Functional inoperability of oral and oropharyngeal cancer
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Chapter 1

General introduction to the concept of functional inoperability of oral and oropharyngeal cancer.
Chapter 1

Definitions
This thesis deals with inoperability of oral and oropharyngeal cancer. Inoperability refers to a situation that surgery is not possible, although there is a vital indication. If radical resection is technically impossible, due to invasion in structures that cannot be resected, this can be called anatomic inoperability. The term functional inoperability can be applied for a patient with advanced head and neck cancer that is technically operable, but organ-sparing therapy is advised because the expected functional result after resection is unacceptable, see table 1. This thesis will describe the scope and current practice of functional inoperability of advanced oral and oropharyngeal cancer.

<table>
<thead>
<tr>
<th>Inoperability</th>
<th>Definition</th>
<th>Tumour extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomic</td>
<td>Radical tumour resection not possible</td>
<td>Invasion in vital structures like the base of skull or internal carotid artery</td>
</tr>
<tr>
<td>Functional</td>
<td>Radical tumour resection possible, but expected postoperative function not acceptable</td>
<td>Invasion in critical structures for oral transport, swallowing and speech</td>
</tr>
</tbody>
</table>

Anatomy
By definition, the oral cavity comprises the buccal mucosa, the upper gums, the lower gums, the hard palate, the tongue (anterior two-thirds or anterior to the vallate papillae) and the floor of mouth, see figure 1. The pharynx consists of the nasopharynx, oropharynx and hypopharynx. The oropharynx comprises the base of the tongue (posterior to the vallate papillae or posterior third), vallecula, tonsils (including tonsillar fossa and pillars), posterior oropharyngeal wall, inferior surface of the soft palate and uvula. The nasopharynx starts from the horizontal level between the junction of the hard and soft palate and ends at the base of the skull.

The tongue is essentially a mass of muscles, which can be separated in intrinsic and extrinsic muscle groups. Extrinsic muscles, having an attachment to structures outside the tongue, are the genioglossal, hyoglossal, styloglossal and palatoglossal muscles. Four different intrinsic tongue muscles can be defined: the transversal, vertical, superior longitudinal and inferior longitudinal muscles. In general, the extrinsic tongue muscles alter the position of the tongue and the intrinsic tongue muscles alter the shape of the tongue. All, except for the palatoglossal muscle, receive motor innervation via the hypoglossal nerve, cranial nerve XII. The hypoglossal nerve passes between the external carotid artery and jugular vein and curves anteriorly to enter the submandibular triangle deep to the posterior belly of the digastric muscle. There it passes along with the lingual artery on the superior surface of the mylohyoid muscle. The tongue is vascularised by the lingual artery, a branch of the external carotid artery, that enters the tongue deep to the hyoglossal muscle.
Figure 1: Anatomy of the oral cavity, oropharynx and paranasal sinuses

1. buccal mucosa
2. upper gum
3. uvula
4. tonsil
5. palatoglossal muscle
6. vallate papillae
7. tongue
8. hard palate
9. nasal cavity
10. hard palate
11. soft palate
12. oral cavity
13. tonsillar fossa
14. base of tongue
15. vallecula
16. hyoid bone
17. epiglottis
18. nasopharynx
19. oropharynx
20. hypopharynx/larynx
21. styloglossal muscle
22. intrinsic tongue muscles
   A. transversal
   B. vertical
   C. inferior longitudinal
   D. superior longitudinal
23. floor of mouth
24. lower gum
25. mandible
26. genioglossal muscle
27. mylohyoid muscle
28. hyoglossal muscle
29. internal carotid artery
30. jugular vein
31. hyoglossal nerve
32. external carotid artery
33. ethmoid cells
34. orbit
35. maxillary sinus

Nasal and paranasal sinus carcinomas may originate in the maxillary, sphenoid or ethmoid sinus or the nasal cavity itself. The maxillary sinus is enclosed by the orbit superiorly, the nasal cavity medially and the oral cavity caudally. The ethmoid and sphenoid sinus are located more posteriorly and are very close to the orbit, base of skull, internal carotid artery and the optic nerve.\textsuperscript{2}

**Incidence of oral and oropharyngeal cancer**

Oral cancer is the sixth most common cancer worldwide\textsuperscript{4} and estimated global incidence is around 275,000 per year.\textsuperscript{5} In the Netherlands 3.6 people per 100,000 inhabitants were diagnosed with oral cancer in 2010, which is standardised for age based on the global population.\textsuperscript{6} Oropharyngeal cancer is less common than oral cancer. Age-standardised incidence of oropharyngeal cancer was 2.7 per 100,000 inhabitants in the Netherlands in 2010, calculated by the Dutch National Cancer Registry.\textsuperscript{6} The annual estimated incidence worldwide is around 50,000.\textsuperscript{7} The incidence of oropharyngeal cancer is not well documented, as it is rarely described according to the anatomic definition,\textsuperscript{8} but usually grouped with oral or pharyngeal tumours, including hypo- and nasopharynx. However, oropharyngeal cancer should be regarded as a separate entity, because etiologic factors differ.

