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ORIGINAL ARTICLE

## The Danish national guidelines for treatment of oral squamous cell carcinoma

ANDERS BILDE<sup>1</sup>, CHRISTIAN VON BUCHWALD<sup>1</sup>, JØRGEN JOHANSEN<sup>2–6</sup>,  
LARS BASTHOLT<sup>2</sup>, JENS A. H. M SØRENSEN<sup>3</sup>, PETER MARKER<sup>4</sup>, ANNELISE  
KROGDAHL<sup>5</sup>, HANNE SAND HANSEN<sup>6</sup>, LENA SPECHT<sup>6</sup>, JØRGEN KIRKEGAARD<sup>1</sup>,  
ELO ANDERSEN<sup>7</sup>, JENS BENTZEN<sup>7</sup>, CHRISTIAN HJORT-SØRENSEN<sup>8</sup>, LISBETH  
JUHLER ANDERSEN<sup>9</sup>, BENGT AGATHON NIELSEN<sup>10</sup>, TROELS BUNDGAARD<sup>11</sup>,  
MARIE OVERGAARD<sup>12</sup> & CAI GRAU<sup>12</sup>

<sup>1</sup>Department of Otolaryngology, Head & Neck Surgery, Copenhagen University Hospital, Copenhagen, Denmark,

<sup>2</sup>Department of Oncology, Odense University Hospital, Odense, Denmark, <sup>3</sup>Department of Plastic Surgery, Odense University Hospital, Odense, Denmark, <sup>4</sup>Department of Oral and Maxillofacial Surgery, Odense University Hospital, Odense,

Denmark, <sup>5</sup>Department of Pathology, Odense University Hospital, Odense, Denmark, <sup>6</sup>Department of Oncology, Copenhagen University Hospital, Copenhagen, Denmark, <sup>7</sup>Department of Oncology, Herlev University Hospital, Herlev, Denmark,

<sup>8</sup>Department of Otolaryngology, Head & Neck Surgery, Gentofte University Hospital, Hellerup, Denmark, <sup>9</sup>Department of Oncology, Aalborg Hospital, Aalborg, Denmark, <sup>10</sup>Department of Otolaryngology, Head & Neck Surgery, Aalborg Hospital,

Aalborg, Denmark, <sup>11</sup>Department of Otolaryngology, Head & Neck Surgery, Aarhus University Hospital, Aarhus, Denmark, <sup>12</sup>Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

### Abstract

The treatment strategy for oral squamous cell carcinoma in Denmark has traditionally varied between the different head and neck oncology centres. A study group within the Danish Society for Head and Neck Oncology (DSHHO) was formed with the aim of optimising and standardising the treatment strategy. The approach was to use single modality treatment for stage I, stage II and some stage III and combined modality treatment for stage III and IV. Surgery was the preferred treatment when it was considered possible to perform a radical excision of the tumour and possible lymph node metastases with acceptable aesthetic and functional outcome. The implementation of a recognised national guideline facilitates prospective studies on a large well-characterised cohort. This increases the possibility of obtaining valid data on parameters such as morbidity, loco-regional control and survival. In addition the establishment of a reference program facilitates national monitoring of the treatment using defined indicators and standards.

Malignant tumours of the head and neck are among the ten most common tumours in males and the twentieth in females in Denmark [1]. In recent years there has been an increase in the incidence of head and neck malignant tumours mainly due to the increase of tobacco and alcohol consumption [2]. The incidence of malignant tumours of the oral cavity in Denmark (5.4 million inhabitants) is 310 new cases per year comprising 20% of all head and neck tumours, the far majority being squamous cell carcinoma [1].

In Denmark, the malignant tumours of the oral cavity as well as other malignant head and neck tumours are treated in five university head and neck oncology centres. The treatment is based on a multidisciplinary collaboration involving head and neck surgeons (ENT or plastic surgeon), oncologists, oral and maxillofacial surgeons, pathologists, radiologists and nuclear medicine specialists. A permanent working group under the Danish Society for Head and Neck Oncology (DSHHO) named The Danish Head and Neck Cancer Study Group

(DAHANCA) coordinate these activities and maintains a national database for the treatment of all malignant head and neck tumours. All patients are referred to a university head and neck oncology centre according to their home address. Prior to therapy all patients are examined at a joint conference between head and neck surgeons and oncologists for clinical tumour classification and treatment planning. After completing treatment the patients are followed up on a regular basis at the same centre for two to five years in order to detect a possible recurrence or a new primary tumour.

