THE VALUE OF NECK DISSECTION IN HEAD AND NECK CANCER — Ch.R. LEEMANS — 1992

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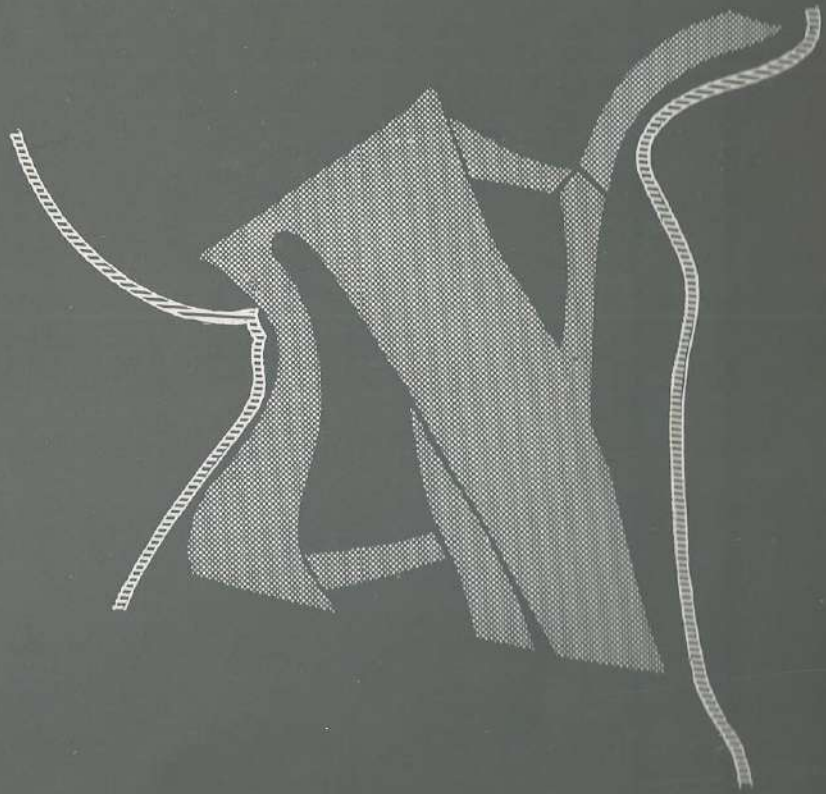
a therapeutic and staging procedure



Ch.R. LEEMANS

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VRIJE UNIVERSITEIT

THE VALUE OF NECK DISSECTION IN HEAD AND NECK CANCER

a therapeutic and staging procedure

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CHARLES REINIER LEEMANS

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promotor: prof.dr. G.B. Snow

copromotor: dr. R.M. Tiwari

referent: prof.dr. H. Bartelink

CONTENTS

GENERAL INTRODUCTION

Squamous cell carcinomas of the head and neck have a tendency to spread to the regional lymphatics in an early phase of the disease rather than to the bloodstream. Lymph node metastases can be a source of further dissemination. Thus, the regional lymphatic spread of head and neck squamous cell carcinoma and, consequently, the therapeutic approach to the neck nodes, play a central role in determining the ultimate prognosis.

The treatment of the neck, however, raises considerable controversy. This is evidenced, for instance, by the emergence of modifications of the classical radical neck dissection and the different opinions concerning their applications. The problem is further complicated by the lack of uniformity with respect to the indications for combined surgery and radiation therapy.

It is well known that the histopathologic extent of disease in the neck is not only a prognostic factor in terms of regional tumor-recurrence, but also in terms of distant metastases. Besides, the presence of cancer in the neck nodes could be considered a reflection of the aggressiveness of the disease, and possibly influences prognosis at the level of the primary tumor in terms of recurrence after treatment. Thus, the neck dissection must also be considered as a staging procedure. However, accurate data on the prognostic significance of the different histopathologic parameters with regards to distant metastases and recurrence at the primary site is scarcely available.