A geographical variance in incidence of oral and oropharyngeal cancer is observed, with higher incidences in parts of South-East Asia, Eastern Europe and France.\textsuperscript{5,7,9} This has to do with distribution of risk factors for developing head and neck cancer, such as cultural differences in smoking and alcohol use.\textsuperscript{5} The tradition of chewing filled betel leaf, which is a known risk factor,\textsuperscript{8} makes oral cancer the most common cancer in men in South-East Asia.\textsuperscript{5}

For oropharyngeal cancer also prevalence of human papilloma virus (HPV) plays a role, which has become a recognised causative factor in development of oropharyngeal cancer.\textsuperscript{8,10} The proportion of oropharyngeal cancer that is HPV-positive varies geographically widely between 18 to 93%.\textsuperscript{11} Between 2008 and 2010 in the Netherlands around 24\% of all oropharyngeal cancer was HPV-positive.\textsuperscript{12}

Over the past decade, a rise in incidence of oropharyngeal cancer has been noted in Western countries, despite effective control of alcohol and tobacco abuse.\textsuperscript{7} It is thought that increasing HPV prevalence has caused this rise in incidence.\textsuperscript{7} HPV-positive cancer is typically in white men younger than 50 years, without a history of alcohol and tobacco use, who develop a malignancy of the lingual and palatine tonsils.\textsuperscript{10}
The lateral borders of the tongue are the most ‘cancer-prone’ areas for oral cancer, along with the floor of the mouth. Approximately 1/3 of all oral cancers is localised in the tongue. Only 9% is localised in the hard palate and 12% in the gums. The tonsils and base of tongue are the most frequent subsite for oropharyngeal cancer, comprising both around 1/3 of all oropharyngeal malignancies. The soft palate is the least frequent subsite. The most frequent histology for oral and oropharyngeal cancer is squamous cell carcinoma, which is the pathologic diagnosis in respectively 95% and 90% of all oral and oropharyngeal cancers.

**Incidence of paranasal sinus cancer**

Paranasal sinus cancer is important to discuss here as well, since the paranasal sinuses are located at the superior border of the oral cavity and oropharynx, and surgical cancer treatment encompasses these latter structures quite often. Paranasal sinus cancer is quite rare. Although incidence numbers of paranasal sinus cancer are grouped with nasal cavity and middle ear cancer by the Dutch National Cancer Registry Database, this incidence was low, namely 0.58 people per 100,000 inhabitants in 2010 in the Netherlands, which is age standardised for the global population. The reported incidence of malignant paranasal sinus cancer in the United States between 1973 and 2006 is 0.56 cases per 100,000 people. The proportion of tumours originating from the maxillary sinus varies, but is generally 1/3 to 1/5 of all paranasal sinus malignancies. More than 50% of all malignant sinonasal tumours are squamous cell carcinomas, other histopathologic diagnoses include adenocarcinoma, melanoma, adenoid cystic carcinoma, salivary gland carcinoma and esthesioneuroblastoma.

**Staging**

Staging systems for all cancers are described by the American Joint Committee on Cancer in the United States and the International Union against Cancer Committee in Europe. The classification is based on three components; T, N and M. The size and extension of the primary tumour is described by T classification, see table 2. Nodal status is represented by N, N0 meaning no regional lymph node metastasis. N1 describes an ipsilateral single node smaller than or equal to 3 cm. N2a describes an ipsilateral single node of 3 to 6 cm, N2b multiple ipsilateral nodes, N2c bilateral or contralateral node(s). N3 describes a node larger than 6 cm. Distant metastasis are represented by the M; M0 meaning no distant metastasis or M1 any distant metastasis.
Table 2: T classification of malignancies in oral cavity, oropharynx and maxillary sinus\textsuperscript{20}

<table>
<thead>
<tr>
<th>Oral cavity</th>
<th>Oropharynx</th>
<th>Maxillary sinus</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 ≤ 2 cm</td>
<td>≤ 2 cm</td>
<td>Limited to mucosa</td>
</tr>
<tr>
<td>T2 &gt; 2-4 cm</td>
<td>&gt; 2-4 cm or more than 1 subsite</td>
<td>Bone erosion or destruction of hard palate and/or middle nasal meatus</td>
</tr>
<tr>
<td>T3 &gt; 4 cm</td>
<td>&gt; 4 cm</td>
<td>Invasion of bone of posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses</td>
</tr>
<tr>
<td>T4a Invasion of cortical bone, deep tongue muscle, maxillary sinus, skin</td>
<td>Invasion of the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, mandible</td>
<td>Invasion of anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribiform plate, sphenoid, frontal sinuses</td>
</tr>
<tr>
<td>T4b Invasion of masticator space, pterygoid plates, skull base, internal carotid artery</td>
<td>Invasion of the prevertebral fascia, carotid artery, mediastinal structures</td>
<td>Invasion of orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, clivus</td>
</tr>
</tbody>
</table>