Parallel to other international centres the treatment of oral squamous cell carcinoma has varied between the different head and neck oncology centres depending on the prior experience and tradition of each centre [3–9]. The treatment options for early stage oral squamous cell carcinoma consisted of surgical resection of the primary tumour with or without elective neck dissection with or without postoperative radiotherapy while radiotherapy in some cases was used as the only treatment. For advanced stage oral squamous cell carcinoma treatment options consisted of surgery or radiotherapy alone or a combination of these. Chemotherapy is only being used for recurrent incurable disease. Due to the existing differences the DSHHO decided at the annual assembly in 2002 to work towards the development and implementation of clear national guidelines for the treatment of squamous cell carcinoma of the oral cavity. The guidelines should reflect the existing treatment modalities used at the different national centres in order to facilitate the practical implementation of a uniform treatment policy. In addition, the guidelines should be in accordance with international recommendations. A study group was established with members of the DSHHO. Parallel to the making of the guidelines a Nordic group within The Swedish Council of Technology Assessment in Health Care (SBU) has made a systematic review focusing on the radiation therapy effects in head and neck cancer [10].

## Material and methods

Deadline for the completion of the national guidelines was scheduled to the annual meeting of DSHHO in June 2003. At the first meeting of the study group each representative described the treatment modality used at their centre as well as the treatment capacity. At subsequent meetings each representative reviewed the literature related to the treatment options pertinent to their speciality and delivered a draft with recommendations on treatment focusing on treatment morbidity. For literature

searches the Medline/Pubmed and the Cochrane Library databases were used. Consensus on the recommendations was reached after several meetings within the study group during the autumn of 2002 and spring 2003 and a final draft was submitted to all centres for comments. Revisions were made and the final version was discussed at the annual general assembly in DSHHO and approved subsequently at the board meeting June 2003.

## Results

All squamous cell carcinomas of the oral cavity are staged clinically according to the UICC 1997 TNM classification with use of prior panendoscopy, chest X-ray, CT or MRI of the primary tumour and neck and fine-needle aspiration biopsy when indicated. In a single centre, ultrasound is included in the diagnostic armamentarium.

Primary surgery is characterized by the excision of the tumour allowing for a histological examination of the surgical margins in order to determine if radical resection has been achieved. Conversely, primary radiotherapy is characterized by the intention of preserving the anatomy and possibly the function of the tissue. However, compared with surgery, it is a prolonged treatment modality, which is associated with acute complications like mucositis and dysphagia as well as late complications like xerostomia and osteoradionecrosis [11–13]. The complications associated with surgery are mainly intra- and post-operative bleeding, infection and nerve injury. For patients undergoing postoperative radiotherapy the major complications are related to lack of wound healing including skin necrosis and wound breakdown [14].

In early-stage oral cancer single modality treatment with either surgery or radiotherapy are equally effective whereas single modality treatment is inferior to combined treatment in advanced-stage oral cancer. [7,15–19].

The initial path of metastases in head and neck cancer is, in most cases, via the lymphatics to the regional lymph nodes of the neck. The presence of cervical metastasis is the single most important prognostic factor for survival [20]. The estimated incidence of lymph node metastasis (pN+) in oral cancer patients with clinically negative neck (N0) is approximately 22 – 52% depending on the localisation of the tumour [21]. In order to delineate the location of lymph node metastases The Committee for Head and Neck Surgery and Oncology of the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) has proposed a classification system dividing the neck into six levels [22]. Cervical lymph node metastases in oral cancer follow

a predictable pattern with involvement of mainly level I–III. The anterior tongue tumour may behave differently to this involving separately level IV in approximately 15% [23–25]. Selective treatment of the neck covering level I–III, and for anterior tongue level I–IV, is therefore considered appropriate as the rate of metastases in untreated levels is less than 10% [25–29].

On the basis of these considerations the national guidelines were proposed with the following recommendations [30]:

The UICC 1997 TNM classification was used for stratification.

It was decided to use a single modality treatment (surgery or radiotherapy) for stage I (T1N0), stage II (T2N0) and early stage III (T1–2N1) and a combined modality treatment (surgery and radiotherapy) for stage III and IV (Table I) [7,15–19]. In order to reduce excessive treatment, it was decided only to treat levels with a risk estimate of more than 10% of harbouring metastases. For tumours involving the midline, the neck dissection should be bilateral and for tumours involving the anterior tongue, level IV should be included. The neck dissection should include the subsequent level in case of a clinical lymph node metastasis or a tumour positive lymph node using frozen-section analysis. Surgery is the preferred treatment when it is considered possible to perform a radical excision and reconstruction on the basis of the clinical and radiological work-up with acceptable aesthetic and functional outcome. Primary curatively intended radiotherapy is recommended for patients not eligible for surgery. With regard to the primary tumour

the resection of the tumour has to be made with a minimum macroscopic surgical margin of 10 mm. The microscopic surgical margin has to be clear in order for the operation to be considered radical, i.e. when there is no evidence of tumour (invasive carcinoma) within 5 mm of the margin on histological assessment of formalin fixed, routinely processed tissue samples [31]. With regard to the lymph nodes the resection is considered radical when there is no evidence of extra-capsular spread (capsular rupture) both macro- and microscopically.

