_{50}=62.3$ Gy with confidence intervals between 52.4-87.3 Gy, $\gamma = 1.14$ with confidence intervals between 0.74-2.28 and $s = 0.11$ with confidence intervals between 0.01-0.33. For the treatment period 1991-2000, the calculations of the dose response parameters are in progress.

Table V: Best estimates and confidence intervals of the relative seriality model parameters derived from the patient material of the study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Best estimates and confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{50}$ dose giving 50% of complication probability (Gy)</td>
<td>62.3, 52.4-87.3</td>
</tr>
<tr>
<td>$\gamma$, maximum normalized gradient of the dose-response curve</td>
<td>1.14, 0.74-2.28</td>
</tr>
<tr>
<td>$s$, relative seriality parameter</td>
<td>0.11, 0.01-0.33</td>
</tr>
</tbody>
</table>
Figure 3.5: In the above diagram, the corresponding dose-response curve of the estimated radiobiological parameters is presented for a range of uniform doses. The parameters’ volume dependence is demonstrated by assuming that: (a) the whole organ (100%) receives a uniform dose; (b) two thirds (66%) of the organ receives a certain uniform dose and the remaining part receives 5% of this dose; and (c) one third (33%) of the organ receives a uniform dose and the rest 5% of this dose. We can see that by decreasing the volume of oesophagus irradiated, higher doses can be sustained for the same incidence rate of oesophageal strictures. The grey surface area indicates the percentages of patients with oesophageal stricture in dose intervals 20-35Gy, 35-50Gy, 50-65Gy. The unit of the dose axis is the biologically effective uniform dose $D$: By using this dose unit the position of every patient of the study population can be found on the theoretical response curve (crosses for the patients with complications, white circles for the complication-free patients). The small diagram shows the dose-response curve in full range with the patients being placed according to their clinically observed response (0 or 1). Three dose intervals between the $D$ values of 24 and 35Gy (24-35, 35-50, 50-65) are observed where 1.18 %, 20.0 % and 28.6 % of the patients had complications. The expected complication rates of the patients in those intervals are 1.55 %, 13.2 % and 40.8 %, respectively, which are fairly close to the clinical observation regarding the small number of patients selected.

3.3 Statistics

Dividing the patient population in 2 subgroups according the treatment techniques, which are represented by the two treatment periods, the Pearson’s $x^2$ test has been used and the calculated $x^2$ value is . The probability that stems from this value of $x^2$ (for one degree of freedom) for having a perfect agreement between the expected and the observed
complications results is 0.95. This value indicates that the relative seriality model and the estimated parameters reproduce very well the pattern of the clinically recorded complications. Using the data of the patients subgroup treated during 2001-2005, ROC curves and odds ratio have been calculated. The area under the ROC curve is another way to evaluate the predictive power of the applied radiobiological model, which measures the ability of the model to classify the patients with and without oesophageal strictures. The value of the area under the ROC curve is for the treatment period 1991-2000 is 0.62, while that area for the treatment period 2001-2005 is 0.92, which indicates that the relative seriality model seems to differentiate well the patient groups with and without stricture. Odds ratio was found to be (OR) = 13.0 with 95% confidence interval (CI) of 2.9-58.6 and the cut-off chosen was 50 Gy. That means, that a statistically significant positive association of radiation induced esophageal stricture with the biologically effective uniform dose was found.

**Table VI:** Results from the fit of the biological model on the patient data. The goodness of fit was determined for the patient subgroup treated between 2001-2005 by different methods (Odds ratio, Pearson’s test, ROC analysis)

<table>
<thead>
<tr>
<th>Statistical method</th>
<th>Association of theoretical and clinical results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Odds ratio</strong></td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td>95% CI = 2.9-58.6</td>
</tr>
<tr>
<td><strong>Pearson’s $x^2$ test</strong></td>
<td>$\chi^2$</td>
</tr>
<tr>
<td></td>
<td>$p_{\chi^2}(\chi^2, v)$</td>
</tr>
<tr>
<td></td>
<td>0.072</td>
</tr>
<tr>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td><strong>ROC (1991-2000)</strong></td>
<td>0.62</td>
</tr>
<tr>
<td><strong>ROC (2001-2005)</strong></td>
<td>0.92</td>
</tr>
</tbody>
</table>
Figure 3.6: the grey surface corresponds to the group of patients who have been treated during the treatment period 2001-2005, while the black striped area corresponds to the patients who have been treated during the treatment period 1991-2000. The grey surface gradually increases while we move on to higher dose columns and is bigger to the last column, which corresponds to high doses (45-65Gy). This fact shows that, as it is expected, when we have higher doses we have more complications. Taking into consideration this fact we can choose a cut off at 45 Gy. From the black strips surface it is observed that there are no big differences to the number of complications when we increase the dose. The calculated value 0.06 shows that the two techniques have great differences.