The aim of this thesis is twofold. First, to determine the efficacy of the management of the neck nodes at the regional level, on the basis of a large series of patients treated in one institution during a period, in which the indications for postoperative radiotherapy remained unchanged. In view of these data and the literature, the feasibility of surgical modifications, and the question whether the current results can be improved by extending the indications for postoperative radiotherapy, will be discussed. The second aim is to obtain accurate data on the significance of the histopathologic involvement of the neck with respect to dissemination to distant sites and recurrence at the primary site. The possible consequences with regards to adjuvant systemic treatment, will be mentioned.

An introductory chapter deals with the surgical treatment of the neck and adjuvant radiotherapy, and with factors relating to failure after such treatment. The first objective is

discussed in chapters 2 and 3, whereas the second objective is discussed in chapters 4 and 5. Finally, in chapter 6, both these objectives are elaborated further.

Chapter 1

SURGICAL MANAGEMENT OF THE NECK: AN OVERVIEW

1.1 Introduction

The management of nodal metastases of squamous cell carcinoma of the head and neck, as described in this thesis, is mainly surgical with radiotherapy as an adjuvant modality. It is generally accepted that radiotherapy alone can be effective in the treatment of neck node metastases, especially in highly radiosensitive tumors, such as nasopharyngeal carcinoma. The discussion of radiotherapy as a single modality, however, is beyond the scope of this thesis.

1.2 Historical notes

The mere occurrence of spread of head and neck cancer to the neck, that it could have a detrimental effect on the outcome, and that it should be removed were already appreciated by clinicians in the nineteenth century[1].

The first systematic description of the operation, we know today as radical neck dissection, was by George Crile[2] in 1906, in his outstanding publication in the Journal of the American Medical Association, based on his experience with 132 surgical operations. He even called the described procedure a 'neck dissection' and also mentioned the term 'comprehensive'. He outlined a thorough radical approach towards complete en bloc excision of all lymphatic structures of the neck thereby removing several nonlymphatic structures, such as the omohyoid muscle, the sternocleidomastoid muscle and the internal (and external) jugular vein, with the only exception of the submaxillary (submandibular) salivary gland which was left in situ in cases 'in which the lymphatics were free of metastases'.

Already in 1926, Bartlett and Callander[3] described less radical procedures, such as suprahyoid dissection (Eisendrath in his discussion at the end of Crile's paper refers to an operation that probably also could be called a suprahyoid dissection), supraomohyoid

dissection and dissections with preservation of various 'non-vital' anatomic structures; e.g. the spinal accessory nerve, the internal jugular vein, the sternocleidomastoid muscle and the platysma, stylohyoid and digastric muscles.

In the following years, however the pendulum swung back to radical neck dissections once more as the surgical treatment of choice in the treatment of most cervical metastatic growths. In his classical publications of 1941[4] and 1951[5] Hayes Martin outlined the philosophy, indications, operative technique and complications of radical neck dissections and stated the importance of the localization of the primary tumor with respect to regional metastases. Furthermore he emphasized the prognostic influence of the presence of neck node metastases on prognosis and in his latter paper he indicated the significance of one involved node versus multiple involved nodes. The technique and surgical anatomy of radical neck dissection were also extensively described by Beahrs et al.[6] in 1955.

In the 1960s the principle of functional neck dissection was put forward, its most prominent proponents being Bocca[7] in Europe, and Jesse and Ballantyne in North America. This procedure, which was said not to make any concessions to oncologic principles, was based on the anatomic grounds of the enveloping fasciae of the neck[8]. In the ensuing years the principle on which the preservation of the spinal accessory nerve was based, namely the fact that it can safely be left in situ provided there is no involvement of the surrounding nodes, was firmly established. In this way the resulting 'shoulder syndrome', described in detail by Ewing and Martin[9], and by Nahum et al.[10], could to a certain extent be avoided.