Postoperative radiotherapy is indicated in all cases of non-radical resection of the primary tumour or the lymph nodes, as well as cases with a classification of the regional lymph nodes of pN2 or higher.

The selection and delineation in conformal radiotherapy of lymph node target volumes follows the guidelines of DAHANCA as does radiotherapy of the primary tumour [32].

If primary curatively intended radiotherapy is used for a patient having a lymph node metastasis classified as N0–N1, surgical treatment of the neck is only indicated in case of a persistent lymph node metastasis or recurrence. For N2–N3 patients, surgical treatment of the neck is planned within two months to remove residual lymph node metastases after the completion of radiotherapy (Figure 1).

## Discussion

The highest level of evidence for the appropriate (or best) treatment strategy in cancer diseases is achieved on the basis of randomised trials. Most of the studies on the treatment of oral cancer are

Table I. Treatment modality based on the UICC 1997 TNM classification.

Stage	I	II	III	IV
TNM	T1N0	T2N0	T1N1	T2N1
T-site		Single modality treatment		Combined modality treatment
N-site		Surgery <i>or</i> radiotherapy		Surgery <i>and</i> radiotherapy

Table II. National guidelines in brief.

- Single modality treatment and combined modality treatment are used (Table I)
- Surgery is the preferred treatment in all cases where radical excision and reconstruction are judged to be possible
- The operation is considered radical only if the microscopic surgical margin show no evidence of tumour within 5 mm of the margin on histological assessment
- The resection of the lymph nodes is considered radical when there is no evidence of extra-capsular spread (capsular rupture) both macro- and microscopically
- Levels with a risk of less than 10% of harbouring metastasis are *not* treated
- Selective neck dissection (I–III) and level IV for anterior tongue tumour is considered appropriate
- Postoperative radiotherapy is indicated in case of a non-radical excision with regard to the primary tumour or the lymph nodes or if the classification of the regional lymph nodes is pN2 or higher.

