Functional inoperability of oral and oropharyngeal cancer
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Chapter 1

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

Advanced head and neck cancer may be treated by two treatment regimes; surgery and concurrent chemoradiation. Both have comparable oncologic results, but different factors influence the functional outcome. In the preoperative stage the operability is assessed for surgical treatment. In this setting, one speaks about functional inoperability if a tumour is technically resectable, but the functional result after treatment should be considered unacceptable. Nowadays for functional inoperability of oral and oropharyngeal cancer predominantly subjective arguments are used that cannot be verified. In the current scientific literature, this subject has not been described, even though it is important to bring this problem under attention among head and neck surgeons, oncologists and radiotherapists.

The aim of this thesis is to examine functional inoperability of oral and oropharyngeal cancer, by the evaluation of the current practice and the clinical decision-making process about functional inoperability. Possibilities to solve this clinical dilemma are being explored, partly by searching for more objective parameters to assess functional inoperability.

Chapter 2

Speech and swallowing after surgical treatment of advanced oral and oropharyngeal carcinoma: a systematic review of the literature.

The purpose of this review is the evaluation of the speech and swallowing functions after surgical treatment for advanced oral and oropharyngeal carcinoma.

A systematic literature search (1993-2009) yields 1,220 hits. The criteria for inclusion in this systematic review are: patients with oral or oropharyngeal cancer, surgical treatment, T classification ≥ 2, patient cohort > 20, adequate description of the patient cohort and the tumour location, speech and/or swallowing function as outcome and low risk of bias (according to Cochrane criteria). Twelve studies fulfilled the predetermined criteria.

The results for speech more than 1 year after resection of oral or oropharyngeal cancer are reported to be moderate to good, although in most patients speech is evaluated as deviant. Overall sentence intelligibility is normal (92-98%). Swallowing is reported to be often disturbed already before treatment and is even more severely compromised after treatment. Aspiration rates of liquids vary from 12% to 50%. Especially after oropharyngeal resection, mean pharyngeal
transit times are delayed. Postoperative radiotherapy significantly increases function loss. Anatomic structures important to preserve for the speech function are the mobile tongue and the soft palate. For swallowing, the base of tongue, the soft palate, the hard palate and the floor of mouth are important structures. Prosthetic appliances (e.g. obturators, palatal augmentation prostheses) can diminish the function loss considerably.

This review shows that surgery for oral and oropharyngeal cancer can result in functional deficits, most notably with regard to swallowing, although series are small and outcome measurements of the included studies are variable.

Chapter 3
The surgical dilemma of functional inoperability in oral and oropharyngeal cancer: current consensus on operability with regard to functional results.
A web base survey is conducted among Dutch head and neck surgeons and radiotherapists in order to assess the borders of functional inoperability and to evaluate its current use.

The response rate to the survey is 93% (n=69). Responses vary slightly by the size of the clinic or discipline (radiation oncology versus head and neck surgery). There is agreement about the unacceptable functional loss after a total glossectomy. The functional outcome after certain surgical procedures is controversial, namely:

- a bilateral maxillectomy
- resection of a tonsil and base of tongue carcinoma including removal of the vallecula and epiglottis
- a total soft palate resection.

Disagreement about functional inoperability is also observed for T3 and T4 base of tongue carcinomas based on case descriptions and magnetic resonance imaging (MRI). Assessing whether whether one hypoglossal nerve can be preserved seems a key factor for functional inoperability.

The term functional inoperability is clinically used by 100% of the Dutch experts in the decision-making process in the treatment of locally advanced head and neck carcinomas. According to the experts who took part in the survey, primary total glossectomy or a subtotal glossectomy sacrificing both hypoglossal nerves is an operation that causes unacceptable functional loss. In several case scenarios a consensus about operability could not be observed. The reactions varied per physician, institute and patient. Functional inoperability appears to be interpreted quite variable, which makes it difficult to determine. The concept of functional inoperability is clinically used and therefore it is important to bring this under attention.
Chapter 4

A worldwide survey on expected function after surgery for oral and oropharyngeal cancer.

A similar web based survey as described in chapter 3 is conducted among experts in the international field of head neck oncology and surgery to evaluate current practice in treating advanced oral and oropharyngeal cancer. The aim was to compare the worldwide differences and to define the borders of functional inoperability in advanced oral and oropharyngeal carcinoma.

The response rate to the survey is 20% (n=179). Fifty-one per cent of the respondents use the term functional inoperability in their current practice. More than half of all respondents consider the functional loss after tumour resection unacceptable if resection of both hypoglossal nerves is needed. In the Dutch survey this percentage is higher, namely 84-97%. The functional result after resection of a tonsil/base of tongue carcinoma with invasion of the vallecula is considered by 53% of the international experts as unacceptable, which is comparable to the Dutch survey, with 52% of the respondents opting for functional unacceptable in this case. There are more geographical differences noted; respondents from Northern America are more inclined to opt for surgical approach than European respondents. In comprehensive oncology institutes the term functional inoperability is more commonly used (73%) than in university hospitals (48%) and community hospitals (48%).