The TNM staging system is used to describe the anatomical extent of disease. For purposes of tabulation and analysis it is useful to condense these categories into stage groups, see table 3. For head and neck cancer, invasive tumours localised within the organ of origin are staged as I and II. Advanced cancer means stage III, defined by local extension or with regional lymph node metastases. Stage IV represents patients with a T4a or T4b primary, e.g. beyond the organ of origin, an N3 neck or distant metastasis.\textsuperscript{20} Oral, oropharyngeal and paranasal sinus cancers present often at a late stage of disease.\textsuperscript{14,18} Especially oropharyngeal cancer, as more than half of the cancers are grouped in stage IV at the time of diagnosis.\textsuperscript{14} Survival is dependent on T, N and M classification, and on stage grouping.\textsuperscript{17}

Table 3: 5-year relative survival rate of oral and oropharyngeal cancer divided per tumour stage

<table>
<thead>
<tr>
<th>Tongue</th>
<th>Floor of the mouth</th>
<th>Gum and other mouth</th>
<th>Oropharynx</th>
<th>Paranasal sinus/nasal cavity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>71%</td>
<td>73%</td>
<td>81%</td>
<td>56%</td>
</tr>
<tr>
<td>II</td>
<td>59%</td>
<td>60%</td>
<td>62%</td>
<td>58%</td>
</tr>
<tr>
<td>III</td>
<td>47%</td>
<td>36%</td>
<td>45%</td>
<td>55%</td>
</tr>
<tr>
<td>IV</td>
<td>37%</td>
<td>30%</td>
<td>40%</td>
<td>43%</td>
</tr>
</tbody>
</table>

Five-year relative survival rate: survival rate of people with cancer compared to survival rate of people without cancer. These survival statistics originate from the National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) program, based on 40,881 patients treated for head and neck cancer between 1988 and 2001 in the United States.\textsuperscript{21,22}
General Introduction

More recent data of the SEER database show higher survival rates for oral and oropharyngeal cancer than in the past. Between 2002-2008 relative 5-year survival for localized cancer of the oral cavity and oropharynx was 82.4%, and if there was spread to regional lymphnodes 57.3%. However, these numbers have not been grouped per tumour localisation, only for tongue cancer. For the patients with tongue cancer relative 5-year survival for localized cancer was 77.5% (see above stage I and II) and if there was spread to regional lymphnodes it was 58.2% (see in table 3 stage III).23

Therapy

Surgery for advanced oral and oropharyngeal cancer

Beginning with Bilroth’s total laryngectomy on New Year’s Eve in 1873, radical surgery has been the first treatment for head and neck cancer.24 It is still the preferred treatment for many head and neck cancers. The Dutch guideline for oral and oropharyngeal cancer of 2004,14 recommends surgery with adjuvant radiotherapy for T3 and T4 oral and oropharyngeal cancer, except for base of tongue tumours.

Surgical approach depends on tumour location and proximity to the mandible.4,25 Options are a transoral approach, with or without use of a skin flap, or a transmandibular approach. Mandibulotomy is used for more posterior oral lesions or oropharyngeal tumours. Including in continuity resection of the lymph nodes in the neck, it is traditionally called a ‘commando procedure’. This technique was formerly the mainstay in oral and oropharyngeal cancer surgery, but recently other techniques, like robotic or CO2-laser surgery and photodynamic therapy, have resulted in more preserving surgery.26 Tumour invasion in the bone of the mandible requires a segmental mandibulectomy and bony invasion of the maxilla requires a maxillectomy.

Reconstruction of major surgical defects can be achieved using a free revascularised tissue graft. The donor site is chosen depending on the location of the defect.27 The free radial forearm flap is the most frequently used free flap in head and neck surgery. It is a fasciocutaneous flap, providing excellent tissue bulk and lining for soft tissue defects in the oral cavity. The fibula free flap is an osseocutaneous flap and remains the first choice for mandibular reconstruction.4 If making a microvascular anastomosis is not possible or contraindicated, a pedicled flap may be used, like a pectoralis major or latissimus dorsi flap.