In the 1980s, the concept of selective neck dissections was developed. This is based on the knowledge of specific regional lymphatic spread for different primary tumor localizations[11,12]. In selective neck dissections only those lymph node groups are removed that, depending on the site of the primary tumor, are most likely to contain metastases.

1.3 Anatomy of the lymphatic system

Surgery of the neck nodes actually is surgery of the lymphatic system and therefore calls for an understanding of the anatomy of the lymphatic structures. The lymphatic system consists of capillaries, vessels and nodes and is divided into a superficial and a deep

part, which communicate with each other. The superficial part collects the lymph from the skin and drains into the lymphatic vessels along the external jugular system. The deep part collects the lymph from the mucosal linings of the upper respiratory and digestive tracts, the thyroid and the salivary glands, eventually draining into the larger vessels along the internal jugular vein, the spinal accessory nerve, and the transverse cervical blood vessels.

Lymphatic capillaries consist of only endothelial cells, lacking a basement membrane as is seen in blood capillaries[13]. This fact probably accounts for their ability to absorb macromolecules, lymphocytes and, consequently, tumor cells more readily than blood capillaries[14]. Epithelium lacks lymphatic capillaries and therefore a tumor must extend into the lamina propria of the mucous membrane to be able to enter the lymphatic system[14]. It has been postulated that carcinomas exhibit a greater tendency to release single cells from the margins - which then pass into capillaries between endothelial cells - than sarcomas, hence their greater proclivity to lymphogenic spread may be explained[15]. The most prominent lymphatic capillary network in the head and neck is encountered in the nasopharynx and the pyriform sinus[14]. The true vocal cords conversely have few lymphatics, which is in agreement with the rarity of lymph node metastases in a carcinoma confined to this primary site.

The capillaries converge and form lymphatic vessels, which consist of an intima, a media and an adventitia as do blood vessels and only have a transport function. The vessels possess numerous valves, that are located close together[14]. The propulsion of lymphatic fluid from one segment to another is either by way of active contraction of that segment, or more important, by compression of the surrounding muscles. In this way the lymphatic flow occurs in a predictable manner in the untreated (unoperated, non-irradiated) neck. It is noted that the dermal lymphatic vessels have no valves and once cancer has entered these structures the spread is unpredictable and skin metastases may thus develop at remote distances from the original area of skin involvement.

The vessels drain into lymph nodes. The efferent flow from the nodes is through lymphatic vessels, which eventually drain into the venous system at the junction of the internal jugular vein and the subclavian vein. On an average 300 lymph nodes are located in the neck comprising approximately 30 % of all lymph nodes in the body. One neck dissection specimen may thus contain 150 nodes. These encapsulated structures contain a subcapsular sinus into which the lymph vessels drain and early lodging of tumor cells can

occur. The lymphatic fluid subsequently permeates through the cortex and the medulla to exit the node through the hilus into another lymphatic vessel. Since lymph nodes are located between the investing and deeper (pretracheal and prevertebral) layers of the deep cervical fascia many of them are easily accessible to surgical removal.

1.4 Nomenclature of lymph nodes

Several methods for describing the various clusters of lymph nodes are in use. The original nomenclature of lymph nodes is based on the classical work of Rouvière in 1932[16]. The anatomic principle for this classification is the fact that, although lymph nodes are distributed everywhere in the neck, at certain points a congregation of nodes is present comprising a lymph node group. These groups are termed according to their localization: the occipital, the mastoid, the parotid, the submaxillary, the submental, the facial, the anterior cervical, the lateral cervical and the transverse cervical nodes, and the nodes along the spinal accessory nerve (Fig.1).