Figure 3.7: The above diagram illustrates the receiver operating characteristic (ROC) curve for the clinical endpoint of oesophageal stricture for the two subgroups concerning the treatment time. These curves were constructed using different cut-off thresholds and calculating the corresponding true positive ratio (TPR) and false positive ratio (FPR) values. [20] The accuracy of the test is measured by the area under the ROC curve. For the left diagram the area under the curve is 0.62, so the test does not separate well the two groups (with and
without the stricture). For the right diagram the area under the roc curve has been calculated 0.92, which means that the test separate well the case and control.

**Discussion**

4.1 *Dose distributions*

From the figures 3.1, 3.2, 3.3 can be observed that the corresponding DVHs show a significant difference to the dose distribution between the case and the control group for patient who have been treated during the treatment period 2001-2005. On the contrary, there is no significant difference between the DVHs for patients who developed oesophageal stricture after radiation therapy and patients that did not have any swallowing problems, for the treatment period 1991-2000. Especially for high doses (50-65Gy) we can see that the dose distribution in oesophagus is almost the same. From the dose distributions for the treatment period 1991-2000 we could not say that there is an obvious correlation between the dose and the symptom, while from the DVHs of 2001-2005 we could say that dose is an important factor for the development of oesophageal stricture. The difference between the dose distributions for these two different treatment periods is probably due to the change of the treatment technique which happened during the year 2000. After 2000, the technique became more conformal and larynx was taken out of the field when it was possible or was protected by using block. By protecting larynx, oesophagus was also protected. Furthermore, the field orientation has been changed after the year 2000. This change could result in different dose distributions. The number of patients who belong to the case group and have been treated during the treatment period 2001-2005 is quite low (8 patient) and this fact can insert an uncertainty. Furthermore, one possible reason that there is no significant difference between the dose distribution for the case and the control group for the patients who have been treated during the period 1991-2000 is intrapatients’ radiosensitivity.

Figure 3.4 illustrates the DVHs considering the patients’ subgroups made taking into account the tumour site diagnoses. The subgroups (oral, oropharynx, larynx), from which DVHs are presented, are the subgroups with the higher number of patients. We cannot come to a relevant conclusion from the rest subgroups because they include very few patients. From DVHs for oral and oropharynx can be observed that patients with oesophageal stricture for both oropharynx and oral area received higher doses in these areas than symptom free patients. From the diagram with the DVHs of patients with larynx diagnoses we can see that for high doses (60-70Gy) the dose distributions for the case and the control group are the
same in larynx area. For doses lower than 60Gy, larynx receives higher doses for the control than for the case group. In this case other factors except from dose, such as the intrapatient radiosensitivity and the small number of patients included in this group, insert an uncertainty.

### 4.2 Dose response parameters

Usually the calculated radiobiological parameters describing the dose-response relation of an organ refer to a certain uniform dose per fraction. Consequently the dose delivered to the patients has to be adjusted to this dose per fraction before deriving these parameters. Generally it is desirable to have many different treatment techniques in the study material because this usually implies that the clinical data cover a larger dose range on the dose-response curve (since the dose distributions may differ significantly) leading to a more accurate estimate of the curve. Moreover in this case systematic errors that stem from the applied treatment technique smooth out. The radiobiological parameters derived from such analyses refer usually to a certain dose per fraction (most often 2 Gy). So a correction for the fractionation effects has to be applied to the dose plans before using their dosimetric information. In this study the fractionation correction was applied using the linear-quadratic model. Although this model is accurate for high doses it has not been validated for doses lower than 1Gy. Consequently the correction may be approximate in this dose region [2].

Using the material which is presented to the table III the parameters $D_{50}$, $\gamma$ and $s$ of the relative seriality model were calculated.