Organ-sparing therapy for advanced oral and oropharyngeal cancer

Due to evolvement of advanced reconstruction techniques, larger defects could be closed and more advanced and extensive tumours became operable.4,28 However, the oncologic results after resection of very large tumours are controversial, and postoperative morbidity is high,29
so other techniques were explored. Since decades, several attempts were made to study the effect of chemotherapy in head and neck cancer. In 1991, the Department of Veterans Affairs Laryngeal Cancer Study demonstrated equivalence in overall survival between patients treated with a total laryngectomy followed by postoperative radiotherapy compared to patients treated with induction chemotherapy and primary radiotherapy. Since this landmark study, primary nonoperative methods have assumed a greater role in the treatment of patients with head and neck cancer. The first chemoradiation protocol, intra-arterial RADPLAT, was developed in the United States and involved four cycles of targeted intra-arterial cisplatinum infusion with concurrent radiation therapy. Adding chemotherapy to radiotherapy showed improved survival in patients with head and neck cancer. Selective intra-arterial administration of high dose cisplatinum (150mg/m² body surface) aimed at higher survival rates than intravenous cisplatinum, but this could not be proven in a randomised prospective trial. Nowadays, the chemoradiation regime in the Netherlands consists of 7 weeks radiotherapy (70 Gray in 35 fractions) combined with three courses of cisplatinum 100 mg/kg intravenously on day 1, day 22 and day 43.

The RADPLAT regime may have serious toxic side effects, as cisplatinum is nephro-, oto- and neurotoxic. It has acute side effects like nausea, vomiting, and in combination with radiotherapy it causes severe mucositis. Therefore, the treatment is suitable only for patients with normal creatinine clearance and a good performance status. Adding cisplatinum to radiotherapy has shown less effective for patients over 70 years old and in a large meta-analysis there was no significant survival benefit in this age category. However, this age-dependent effect was not demonstrated by others.

Cetuximab with concurrent radiotherapy is a novel treatment approach, which seems to be well tolerated and significantly more effective than radiation alone, although its effect has not yet been compared to cisplatinum-based chemoradiation. Nowadays, administration of cetuximab is limited to patients with low-risk disease, the elderly or patients with a poor performance status. Another organ-sparing option is an accelerated schedule of radiotherapy, consisting of 6 instead of 5 fractions in a week, which is more effective than conventional fractionation. Nevertheless, adding an extra fraction of radiotherapy does not compensate for the absence of chemotherapy. The effect of neo-adjuvant chemotherapy has been debated; in a meta-analysis of 93 trials evaluating chemotherapy for head and neck cancer, a more pronounced benefit of the concomitant chemotherapy as compared to induction chemotherapy was shown.

**Adjuvant therapy after surgery for oral and oropharyngeal cancer**

The goal of oncologic surgery is complete resection of the tumour, with clear surgical margins.
Close surgical margins are frequently defined as tumour-free margins less than 3mm, or otherwise less than 5mm. A description method of the surgical margin status is developed by the American Joint Committee of Cancer. No tumour at the surgical margins is classified as R0, microscopic tumour at the margins as R1. R2 means macroscopic tumour at the margins, or if the tumour is trans-sected.

Adjuvant radiotherapy is indicated in T4 tumours and in case of other tumour-specific histopathologic characteristics; close surgical margins, multiple lymph node metastases and/or extracapsular tumour growth. Adjuvant chemoradiotherapy has proven superior to adjuvant radiotherapy in case there is extracapsular spread of a lymph node metastasis or after surgery with positive surgical margins.

Therapy choice for advanced oral and oropharyngeal cancer

In the past, only anatomically inoperable head and neck cancer was treated non-surgically with chemoradiotherapy, and not with radiotherapy alone, as adding chemotherapy had proven to be superior. Lately, chemoradiation has been used more and more as a primary treatment even for resectable head and neck cancer. A randomised controlled trial showed comparable outcome for advanced head and neck cancer after surgery with adjuvant radiotherapy or primary chemoradiation in 119 patients, of whom 48% had a malignancy originating from the oral cavity and oropharynx. Unfortunately there is not such evidence for separate isolated head and neck tumour sites, such as oral, oropharyngeal or sinusal.

For advanced oropharyngeal cancer, chemoradiation is an acceptable option, as there is evidence that similar locoregional and overall control rates are achieved compared to surgery with postoperative radiotherapy. Also, functional outcome is reported be acceptable after chemoradiation for oropharyngeal tumour sites.