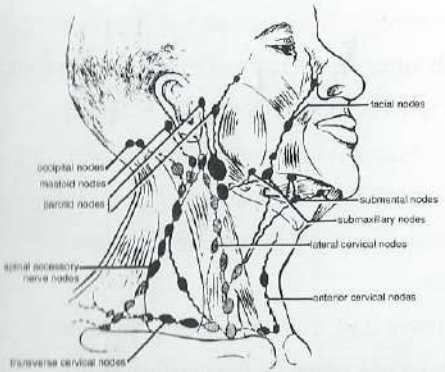

Fig.1 Lymph node groups according to Rouvière[16].

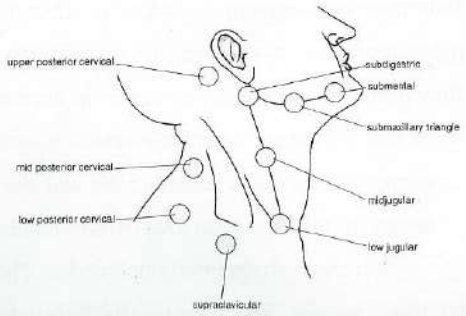

Fig.2 Lymph node classification according to the topographic classification by Lindberg[11].

Lymph nodes can also be classified according to the topographical distribution developed at the University of Texas MD Anderson Cancer Center, Houston, and described by Lindberg[11], which has been in use by many workers. In this classification the neck is divided into nine nodal regions: submental, submaxillary triangle, subdigastric, midjugular, low jugular, upper posterior cervical, midposterior cervical, low posterior cervical, and supraclavicular (Fig.2).

A third classification system of neck nodes, into five levels, was developed by head and neck surgeons from Memorial Sloan-Kettering Cancer Center[17] with particular reference to metastatic spread of tumors originating from the upper respiratory and digestive tracts. In this system, which is depicted in figure 3, five levels are distinguished: Level I includes the contents of the submental and the submandibular triangles. Levels II, III, and IV include the lymph nodes adjacent to the internal jugular vein and the lymph nodes contained within the fibroadipose tissue located medial to the sternocleidomastoid muscle. These are arbitrarily divided into equal thirds. Level V includes the contents of the posterior triangle of the neck. Recently Medina[18] suggested 'Regions' as a preferable term for 'Levels', since the latter carries a connotation of depth or distance from the site of origin that is not intended.

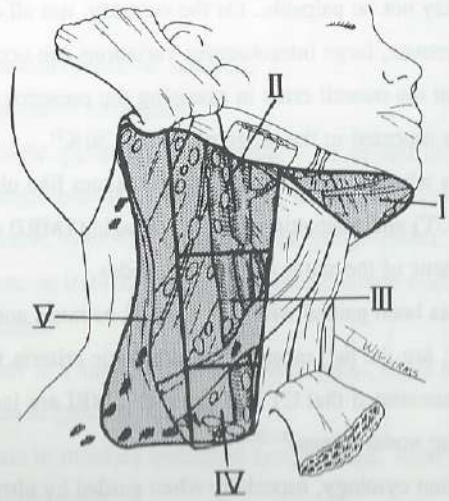

Fig.3 The Memorial Sloan-Kettering Cancer Center classification of lymph nodes[18]. (Courtesy of the C.V. Mosby company)

Based on the Memorial Hospital classification the Subcommittee for Neck Dissection Terminology and Classification of the American Academy of Otolaryngology-Head and Neck Surgery, has recently defined the various lymph node groups in its recent pocket guide[19]. Clinical and surgical landmarks were described for the boundaries of the three jugular regions (II, III, and IV): the hyoid bone and the carotid bifurcation, between regions II and III, and the cricothyroid notch and the omohyoid muscle, between regions III and IV. Furthermore an extra group was added; i.e. the anterior compartment group, which includes the pre- and paratracheal lymph nodes, precricoid (Delphian) node, and the perithyroidal nodes.

