Functional inoperability of oral and oropharyngeal cancer
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Chapter 4

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

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‘The surgical dilemma in advanced oral and oropharyngeal cancer: how we do it.’

ABSTRACT

Objective. If surgical resection of a tumour results in an unacceptable loss of function, this is defined as functional inoperability. The current survey aims to define the borders of functional inoperability in oral and oropharyngeal carcinoma and evaluates its current practice in treating advanced oral and oropharyngeal cancer, comparing worldwide differences.

Design. A web based survey.

Participants. Experts in the international field of head neck oncology.

Main Outcome Measures. Assessment of functional results after tumour resection in eighteen statements about hypothetical surgical interventions and four cases of patients with advanced oral and oropharyngeal cancer.

Results. Response rate on the survey is 20% (n=179). Fifty-one per cent used the term functional inoperability in their current practice. More than half of respondents considered the functional result after tumour resection unacceptable if resection of both hypoglossal nerves was needed (53-85%), and after resection of a tonsil/base of tongue carcinoma with invasion of the vallecula (53%). Geographical differences were noted; respondents from Northern America were more tended to opt for surgical approach than European respondents. In cancer institutes the term functional inoperability was more often used than in university hospitals or community hospitals.

Conclusion. Reactions on functional inoperability varied, especially per geographical location and type of clinic. A majority of the respondents considered a tumour as functionally inoperable if for radical resection both hypoglossal nerves needed to be sacrificied. This and other common denominators may create an opportunity to make internationally accepted guidelines for functional inoperability. Level of evidence: 5
INTRODUCTION

The decision to whether or not treat advanced head and neck cancer surgically is mainly dictated by the estimation of achieving clear margins. Since the availability of advanced reconstruction techniques making larger resections possible, the chances for clear margins have improved considerably. However, as a result of these more extensive resections, function loss will occasionally be so severe that even with the best reconstruction methods it will not be acceptable to many patients. For this situation the term functional inoperability has been coined.¹

No randomised comparative studies between surgery and a non-surgical approach in advanced squamous cell oral and oropharyngeal carcinoma have been performed, neither comparing oncologic outcome nor function.² A cross-sectional study comparing long-term quality of life in patients after treatment for advanced oropharyngeal carcinoma (n=58) reported that better long-term quality of life was observed in patients that underwent chemoradiation, although another study (n=54) reported similar outcomes.³,⁴

Both treatments regimes for advanced oral and oropharyngeal cancer induce functional problems after treatment. The most important long-term side effects of (chemo)radiation are xerostomia and dysphagia.⁵ Also the incidence of osteoradionecrosis should be noted, which overall hovers around 10% after radiotherapeutic treatment of advanced oral cancer.⁶

According to our recently published literature review,⁷ it appears that after surgery for advanced oral and oropharyngeal cancer functional deficits continue to exist, most notably with regard to swallowing. The functional result depends on the amount and location of tissue that is to be removed in order to achieve cancer-free surgical margins. The vital question is at what stage and tumour extension the expected postoperative loss of function will be so severe that treatment in an organ preservation protocol is likely to result in better functional outcome. In the Netherlands, the term functional inoperability appears to be clinically used in the decision-making process in advanced squamous cell head and neck carcinomas, evaluated by a previous web based survey among head neck surgeons and radiation oncologists.¹

As functional results are dependent on multiple factors, we supposed that treatment regimes vary worldwide. Aims of this study were to evaluate the current practice of treatment of oral and oropharyngeal cancer internationally, to investigate the opinion of experts in the field about the function losses to be expected after several surgical interventions, comparing worldwide differences, in order to establish an expert-based definition (level of evidence 5).⁸
Chapter 4

MATERIALS AND METHODS

Respondents
A web based survey was sent to 907 head neck surgeons and radiation oncologists worldwide, based on personal contacts of the Antoni van Leeuwenhoek Hospital/ Netherlands Cancer Institute and the VU University Medical Center in Amsterdam, and along with the newsletter of the American Head Neck Society to all corresponding members.