Treatment choice in oral cancer remains more controversial. A randomised trial comparing radiotherapy to surgery and adjuvant radiotherapy was ceased early after only 35 patients had been recruited due to a profound difference in overall survival in favour of surgery plus postoperative radiotherapy (p= 0.0006). However, the authors acknowledged that radiotherapy was delivered in suboptimally with delays in treatment and equipment failure contributing to the poor outcomes. At this moment, for oral and bone-invasive cancer, the mainstay of treatment remains primarily surgical, although study results of advanced oral cancer treated with chemoradiation are variable. Some studies show acceptable outcomes in terms of local control and survival, while others have shown worse results, see table 4 for a summary of those studies.
### Table 4: Studies evaluating chemoradiation results for oral and/or bone invasive cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N=</th>
<th>T-stage and site</th>
<th>Treatment</th>
<th>Survival</th>
<th>ORN</th>
<th>Comment</th>
</tr>
</thead>
</table>
| Giralt et al. 2000 | P      | 62 | T4: n=44  
T3: n=15  
Oral: n=42  
Oropharynx: n=20 | CRT + cisplatin and 5-FU average RT dose 60Gy                              | 5-yr OS 70%  
5-yr DFS 59%  
CR 46%                         | 6% | 25 patients underwent excisional biopsies                                 |
| Samant et al. 2001 | CC     | 135 | T4: n=135  
Head neck cancer Groups:  
1. Bone/ cartilage invasion. n=45  
2. Without: n=90 | CRT + cisplatin range RT dose 66-74Gy                                     | Group 1: 2-yr OS 46.3%  
CR 66.7%  
Group 2: 2-yr OS 36.9%  
CR 71.1% | ? | No significant difference between bone-invasion or not                   |
| Cohen et al. 2008 | R      | 39 | T4: n=29  
Oral cancer,  
1. Bone/ cartilage invasion. n=16  
2. Without: n=23 | CRT + 5-FU, hydroxyurea and cisplatin or paclitaxel average RT dose 74Gy | 5-yr OS 56%  
5-yr LC 75%  
RR group 1: 38%  
RR group 2: 27% | 18% | No significant difference between bone-invasion or not                   |
| Fuwa et al. 2008 | R      | 29 | Stage 4: n=11  
Stage 3: n=29  
Tongue cancer | CRT + carboplatin average RT dose 54Gy                                     | 5-yr OS 39.5%  
5-yr PFS 32.5%  
5-yr LC 62% | ? |                                                                     |
| Stenson et al. 2010 | R    | 111 | Stage 4: n=99  
Stage 3: n=12  
Oral cancer | CRT + 5-FU, hydroxyurea, paclitaxel, docetaxol, carboplatin, cisplatin, or others range RT dose 36-75 Gy | 5-yr OS 65.9%  
5-yr PFS 66.9% | 18% | 20 patients are spared total glossectomy                                  |
| Kobayashi et al. 2010 | R      | 22 | T4: n=18  
T3: n=3  
T2: n=1  
Oral cancer | CRT + docetaxel and nedaplatin average RT dose 66Gy                       | 5-yr OS 78.5%  
CR 81.8% | 5% | Small patient group                                                       |
| Crombie et al. 2012 | R      | 54 | Stage 4: n=39  
Stage 3: n=9  
Stage 2: n=5  
Stage 1: n=1  
Oral cancer | CRT + cisplatin, 5FU, tirapazamine, carboplatin and/or cetuximab average RT dose 70Gy | 5-yr OS 29%  
5-yr DSS 30% | 11% | All patients were functionally inoperable                                 |

D= Design, ORN= osteoradionecrosis, R= retrospective cohort, P= prospective cohort, CC= case-control study, OS= overall survival, DFS= disease free survival, PFS= progression free survival, CRT= concurrent chemoradiation, 5-FU= 5-fluorouracil, i.a.= intra-arterial, CR= complete response, LC= local control, RR= relapse rate.
General Introduction

For malignancies invading bone or cartilage, chemoradiation seems equally effective, compared to patients without bone or cartilage invasion, as presented by two studies of 39 oral cancer patients and 135 head and neck cancer patients.58,59 The risk on osteoradionecrosis hovers in general around 10%,51 ranging between 5%56 and 18%.51 This is a disadvantage of organ-sparing treatment in case of bone invasion, as several patients need extensive treatments if they develop osteoradionecrosis.

As mentioned earlier, HPV may be detected in a fair number of oropharyngeal cancers (24%)10,60 and a smaller part of oral cavity carcinomas (4-5%).60,61 HPV-positive tumours have shown better survival than HPV-negative tumours which may be attributable to an increased sensitivity for radiotherapy.62 Its consequences for treatment choice remain to be investigated,63 as tumour HPV status is a strong and independent prognostic factor for survival among patients with oropharyngeal cancer, which appeared independent of treatment choice.64

Therapy of paranasal sinus cancer
Assessment of trends in survival and treatment is difficult due to the rarity of paranasal carcinoma.18 Moreover, diverse histopathological tumour types are known with different clinical characteristics. When located in the maxillary sinus, the cancer can be treated by surgery followed by radiotherapy, by radiotherapy alone or by concurrent chemoradiation. The combined modality of surgery and postoperative radiotherapy is currently considered most effective.65-67 However, it is difficult to perform a maxillectomy with tumour-free surgical margins, as high rates of irradical resections are reported.17,68 Adjuvant radiotherapy is often indicated. Defects after a maxillectomy are classified by Brown69 based on horizontal and vertical extension of the resection.