- The value of the estimated $D_{50}$ is 62.3Gy (confidence intervals: 52.4-87.3 Gy), which is close to the prescribed dose whose value is 64Gy. This happens because the radiotherapy technique used is conventional and not IMRT. The reason that the value of $D_{50}$ is close to the value of the prescribed dose, is that oesophagus is located close to the tumour and the technique used is not conformal enough. The value of the prescribed dose is based mostly to NTCP (normal tissue complication probability). In H&N treatment there are PTV-A and PTV-B. PTVA is included tumour (GTV+CTV)+ marginal and effected lymph nodes + marginal (PTVA). In PTVB is included tumour (GTV+CTV) + marginal (PTVB). The effected lymph nodes recieves the full dose of 46 Gy. On the other hand, the tumour full dose is either 64 or 68 Gy, so in order to reach the full dose the tumour target volume (GTV + CTV) + Marginal for internal organ and set –up movement (PTV) receives 18 or 22 Gy more.
The estimated value of the $s$ parameter indicates the behaviour of the organ (serial or parallel) because the CT (Computed Tomography) does not include the functional subunits. The estimated value for the relative seriality parameter in this study is $s = 0.11$ (confidence intervals: 0.01-0.33), which means that oesophagus has parallel behaviour. That means that there is not strong volume dependence and that big volume of oesophagus has to be irradiated in order to see the effect of the radiation. On the other hand, in other studies [21, 22], it is observed, that the relative seriality parameter $s$ is substantially lower and oesophagus seems to behave as a serial organ. There are two main reasons that this occurs. Firstly, the dose delivered to the oesophagus in many of the previous studies was not known to the extent that it is now (3D treatment planning systems, etc). Secondly, almost all of these studies investigated another part of oesophagus while this study is dealing with proximal oesophagus. This difference observed, supports the argument which has been expressed by many authors [21, 22] that the radiosensitivity and possibly the volume dependence of the oesophagus varies along its length. In this case, different radiosensitivity parameters should be used in different radiotherapy sites to associate the delivered dose with the expected clinical outcome. [2]

It should be mentioned that most of the patients that were treated with the unilateral technique had no complications. This is strong evidence that proximal esophagus is a relatively parallel organ being characterized by a high volume dependence. The observed relative seriality can be influenced by the reference length or volume of the organ examined. If a very small part of the oesophagus receiving uniform dose had been selected instead, then the relative seriality would appear to be very low. This is because it would not be possible to differentiate the response of the individual FSUs and identify their association since all of them would receive very similar doses, having consequently very similar response probabilities. The best way to observe the true relative seriality is by selecting a large part of the organ and utilizing irradiation techniques that produce significant dose degradation inside the organ. In this way, the volume effect can be estimated since the sparing of part of the organ will clearly show if this is adequate to retain the function of the organ. [2]

- The value of $\gamma$ parameter shows the distribution of the radiosensitivity, in other words the population inhomogeneity. The estimated value of the $\gamma$ parameter is 1.14 (confidence intervals: 0.74-2.28), which means that the NTCP curve is not so steep.
Generally normal tissues do not have usually high $\gamma$ values, while tumours have usually high $\gamma$ values ($\gamma \approx 4$). The received dose is homogeneously distributed in the tumours contrary to normal tissues. Furthermore dose prescription for tumours which corresponds to the upper part of the dose response curve is quite high for control group. Normal tissues correspond to the lower part of the dose response curve and due to this fact there is an uncertainty about the rest of the curve, based on the lack of data. In this case the used model is very important. Considering tumours, the probability of patient or organ movement has been taken into account by the margin; while in normal tissue is uncertain in which isodose the organ will be probably located.

The corresponding dose-response curve of the estimated radiobiological parameters is presented for a range of uniform doses in figure 3.5. The parameters’ volume dependence is demonstrated by assuming that: (a) the whole organ (100%) receives a uniform dose; (b) two thirds (66%) of the organ receives a certain uniform dose and the remaining part receives 5% of this dose; and (c) one third (33%) of the organ receives a uniform dose and the rest 5% of this dose. We can see that by decreasing the volume of oesophagus irradiated, higher doses can be sustained for the same incidence rate of oesophageal strictures. The grey surface area indicates the percentages of patients with oesophageal stricture in dose intervals 20-35Gy, 35-50Gy, 50-65Gy. The unit of the dose axis is the biologically effective uniform dose $D$: By using this dose unit the position of every patient of the study population can be found on the theoretical response curve (crosses for the patients with complications, white circles for the complication-free patients). The small diagram shows the dose-response curve in full range with the patients being placed according to their clinically observed response (0 or 1). Three dose intervals between the $\bar{D}$ values of 24 and 35Gy (24-35, 35-50, 50-65) are observed where 1.18 %, 20.0 % and 28.6 % of the patients had complications. The expected complication rates of the patients in those intervals are 1.55 %, 13.2 % and 40.8 %, respectively, which are fairly close to the clinical observation regarding the small number of patients selected. This was expected since the parameter values used were derived from the same study population. However it is shown how these parameters should be applied in the clinic and how one could check if some published parameters are suitable for a certain treatment methodology. [2]
4.3 Statistics