The questionnaire
The questionnaire started with general questions and a multiple-choice question concerning factors that influence functional inoperability, followed by four cases and 18 statements, see Appendix A. Respondents were asked to consider the functional result of an intervention acceptable or not, having a possibility to opt for ‘neutral’. Four cases were illustrated by clinical information and magnetic resonance images (MRIs), and respondents were asked whether they regarded the tumour as functionally operable or inoperable. It was to be assumed that all tumours were primary tumours, that patients had no relevant medical history or comorbidity and that the patient’s opinion about treatment choice was neutral. In these hypothetical situations, optimal surgical and prosthetic reconstruction was performed, resulting in the most optimal result. Furthermore, alternative curative therapy was concurrent chemoradiation in an experienced multidisciplinary team with up-to-date treatment protocols.

Statistical analysis was performed using SPSS version 11.1 (IBM Corporation, Somers, New York, USA). Chi-square test was performed in cross-tabulation comparing for several subgroups the number of respondents that answered ‘yes’ and ‘no’ on the cases and statements; neutral and missing answers were filtered out in order to perform the test.

RESULTS

There were 179 responses resulting in a response rate of 20%. Fifty-one per cent used the term functional inoperability in their current practice. The most important factor in determining functional inoperability was total loss of oral and oropharyngeal food transport; 47% of the respondents opted for this factor, followed by wishes and expectations of the patient (45%), comorbidity (41%), total loss of speech (32%), expected compliance of the patient (31%), deterioration of swallowing resulting in a liquid diet (27%) and a cosmetically unacceptable result (22%).
A worldwide survey about functional inoperability

Figure 1: Surgery for oropharyngeal cancer

- Resection of tonsil, lateral part soft palate + ascending part of the mandible: 7
- Resection of a tonsil/ base of tongue carcinoma with preservation of one hypoglossal nerve/ lingual artery: 12
- 2/3 soft palate resection: 16
- Resection of the dorsal and lateral pharynx wall: 16
- Laryngopharyngectomy: 23
- Total soft palate resection: 37
- Resection of tonsil/ base of tongue carcinoma with invasion in vallecula: 53
- Resection of tonsil/ base of tongue carcinoma, dubious preservation a hypoglossal nerve/ lingual artery: 56

The bars represent the percentage of respondents that considered the functional result of surgery as unacceptable.

Figure 2: Surgery for oral cancer

- Hemimandibulectomy with disarticulation: 4
- Subtotal glossectomy, preservation of one hypoglossal nerve: 8
- Floor of mouth + mandibula resection + subtotal glossectomy, preservation of one hypoglossal nerve: 10
- Subtotal glossectomy, preservation of one hypoglossal nerve + segmental lateral mandibulectomy + disarticulation: 14
- Bilateral maxillectomy: 23
- Total mandibulectomy: 50
- Total glossectomy: 53
- Total glossectomy + total laryngectomy: 63
- Floor of mouth + segmental mandibula resection + subtotal glossectomy sacrificing both hypoglossal nerves: 64
- Total glossectomy + supraglottic laryngectomy: 85

The bars represent the percentage of respondents that considered the functional result of surgery as unacceptable.
Two interventions for oropharyngeal cancer are by more than half of the respondents considered as functionally inoperable, namely resection of tonsil and base of tongue carcinoma with invasion of the vallecula, and resection of a tonsil and base of tongue carcinoma with questionable likelihood of preservation of the contralateral hypoglossal nerve and lingual artery. For all results, see figure 1.

Regarding tongue cancer, 53% of the respondents considered total glossectomy as functional unacceptable and even more in combination with a total laryngectomy (63%) and a supraglottic laryngectomy (85%), see figure 2. An anterior segmental mandibulectomy, anterior floor of mouth resection and subtotal glossectomy sacrificing both hypoglossal nerves is considered functional unacceptable by 64% of the respondents.