Extensive resection is possible, and often followed by reconstruction with an osseocutaneous flap,70 for example a free revascularised fibula transplant or an iliac crest transplant. For cancer involving the infratemporal fossa and cribriform plate a craniofacial resection may be planned.71,72 Primary (chemo)radiation with or without endoscopic tumour debulking could serve as an alternative treatment option,73-77 at least for unresectable tumours.78,79,80

Function
Speech and swallowing after therapy
Eating and drinking are basic necessities of mankind. Generally, a healthy adult swallows between 800 and 2400 times a day. Although swallowing seems easy, it requires an extremely complicated interaction between various muscles. Timing, coordination, sensibility and muscular strength all play a significant role. When one or more of these conditions for swallowing are
disturbed, this is called dysphagia, which can have severe impact on patients’ quality of life.\textsuperscript{81,82} Speech is one of the most powerful social interaction tools and plays a major role in the patient’s day to day activities. The importance of speech in a patient’s life cannot be overemphasised, as its loss is often associated with severe functional and psychosocial problems resulting in a poor quality of life.\textsuperscript{83}

Both swallowing and speech are often compromised already before treatment due to growth of cancer that arises in the head and neck area. After treatment these functions may be even more compromised, either by surgical defects or due to radiotherapy induced morbidity. Although there are obvious differences with regard to functional outcomes between the two main curative treatment modalities, surgery (with or without postoperative radiotherapy) and chemoradiation, the magnitude and extent of the difference in functional result of both treatments is controversial.\textsuperscript{84,85}

Eating problems are the most important cause of a decreased quality of life for survivors of head and neck cancer.\textsuperscript{82} Dysphagia may be present after both therapies. Speech seems less impaired after organ-sparing therapy.\textsuperscript{86} Unfortunately, no randomised comparative studies between chemoradiation and surgery in advanced oral and oropharyngeal carcinoma have been performed neither on oral function nor on evaluating quality of life.\textsuperscript{87}

Quality of life is a very complex entity that is influenced by many factors. Studies in patients with oral and oropharyngeal cancer have shown that quality of life decreases during and directly after treatment, but on long-term quality of life scores are equal to pretreatment scores.\textsuperscript{88,89} Residual functioning after treatment and general quality of life are strongly interrelated, but this thesis focuses only on function after treatment, and general quality of life issues will not be discussed.

\textit{Function after surgery}

Despite advanced surgical reconstructions that limit the functional side effects of the resection,\textsuperscript{27} postsurgical speech and swallowing problems continue to exist.\textsuperscript{88,90-93} The tumour tissue already diminishes the swallowing and speech function, due to the stiff, immovable tumour mass that invades the oral cavity and oropharynx. Functional losses after surgery are mainly dependent on the location and extension of the tumour,\textsuperscript{92,94} as this defines the amount of tissue that should be removed in order to achieve clear margins. A defect after surgery may cause pooling and incomplete occlusion of the (nasopharynx or larynx. Reconstruction with tissue grafts resolves this problem, but in that case bulky and stiff tissue may replace sensate mucosal and muscular tissue, which also hampers oral and pharyngeal function.
It is known that surgery for base of tongue cancer causes significant dysphagia. Other key anatomical sites in terms of functional outcome are the floor of the mouth and the posterior oral cavity. Loss of integrity in the genioglossal and geniohyoid muscles (important in providing tongue mobility) or the geniohyoid and mylohyoid muscles (fundamental for the normal elevation of the larynx) severely impairs speech quality and swallowing. Resection of the soft palate may lead to velopharyngeal insufficiency, meaning insufficient separation of the oral and nasal cavity. This causes nasal regurgitation during swallowing and hypernasal speech. The tongue is very important in both speech and swallowing. To keep the tongue vital and functional, the arterial blood supply by the lingual artery and motor nerve innervation of the tongue by the hypoglossal nerve have to remain intact, at least on one side.

Function after chemoradiation

After chemoradiation patients may suffer from severe swallowing complaints, depending on the radiation dose and tumour location. Dysphagia is present as an acute side effect of radiotherapy, predominantly caused by pain, ulcerations and mucositis. Long-term dysphagia is elicited by xerostomia, a dry mouth and fibrosis, due to radiation-induced damage of the salivary glands, oral and pharyngeal muscles and soft tissues. These side effects are worse, if concurrent chemotherapy is added to radiotherapy. This can be so disabling that permanent tube feeding is necessary, which is reported in 13 to 60% of all patients who undergo chemoradiation for head and neck cancer. Another common side effect of radiotherapy is reduced mouth opening (trismus), defined as a mouth opening of smaller than 35mm. Speech is relatively unaffected, although voice and perception of speech is thought to be changed after treatment. After all, it is important to keep in mind that ‘organ-sparing’ is not the same as ‘function-sparing’.