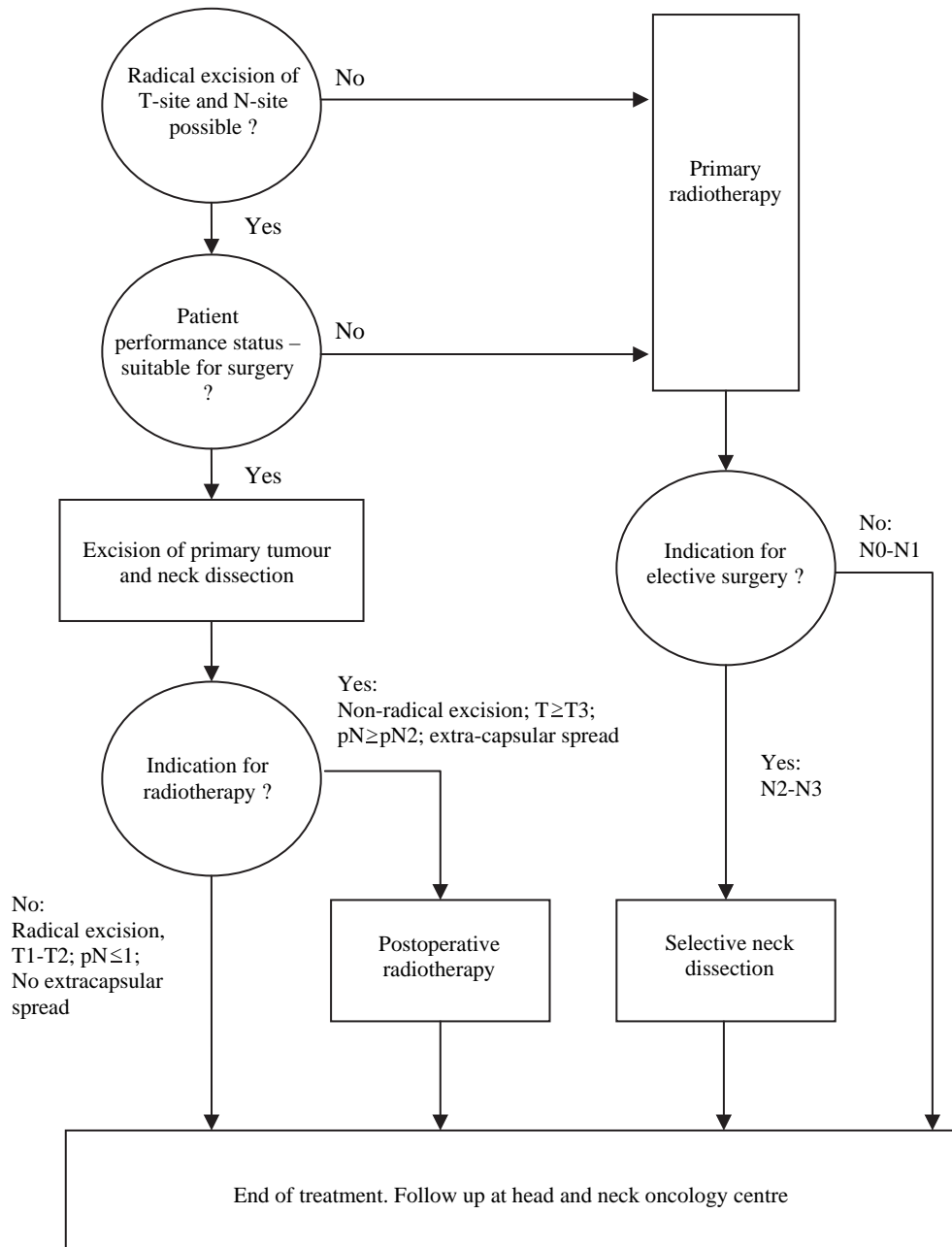


Figure 1. Decision tree for the treatment of oral SCC.

retrospective analyses of selected series. Consequently, the outcome of these studies might be biased and the conclusions not universally applicable. Without performing a randomised trial it is difficult to obtain evidence for the merits of any new treatment modality regarding measurable parameters such as morbidity, loco-regional control or survival [33].

Implementing national guidelines for the treatment of oral cancer gives the opportunity to optimise and standardise the treatment procedures. The precondition for a standardised treatment comprises the use of well-characterised definitions and

methods. Especially, the definition of a clear radical resection as well as the N0 neck is varying or is not always defined explicitly when reviewing the literature [8,9,15,18]. Moreover, the access to CT and especially MRI is still limited in Denmark.

Furthermore, implementing a standardised treatment strategy will facilitate prospective studies of issues that have traditionally been analysed in selected series retrospectively, e.g., the distribution of lymph node metastases. Much of the current knowledge about lymph node metastases is based upon analyses of large series comprising more than 1 000 patients [23,25,28,34]. Even though these series

are very large the conclusions are still limited by the unavoidable restrictions of retrospective studies with selected patients. With the implementation of the national guidelines a prospective database is established comprising an unselected and well defined large cohort treated according to a well-defined method. This makes it possible in case of a clinical N0 neck to gain valid information about e.g. the occurrence and distribution of occult lymph node metastases including micro-metastases and their effect on loco-regional control and survival. It makes it possible to validate new treatment strategies in oral cancer e.g. sentinel node biopsy technique where a selective neck dissection is solely performed if the sentinel nodes contain tumour [35]. Currently a sentinel node biopsy trial within the Sentinel European Node Trial is being prepared. Another trial associated with the guidelines is the forthcoming DAHANCA 16 which will elucidate whether planned post-radiation neck dissection, compared to salvage neck dissection, has an effect on loco-regional control and disease-specific survival in patients with N2–N3 squamous cell carcinoma of the head and neck treated with primary radiotherapy.

An early outcome of developing a national guideline has been a better and more active cooperation between physicians involved in the treatment as well as with the patient network group. Acceptance of a reference program facilitates national monitoring of the treatment using defined indicators and standards thus securing a prompt and an effective course of treatment.

With the implementation of the national guidelines each head and neck oncology centre are responsible for the continuing monitoring of the treatment of patients with oral cancer. DAHANCA will analyse the outcome and will be capable of initiating new evidence-based treatment strategies.

The guidelines can be downloaded from the Internet at the following address [http://www.dshho.-suite.dk/OralRefProg\\_24juni2003.pdf](http://www.dshho.-suite.dk/OralRefProg_24juni2003.pdf).

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