**Figure 3**: Cases of oral and oropharyngeal cancer

<table>
<thead>
<tr>
<th>Case</th>
<th>Examination</th>
<th>MR Images</th>
<th>MRI report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man 63 yrs T4N2a cheek/ inferior alveolar process</td>
<td>Large ulcerating tumour of the alveolar process extending tot the tuber maxillae, tongue/ skin is free</td>
<td>Tumour of 6cm, extensive erosion of the horizontal part of mandible, extending to the lateral floor of mouth and buccal sulcus, tongue is free</td>
<td></td>
</tr>
<tr>
<td>Man 48 yrs T2N0 oral tongue</td>
<td>Tumour of the left lateral border of the tongue, submucosal extending over the midline, tip of tongue is free</td>
<td>Tumour of 2.5cm in the oral tongue, extending to the base of tongue on the left side and over the midline</td>
<td></td>
</tr>
<tr>
<td>Man 54 yrs T3N2b base of tongue</td>
<td>Tumour at the base of tongue, vallecula seems free</td>
<td>Tumour of max 5cm at the left base of the tongue extending over the midline and to the left tonsil and vallecula caudally</td>
<td></td>
</tr>
<tr>
<td>Woman 50 yrs T3N0 base of tongue</td>
<td>Tumour at the base of tongue extending to the whole base of tongue, vallecula is free</td>
<td>Exophytic tumour medially in the base of tongue</td>
<td></td>
</tr>
</tbody>
</table>

Cases in the international survey on functional result after surgery for oral and oropharyngeal cancer (n=179)
There were four cases in the questionnaire. The first two cases described a patient with a T4aN2a carcinoma of the cheek and inferior alveolar process and one with a T2N0 oral tongue carcinoma. These tumours were considered as operable by 84% and 89% respectively, see figure 3 for all case descriptions. Opinions varied more in the other two cases. The third case described a 54-year-old man with a T3N2b base of tongue carcinoma, 61% of the respondents considered this tumour as functionally inoperable, 32% as operable, 7% was undecided. The main reason for being deemed inoperable was deterioration of oral and oropharyngeal food transport and restriction to liquid diet, ticked by 65% of the respondents that opted for inoperability, followed by total loss of swallowing (58%), and severe deterioration of speech (58%). The last case described a 50-year-old woman with a T3N0 base of tongue carcinoma. Fifty-four per cent of respondents considered this tumour as functionally inoperable, 41% as operable, 5% was undecided. Main reason for inoperability was total swallowing loss, chosen by 65% of respondents that opted for inoperability, followed by deterioration of oral/ and oropharyngeal food transport (50%) and severe deterioration of speech (45%).

Regional differences
The majority of the respondents was from the United States, see figure 4. European response rate was 42%, American/Canadian 14% and response from the remaining parts of the world 26%. For analytic purposes, three groups were composed: from North America (United States and Canada) (n=81), from Europe (n=57) and from other parts of the world (n=33). A Dutch group of our previous survey on this subject was added (n=67).1

Figure 4: Origin of respondents

Origin of respondents participating on the international e-mail survey on functional result of surgery for oral and oropharyngeal cancer (n=179)
There were several significant differences between these groups. First of all, the use of the term functional inoperability was much wider in the Dutch group (100%) compared to the remaining parts of the world (71%) and the European group (65%) and especially compared to the United States/Canada group (37%, p=0.00). Answers on all four cases and on seven statements were significantly different. For example, a total glossectomy was considered as functionally inoperable by 97% of the Dutch respondents, compared to 68% of the North American respondents, 69% of the European respondents and 52% of the group comprised of respondents of the other parts of the world (p=0.00). For all other differences see table 1.

Overall, the Dutch respondents appeared to be more inclined to opt for a non-surgical approach, as the percentage of Dutch respondents that considered a certain surgical procedure as functionally unacceptable is frequently higher than the other groups. The respondents from North America more often tended to choose for surgery, as the percentage of this group that considered the statements and cases as unacceptable is frequently lower than the other groups, see table 1.