To diminish toxicity to surrounding structures, intensity-modulated radiotherapy was developed. Using complex computerised treatment planning, it delivers an increased dose of radiation to areas at risk for harbouring cancer, while reducing the dose to normal tissue. The use of intensity-modulated radiotherapy has increased significantly in recent years, as survival is equal compared to standard radiotherapy and the rate of long-term xerostomia lower. Another way to dwindle dysphagia seems to be preventive rehabilitation on swallowing and mouth opening during treatment. This reduces the problem of non-use atrophy provoked by the lack of swallowing muscle practice during tube feeding. However, a definitive evidence for this therapy by a randomised controlled trial still lacks.
Figure 2: Reconstruction of a maxillectomy defect with an obturator

Function after a maxillectomy

Function after a maxillectomy has traditionally been restored with a palatal prosthesis, called an obturator. These are dentures with a bulb of synthetic material, exactly fitting the maxillectomy defect, see figure 2. A well designed obturator prevents oronasal and oroantral communication, re-establishes normal speech and maxillary dentition, therewith improving the patient’s quality of life.\textsuperscript{105,106} The prosthesis can be supported by osseointegrated implants, especially in edentulous patients.\textsuperscript{107} Direct surgical reconstruction with a free revascularised tissue transfer is another reconstruction option, especially after larger resections.\textsuperscript{70} Both methods have their particular pros and cons. Some authors\textsuperscript{108,109} advocate that free flaps provide the surgeon an opportunity to deal with the problems of prosthetic obturation: nasal leakage, cleaning
and constant prosthetic refinement. It has to be realised that surgical flap reconstruction is still associated with increased operation time, chance for failure and the possibility of donor site morbidity. In contrast, fabrication of an obturator prosthesis shortens the operation time significantly and offers the possibility of immediate and adequate dental rehabilitation. During oncological follow-up the maxillectomy defect can be easily examined after removing the obturator prosthesis, so tumour recurrence, the most common therapy failure,\(^{16,110}\) may be detected and treated in a timely manner. The optimal reconstruction of the maxillectomy defect, whether it is an obturator prosthesis or a free flap reconstruction, however, remains controversial.\(^{111-114}\)

Mastication may be impaired due to disabling alterations in the functional components of occlusion,\(^{115}\) especially after large resections including bone. Next to mastication, other functional problems may exist after a maxillectomy, due to scarring and resection of parts of the oral cavity, for example the soft palate. Also the vision may be compromised after surgical treatment of maxillary sinus cancer, if the resection has to be combined with an orbital exenteration. On the other hand, radiation may cause injury to the optic nerve or retina resulting in visual loss as well.\(^{116}\) However, currently, if the tumour extension allows it, intensity-modulated radiotherapy can spare the optic tract.\(^{117}\)

**Measurement of function**

The focus of research in head and neck oncology has shifted from survival and locoregional control towards evaluating remaining function and quality of life after treatment, resulting in a fast growing volume of literature on these subjects published in the recent years.\(^{118,119}\) Several methods of outcome measurement are used in studies. Swallowing is usually assessed by videofluoroscopic studies or endoscopic assessment of swallowing. Likewise, clinical observations, like descriptions of diet, can serve as an indicator of swallowing.\(^{118}\) Speech is often evaluated using perceptual analysis,\(^{118}\) but also a large diversity of other tools is used to assess the patients’ speech.\(^{118}\) Frequently, chewing performance is assessed by sieving chewed food or artificial material and measuring the degree of breakdown. Another option is evaluation of the ability to mix and knead a food bolus by using a two-coloured chewing gum or paraffin wax.\(^{120}\)

The use of subjective ratings from patients via quality of life questionnaires recently has become popular to describe function,\(^{119}\) next to general quality of life. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire and the specific head and neck module (H&amp;N35) are the most frequently used,\(^{118}\) followed by the University of Washington Quality of Life Scale (UW-QOL).\(^{119}\) There are some other well-organised, standardised questionnaires that have been validated throughout the literature.\(^{119}\) Sometimes a study specific
questionnaire is necessary to evaluate a particular patient group.\textsuperscript{121} For example, functioning of a maxillary obturator can be assessed by the Obturator Functioning Scale, developed and tested at Memorial Sloan Kettering Cancer Center, New York.\textsuperscript{122,123}

\textbf{Clinical dilemma: functional inoperability}

The availability of two treatment regimes (surgery with adjuvant radiation and chemoradiation) that have comparable initial oncologic response rates, but different factors that influence functional outcome, leads to our main issue, functional inoperability. The key question is which tumours can be denominated as functionally inoperable. Nowadays, these decisions are made by head and neck surgeons, or preferably by multidisciplinary head and neck oncology boards, and advice is given based on personal experiences and preferences. For this dilemma no guidelines are available and even no useful definition of functional inoperability can be found in literature.\textsuperscript{124,125} This thesis will focus on evaluating current practice of functional inoperability in advanced oral and oropharyngeal cancer and an attempt will be made to describe the anatomical borders of functional inoperability.