The purpose of using statistics is to show that the estimated parameters lead to a very good agreement between the predicted complications and the true complication incidences for the study population. This is expected to some extent, since the estimation of the model parameters was done using the study population. However, they also serve the purpose of recommendation as a mean to check whether another patient population (meaning another irradiation technique or treatment methodology) is compatible with the derived model parameters. This is something that should always be done before using parameters that have not been derived from the clinic. The aim of this process should be to derive the local data in order to support the validity of the initially used parameters. [2] Figure 3.6 illustrates the difference between the techniques, showing the relation between the mean dose and the number of complications. The grey surface corresponds to the group of patients who have been treated during the treatment period 2001-2005, while the black striped area corresponds to the patients who have been treated during the treatment period 1991-2000. The grey surface gradually increases while we move on to higher dose columns and is bigger to the last column, which corresponds to high doses (45-65Gy). This fact shows that, as it is expected, when we have higher doses we have more complications. Taking into consideration this fact we can choose a cut off at 45Gy. From the black strips surface it is observed that there are no big differences to the number of complications when we increase the dose. The calculated value 0.06 shows that the two techniques have great differences. Another statistical test is illustrated by the figure 3.7, which shows the receiver operating characteristic (ROC) curve for the clinical endpoint of oesophageal stricture for the two subgroups concerning the treatment time. These curves were constructed using different cut-off thresholds and calculating the corresponding true positive ratio (TPR) and false positive ratio (FPR) values. [20] The accuracy of the test is measured by the area under the ROC curve. For the left diagram the area under the curve is 0.62, so the test does not separate well the two groups (with and without the stricture). For the right diagram the area under the roc curve has been calculated 0.92, which means that the test separate well the case and control.

4.4 Uncertainties

An important limitation in the current study is the uncertainty regarding oesophagus delineation, which means how the organ has been defined. Oesophagus delineation was more
accurate when the slice distance in the CT scanning was 0.5cm rather than 1cm, because in that case it was easier to follow the organ. Despite that oesophagus is a tube; the fact that the whole volume of oesophagus has been included in the delineation does not insert big uncertainties to our results. Therefore the important value in this case is not the volume of this organ but its length and due to this fact 5 cm of oesophagus has been chosen to be studied. Another reason that 5cm of oesophagus has been chosen is that most of esophageal strictures are formed to the upper esophagus. The lower part of the organ receives considerably lower dose due to the irradiation techniques used. Other possible uncertainties are set-up errors and the unaccounted organ movement.

The risk for the development of oesophageal stricture is not only influenced by radiation therapy but also by surgery and chemotherapy. Therefore the fact that the collection of clinical data has not yet been completed introduces an uncertainty.

The quantification of the dose-response curve uncertainty as a function of the parameter uncertainties was calculated from the whole hyper-volume of the log-likelihood space, and not only from a selected plane in the parameter space. It constitutes primarily a qualitative evaluation of the effect of including parameter uncertainties. Dose-response parameters for oesophageal stricture in the radiobiological model analysis show that the final result of the fitting process is a dose-response curve within an interval. The inclusion of the uncertainties characterizing the dose-response curves is important for the introduction of radiobiological modelling into the clinical routine. [2]

**Conclusions**

The main observations made from this thesis are the following:

- The differences between the dose distributions of the two subgroups made, considering the treatment time, indicates that there are other factors except from dose, which influence the development of oesophageal stricture after radiation therapy.
- The relative seriality value calculated from the data of the subgroup treated during the period 2001-2005, is low. That means that there is not strong volume dependence and that big volume of oesophagus has to be irradiated in order to see the effect of the radiation.
- Different parameters sets have been published from different studies, which have considered the lower part of oesophagus (thoracic part). [21, 22]
Knowing the values of the estimated dose-response parameters, which mean knowing the volume dependence of the organ, we can avoid complications of the organ at risk such as oesophagus stricture. This could happen by justifying the dose distribution in the oesophagus.

From data analysis for the treatment period 2001-2005 we assume that there is a safe cut off of 45Gy, due to the observation that over this dose, the number of complications are significantly increased.
Acknowledgments

First of all I would like to thank Associate Professor (Docent) Panayiotis Mavroidis, my supervisor, for the opportunity he gave to me to participate in this research, his lively interest and friendly support and his help in the scientific part of this work.

I would like to thank especially Dr. Massoud al-Abany, for the supervision and for spending much of his time helping me to develop my scientific skills, supporting and offering me his friendship.

Adjunct Professor Bengt K. Lind for the great supervision, his scientific advises and his friendly support.

My examination committee, Professor Georgios Nikiforidis, Assistant Professor Georgios Sakellaropoulos from the Department of Medical physics of Patras University.

I would like to thank Professor Georgios Panayiotakis (member of my examination comity) for the opportunity he offered me to do part of my studies in Sweden and his support.

Helena Lind, MD for her valuable help in this project.

Alexander Ahlberg, MD and Professor Göran Laurell for the cooperation and their help in the clinical part of this project.

Dr. Aris Tilikidis, the staff of Karolinska University Hospital and especially the staff of Treatment planning Radiumhemmet, Karolinska Hospital.

The entire staff of medical radiation Physics Department and particularly Lil Engström for her valuable help with the administrative and bureaucratic part.

The staff of Medical epidemiology Department.

My colleagues from the master of Medical Radiation Physics, University of Patras for their warm friendship.

My Family and friends who support me all these years.
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