**Type of institution**
The majority, consisting of 121 respondents (68%), worked in a university hospital, 31 in a specialised oncology or radiotherapy centre (17%), 21 in a peripheral clinic (12%) and for six respondents this was unknown (3%). It appeared that in a specialised oncology or radiotherapy centre a higher percentage of the respondents (73%) used the term functional inoperability, compared to 48% of those that practice in a university hospital or community hospital (p=0.04). In the cases and statements there were no significant differences in the answers of the respondents of the different types of institutions.

**Size of institution**
Fifty-one respondents (28%) treat less than 200 new head neck cancer (HNC) patients per year, 92 respondents (51%) treat 200-600 new HNC patients per year and 31 respondents (17%) treat more than 600 new HNC patients per year, in 5 (3%) it was unknown. There were no significant differences between the answers from these subgroups.
Table 1: International controversies on expected function after surgery for oral and oropharyngeal cancer.

<table>
<thead>
<tr>
<th>Functional result not acceptable after a</th>
<th>United States/Canada</th>
<th>Europe</th>
<th>Rest of the world</th>
<th>The Netherlands</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total glossectomy</td>
<td>69%</td>
<td>69%</td>
<td>52%</td>
<td>97%</td>
<td>0.00</td>
</tr>
<tr>
<td>Total glossectomy and total laryngectomy</td>
<td>69%</td>
<td>78%</td>
<td>67%</td>
<td>89%</td>
<td>0.03</td>
</tr>
<tr>
<td>Anterior segmental mandible resection, resection of the anterior floor of mouth and subtotal glossectomy with unilateral preservation of the hypoglossal nerve</td>
<td>11%</td>
<td>10%</td>
<td>13%</td>
<td>29%</td>
<td>0.04</td>
</tr>
<tr>
<td>Anterior segmental mandible resection, resection of the anterior floor of mouth and subtotal glossectomy sacrificing both hypoglossal nerves</td>
<td>68%</td>
<td>86%</td>
<td>69%</td>
<td>94%</td>
<td>0.00</td>
</tr>
<tr>
<td>Total mandibulectomy</td>
<td>47%</td>
<td>64%</td>
<td>63%</td>
<td>72%</td>
<td>0.02</td>
</tr>
<tr>
<td>Resection of a tonsil and base of tongue carcinoma with dubious possibility of preservation of one hypoglossal nerve and lingual artery</td>
<td>67%</td>
<td>64%</td>
<td>68%</td>
<td>91%</td>
<td>0.01</td>
</tr>
<tr>
<td>Total laryngopharyngectomy</td>
<td>17%</td>
<td>38%</td>
<td>20% n.a.**</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

The functional result after surgery is not acceptable

- **Case 1:** 63-year-old man with a T4N2a carcinoma of the right cheek and inferior alveolar process. 1% 7% 16% 10% 0.04
- **Case 2:** 48-year-old man with a T2N0 oral tongue carcinoma. 4% 11% 13% 25% 0.00
- **Case 3:** 54-year-old man with a T3N2b base of tongue carcinoma. 64% 65% 71% 92% 0.00
- **Case 4:** 50-year-old woman with a T3N0 base of tongue carcinoma. 58% 53% 63% 79% 0.02

Answers on the worldwide survey on functional inoperability in oral and oropharyngeal cancer among respondents from the international survey (n=179) and a previous published Dutch survey (n=67).

* p-value calculated by Chi-square test.
** Not applicable: this statement was not included in the Dutch survey
DISCUSSION

Synopsis of results
Half of all respondents used the term functional inoperability in their current practice. More than half of the participants considered the functional result as not acceptable after a resection of tonsil and base of tongue carcinoma with invasion in the vallecula and epiglottis and after a surgical procedure sacrificing both hypoglossal nerves. From these answers it may be concluded that if both hypoglossal nerves should be sacrificed the majority of clinicians declines from surgery and may recommend chemoradiation. This may create an opportunity to make internationally accepted guidelines for functional inoperability.