Factors influencing treatment choice to be taken into account are patient related, for example age, comorbidity, willingness to be treated, and other factors are physician related, for example expertise in various disciplines including surgery, radiotherapy, chemotherapy, rehabilitation, dental and prosthetic support, and psycho-social support.\textsuperscript{33} Nevertheless, tumour invasion and the required resection of tissue are the critical factors determining the remaining swallowing and speech functions after surgery and these will be regarded as the most important factors for functional inoperability.

\textbf{Future perspectives}

Knowledge is moving fast in this era of evidence based medicine. The surgical pendulum that was historically on the side of radical surgery has moved over the last decades towards the side of organ-sparing protocols. The question is if it will swing back to the side of surgery, thanks to the development of minimal invasive surgery, like CO\textsubscript{2}-laser surgery, photodynamic therapy or robotic surgery with the Da Vinci robot. On the other hand, the pendulum may stay at the centre between surgery and organ-sparing approach, because of better patient selection.\textsuperscript{24} This may be based on recognition of biomarkers and its consequences for therapy, like HPV, more precise preoperative imaging, or more influence of the individual patient on the decision-making process.

Selection of patients for surgery might be ameliorated by better radiological examinations, keeping in mind the dynamics of the oral cavity and oropharynx. Nowadays tumour extension
General Introduction

is evaluated on static Magnetic Resonance Imaging (MRI), which has excellent soft tissue contrast. The only dynamic functional imaging in current practice is videofluoroscopy, which gives a 2D impression of the contour of the oral cavity and oropharynx. Mobility and function of involved structures remain difficult to evaluate. Cine MRI is a series of several consecutive MRI's that are made during swallowing, a technique that has shown extra value in visualising the dynamic structures of the oral cavity and oropharynx. This might have an additional value in preoperative assessment of oral and oropharyngeal tumours, as well as in evaluation of posttreatment dysphagia.

Better patient selection can also be pursued by involving the patient more in the decision-making process. The traditional patient–doctor relationship has been based on a paternalistic and passive decision-making model, in which the doctor supplies patients with information about their medical condition and relevant treatment options. Even yet, some patients prefer deferring the final decision to their doctor, especially older patients and those with a lower level of education. Currently, the general opinion is that clinical decisions should be made based on integrating clinical expertise, best available evidence and patient values. The integration of these three elements increases the potential for positive health outcomes. In the absence of research evidence to guide decisions, like in the debate about functional inoperability, greater emphasis is placed on the interaction between patient and doctor. Decision-making relies on individual preferences and values, which are central to the patient. Objective information must be made available to patients, so they have the power and opportunity to implement their decision. The informed patients can then make their decision based on their personal values and with a clear understanding of the potential consequences of their actions.

Nowadays, providing the patient with objective information about the expected treatment result after resection of oral and oropharyngeal cancer, however, is very difficult. A dynamic model of the oral cavity and oropharynx, wherein the surgical resection can be simulated, could be helpful for objectively predicting and visualising the postoperative anatomical and functional results for both patient and doctor.

Aim and brief outline of thesis

Aim of this thesis is to evaluate and define the concept of functional inoperability in advanced oral and oropharyngeal cancer, therewith evaluating current practice of treatment and providing the first steps for future solutions of this clinical dilemma. Chapter 2 summarises literature data on functional results after surgery for advanced oral and oropharyngeal cancer. Chapter 3 describes the results of a web based survey among 67 Dutch head and neck surgeons and radiotherapists, reflecting their opinion on functional inoperability and current practice in
Chapter 1

treatment of oral and oropharyngeal cancer. Chapter 4 reports on results of the same survey among 179 international experts in the field of head and neck oncology, additionally comparing worldwide differences. Chapter 5 evaluates the current surgical management of oral cancer invading the maxilla and maxillary sinus carcinoma in 69 patients that underwent a maxillectomy, exploring risk factors for irradical resection. Chapter 6 describes the function after reconstruction with an obturator in 32 maxillectomy patients, evaluating mastication, mouth opening and quality of life questionnaires. Chapter 7 reports on a feasibility study of cine MRI of the swallowing of 23 patients with advanced oral and oropharyngeal carcinoma, in order to evaluate the additional value of this new technique. Chapter 8 describes the first steps that are taken to design a dynamic 3-dimensional model of the tongue for future development of a model of oral cavity and oropharynx that allows virtual resection and better preoperative assessment of postoperative function. The thesis ends with a general summary and concluding remarks in chapter 9.
REFERENCES


Chapter 1


Chapter 1