These findings show that reactions on functional inoperability vary, especially per geographical location and type of clinic. Most of the respondents consider a tumour functionally inoperable if for radical resection both hypoglossal nerves need to be sacrificed, something also found in the Dutch survey. This may be used to create international guidelines for functional inoperability, with a level of evidence of 5 according to the Oxford Centre for Evidence-based Medicine, as it is based on an expert opinion.

Chapter 5

Preoperative imaging and surgical margins in maxillectomy patients.

High rates of positive surgical margins are reported after a maxillectomy. A large part of tumours that are preoperatively considered operable, are not resected with tumour-free margins. This retrospective study is conducted with the aim of evaluating factors influencing surgical margins status, especially focussed on the role of preoperative imaging.

Medical files of 69 patients that underwent a maxillectomy as primary treatment for a squamous cell carcinoma were evaluated. More than 1/3 (39%) of all resections performed are incomplete, having tumour-positive surgical margins on the dorsal or dorsocranial side in 2/3 of the cases. Tumour extension on preoperative imaging is correlated to surgical margins status. Dorsal
and cranial tumour extensions are significant risk factors for tumour-positive surgical margins (p=0.006 and p=0.031 respectively). Tumour-positive margins are associated with a 2-fold increased risk of death (hazard ratio 2.4; 95% confidence Interval 1.2-4.9).

These results show that cranial and dorsal tumour extension on preoperative imaging is a significant risk factor for positive surgical margins after a maxillectomy. This has a significant negative influence on overall survival.

**Chapter 6**

*Oral function after maxillectomy and reconstruction with an obturator.*

Maxillectomy defects can be reconstructed by a prosthetic obturator or a free revascularised tissue transfer with microvascular anastomosis. There is no consensus about the optimal method. The surveys about functional inoperability showed that 23% of the international and 48% of the Dutch respondents consider the function after a bilateral maxillectomy as unacceptable. The aim is to evaluate 32 maxillectomy patients with prosthetic obturation on function, using as outcomes mastication, subjective oral and swallowing complaints and maximal mouth opening. The outcomes are related to the extent of the resection (on the Brown Maxillectomy classification), presence of remaining dentition and history of adjuvant radiotherapy.

Maxillectomy defects range from 2-1 to 4-B on the Brown classification scale. Most have a defect graded as 2-A or 2-B. The study group does not contain any patients with a defect graded in the horizontal plane as C, which means a total bilateral resection of the maxillae. The mean mixing ability test after 10 chewing strokes is 24.2 and after 20 chewing strokes 19.7, which compares to edentulous healthy individuals. None of the outcomes is influenced by the Brown classification. Radiotherapy negatively influenced the mean maximal mouth opening (29.1 mm versus 40.9 mm, p=0.017) and the subjective functional outcomes are also worse after radiotherapy. Edentate obturated patients have worse functional results than partial dentate patients, measured by the mixing ability test and questionnaire.

In conclusion, mastication after obturator reconstruction of a maxillectomy defect is comparable to mastication with full dentures. The size of the maxillectomy defect does not significantly influence the functional outcome, but adjuvant radiotherapy results in reduced mouth opening and more self-reported oral and swallowing complaints. Residual dentition has a positive influence on mastication and subjective outcomes. However, regarding the function after a bilateral maxillectomy, no statements can be drawn, because in all patients of this study a part of the contralateral maxilla has been preserved.
Chapter 7

Cine MRI of swallowing in patients with advanced oral or oropharyngeal carcinoma: a feasibility study.

Cine MRI is a novel technique that consists of a consecutive series of images made every 800ms during a movement, resulting in a dynamic reproduction of this movement. The purpose of this study is to examine whether cine MRI of swallowing yields additional information next to standard examinations in the evaluation of patients with dysphagia caused by treatment for advanced oral and oropharyngeal cancer.

Thirty-four cine MRIs were made in 23 patients with advanced oral and oropharyngeal cancer. These patients also underwent videofluoroscopy. Their quality of life was assessed by using a questionnaire.

Cine MRI of the swallowing in a midsaggital plane visualises the tumour (if located in the same plane) and important anatomic structures. Postoperatively the surgical reconstructions with free or pedicled tissue transfers are visible. A scoring system is applied to quantify the mobility of the oropharynx on cine MRI and videofluoroscopy. This mobility score ranges from 9 (normal mobility) to 17 (extreme immobility). The mean pretreatment score of the mobility on cine MRI is 10.8 and posttreatment 12.4 (p=0.017). This shows that posttreatment mobility is significantly diminished compared to pretreatment. Relating the mobility scores to the subjective outcomes of the questionnaire, it appears that impaired mobility on cine MRI is significantly correlated to swallowing complaints (Spearman’s correlation coefficient= 0.73, p= 0.04). Impaired mobility on videofluoroscopy is not correlated to subjective swallowing problems.