Reactions on functional inoperability varied, especially per geographical location and type of clinic. It appeared that Dutch clinicians are more tended to opt for non-surgical therapy because of the expected functional deficits postoperatively. Respondents from the United States and Canada considered more frequently a surgical intervention as functional acceptable, moreover they had the lowest percentage of clinicians that used the term functional inoperability in their decision-making process. Reasons for these differences might be the tight organization of the Head and Neck Tumour Board with the multidisciplinary clinical decision-process and the longstanding experience with chemoradiation in the Netherlands, next to differences in health care systems.

Operability
There are numerous difficulties encountered when trying to define functional inoperability in oral and oropharyngeal cancer. Of greatest importance in treatment choice is that the oncological outcome of both treatments is expected to be comparable. For oral and oropharyngeal cancer, there is evidence that we have achieved similar locoregional and overall control rates with organ-preservation protocols compared to surgery. A randomised controlled trial of a cohort head and neck cancer patients, including oral and oropharyngeal tumours, comparing chemoradiation and surgery with adjuvant radiotherapy, showed similar survival rates.9 Several studies showed high survival and locoregional control rates after organ-sparing therapy for oral and oropharyngeal cancer, expressing a slight preference for chemoradiation if this entails that patients may be spared an extensive resection.6 Several other factors also play a role in the expected oncological response to treatment. For example, the increasing knowledge that HPV-positive tumours are especially sensitive to (chemo-) radiation treatment.12 Some of our respondents advocated that surgery has advantages over chemoradiation in controlling tumours invading bone, although comparable survival rates in patients with and without bone invasion have been described.13
Like any decision in medicine, the recommendation is based on balancing risks and benefits. There are gradations of acceptable function that will be affected by comorbidities, the attitude and needs of an individual patient, among other factors. Therefore, a detailed discussion with a patient is needed to explain expectations of function after surgery for oral and oropharyngeal cancer and on the other hand the functional consequences and treatment success rate of chemoradiation.

In case of recurrence after chemoradiation functionally disabling operations are the only means of treating patients to save their lives, and functional inoperability is not applicable anymore. In these cases, it is the responsibility of the surgeon to inform patients about the expected results after such functionally disabling surgery, but also about the prognosis of tumour progression with possible negative impact on the function and quality of life, with increased symptoms of pain, dysphagia, respiratory obstruction and haemorrhage.

The term functional inoperability could be replaced by the term functional unresectability. Strictly considering tumour extension and its resectability, functional unresectability might also be applicable. In this survey inoperability is used, considering current practice and common use, although inoperability may comprise as well the patient, its age and comorbidities.

Possible biases
We did not encourage perspective respondents with financial or equivalent inducements. All data were self-reported voluntarily. A weakness of this study is the low response rate, which may have created a selection bias. Another e-mail survey among academic surgeons had a response rate of 23%, which they considered as appropriate for an online survey. It is known that the response to e-mail surveys is declining, along with the overload of unsolicited e-mail and risk on viruses. In another review it has been evaluated that physicians had the lowest mean response rate among all other branches examined.

It appeared that the European response rate was higher which might have influenced the results. This makes the results of the survey for the American respondents more at risk of selection bias. The difference might be due to the fact that European recipients were contacts of the two participating centres, while recipients if Northern America included the entire American Head and Neck Society (AHNS) membership, which makes it more anonymously. Response rate is also low due to the large amount surveys that was sent (n=907). Goal was to achieve the highest possible number of responses. A high number of responses, rather than a high response rate in a selected group will reflect the views of current practising head neck surgeons. Indeed we reached a fair amount of responses, giving us an idea of the opinions of 179 experts in the field of head and neck surgery.
CONCLUSION

Reactions on functional inoperability varied, especially per geographical location and type of clinic. European head neck physicians were more inclined to opt for an organ preservation approach than their counterparts from Northern America. The most participants considered a tumour as functionally inoperable if for radical resection both hypoglossal nerves should be sacrificed, which may create an opportunity to make internationally accepted guidelines for functional inoperability.

Acknowledgement
We thank the American Head and Neck Society for their support on obtaining responses for this survey.
REFERENCES