Cine MRI is a promising new technique and has additional value next to standard examinations for the evaluation of dysphagia in patients with oral and oropharyngeal cancer. An abnormal cine MRI has proven to be significantly correlated with subjective swallowing complaints of patients. Cine MRI allows visualisation of both the tumour and the dynamics of swallowing, so development and aetiology of dysphagia can be followed more precisely. Preoperatively the extension of the tumour in relation to the dynamic tissues, important for the swallowing function, can be evaluated. Therefore, cine MRI may contribute to the assessment of functional inoperability in the individual patient.

Chapter 8

Development of a dynamic model of the tongue for virtual surgery.

The aim of this study is to design a 3-dimensional model of the tongue. The ultimate goal is to develop a dynamic model of the oral cavity and oropharynx for virtual resection. This will lead
Summary and conclusion

to better assessment and visualization of the postoperative oral function, and, consequently, to objectify functional inoperability.

The finite element method is chosen to model the tongue. This geometrical model divides the tongue in 480 elements, obtained from segmenting an MRI volume scan. Models of the individual tongue muscles are placed according to anatomical descriptions and activated manually. The model shows expected tongue movements by the activation of separate or combined muscle groups. Changing stiffness parameters gives the opportunity to mimic other tissues types, like scarring effects caused by surgery or radiotherapy. Volume changes are noted when individual muscles are activated, but at the end of the movement the volume change on average is 103%.

In conclusion, these first steps in the development of a dynamic 3-dimensional model of the tongue seem promising. The activation of tongue muscles results in realistic movements of the virtual tongue. Refinement is necessary to make this finite element model suitable for future virtual surgery application, in order to assess functional inoperability in the preoperative stage.

Conclusion

This thesis demonstrates that functional inoperability is an interesting clinical concept. This concept should be considered in the treatment of advanced oral and oropharyngeal cancer, weighing up surgery against organ-sparing chemoradiation. In the Netherlands, the concept of functional inoperability is integrated in the current practice of head and neck oncology. According to Dutch clinicians, striking examples of functional inoperability are a primary (base of) tongue tumour that requires for radical resection a total glossectomy or a subtotal glossectomy, sacrificing both hypoglossal nerves and lingual arteries. Other interventions appear controversial, namely a total soft palate resection, a bilateral maxillectomy and a resection of a tonsil carcinoma taking out the vallecula and epiglottis.

Worldwide, there is no agreement about the concept of functional inoperability. There are geographical differences, which may be influenced by financial motives or availability and experience with different techniques. Respondents to our web based survey from Northern America demonstrate a greater tendency to opt for a primary surgical approach than their European counterparts, especially the Dutch. Only half of all international experts in the survey use the term functional inoperability in current practice. This shows the absence of agreement. An attempt to reach agreement could for instance be made by an international consensus-finding meeting in cooperation with the International Federation of Head and Neck Oncology and Surgery (IFHNOS).
A considerable part of the respondents in both surveys consider the functional result after a bilateral maxillectomy as unacceptable. As well for some maxillary sinus tumours or oral tumours with invasion of the maxilla, concurrent chemo- and radiotherapy is a curative option. In order to explore functional inoperability concerning a maxillectomy, this patient group is further examined. Firstly the primary goal, the oncologic result, is evaluated and thereafter the functional result.

On histopathological examination of the resected tissue, it appears that over 1/3 of all maxillectomies is incomplete, having a negative influence on overall survival. Tumour extension dorsally and dorsocranially on preoperative imaging is a risk factor for incomplete surgery. Negative surgical margins can be achieved with more extensive resections, for example by means of an orbital exenteration or a craniofacial resection. These more extensive resections will lead to an increased postoperative morbidity, thus functional inoperability should be kept in mind.

The functional result appears relatively good in the study group that underwent a maxillectomy and reconstruction with an obturator. As long as a part of the contralateral maxilla remains, the size of the maxillectomy cavity does not influence the rehabilitation of function. Adjuvant radiotherapy does increase swallowing complaints and trismus after treatment. It is important to mention is that this study group does not contain any patients that underwent a total bilateral maxillectomy.

To objectify the clinical dilemma of functional inoperability, therewith founding its clinical use, innovative imaging techniques have been explored. Cine MRI is a good example, as this modality can locate the tumour in relation to the important dynamic structures for swallowing and speech. This may lead to better preoperative assessment of the tumour and surrounding dynamic tissues that are important for function. Moreover, this contributes to a better evaluation and understanding of the development of postoperative (and postradiotherapeutic) dysphagia.

A dynamic model of the oral cavity and oropharynx, in which virtual surgery can be drawn, is in development. Eventually, this can involve the patient in the decision-making process around the surgical treatment, providing an objective reproduction of the expected functional result. Herewith functional inoperability can be objectively assessed in the preoperative stage for the individual patient.

Concluding, in this thesis the current national and international practice and clinical decision-making process about functional inoperability are evaluated. An impression is drawn of which clinicians already apply the concept in practice, and which surgical procedures are being
considered as functional inoperable. The decision-making process concerning functional inoperability appears subjective and variable, with evident geographical differences. The first step in objectifying functional inoperability has been taken by development of the cine MRI of swallowing and a dynamic model of the oral cavity and oropharynx.