1.5 Assessment of the status of neck lymph nodes

Assessment of the status of the neck nodes is still mainly based on palpation. The palpability of a lymph node depends on its location, consistency, and size and on the type of neck. In an average individual and in the hands of an experienced examiner the lower limit of palpability is approximately 0.5 cm in a superficial area, such as the submental and the submandibular area and 1 cm in a deeper area[20]. Therefore nodes containing small deposits of carcinoma may not be palpable. On the contrary, not all enlarged nodes contain metastatic deposits. Moreover, large interobserver variations can occur. It is not surprising, therefore, that the overall error in assessing the presence or absence of cervical lymph node metastasis is reported in the range of 20% to 30%[21].

The question arises whether modern imaging techniques like ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) can do better than palpation for the assessment of the status of the neck nodes.

Most experience has been gained with CT. Central necrosis and size, particularly minimal axial diameter[22], are the two most useful radiologic criteria for nodal metastases. Several studies have demonstrated that CT and especially MRI are indeed superior to palpation in demonstrating nodal disease[22,23,24,25].

Fine needle aspiration cytology, especially when guided by ultrasound (USgFNAC), appears to be the best technique of establishing tumor in the neck nodes[26]. Furthermore USgFNAC is useful during follow-up of patients with a clinically negative neck who have not been treated electively[27,28].

With all the modern imaging techniques and particularly with USgFNAC, one should however, bear in mind that the accuracy very much depends on the individual investigator, and as such these techniques will need to prove their efficacy in routine situations.

Our present policy for patients, in whom a CT or MRI is needed for assessment of the primary tumor (all cases except for T1-2 glottic larynx carcinoma and carcinoma of the anterior oral cavity), is to include the neck in the scan as well. If suspicious nodes are detected, a comprehensive neck dissection is performed. In case of doubt an US, and if indicated an USgFNAC is performed. If no CT or MRI is indicated for staging of the primary tumor an US, and if necessary, an USgFNAC of the neck is performed.

1.6 Classification of neck lymph nodes

Until recently, the classification systems of the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) were not similar, whereas both classifications used the same symbols. Fortunately the most recent UICC[29] and AJCC[30] definitions of the regional lymph nodes (N categories) of the neck are identical, making comparison of data from North America and data from other countries possible.

- NX Regional lymph nodes cannot be assessed.
- NO No regional lymph node metastasis
- N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension.
- N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.
  - N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension.
  - N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension.
  - N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.
- N3 Metastasis in a lymph node more than 6 cm in greatest dimension.

An additional optional descriptor in the UICC classification, is the C-factor or certainty factor, which reflects the validity of classification according to the diagnostic methods employed.

Unfortunately, the level of involvement of the cervical lymph nodes, the use of which was recommended in the former UICC classification[31], is now abandoned.

1.7 Histopathologic prognostic factors of nodal metastases

Although the accuracy of clinical assessment of the status of the neck has recently improved considerably by the application of modern radiologic techniques, histopathologic factors are still more reliable. Besides being of prognostic significance for failure at the level of the neck, the extent of nodal disease in the neck is also of prognostic significance for the development of distant metastases[32,33,34], and possibly also for recurrence at the primary site[35,36].

The number of positive nodes and the presence of extranodal spread of tumor beyond the capsule of the lymph node are the two most commonly used prognostic factors. Other characteristics are the size of the node, level of the positive nodes[37,38,39,40,41] and histologic host response to the tumor in the node[42,43,44,45]. It is evident that the first two parameters are closely correlated to extranodal spread and the number of positive nodes respectively.

The studies described in this thesis take into account the number of histologically positive nodes as well as the presence or absence of extranodal spread. Both parameters are routinely reported by the pathologists of the Free University Hospital, Amsterdam since the early 1970s. As the treatment policy regarding the application of adjuvant radiotherapy, for the period under observation, was based on these two parameters and not on one of the other less commonly used features, we will restrict our discussion to these.

1.7.1 Multiple histologically positive nodes

The number of (suspected) tumor positive nodes is a basic component of the staging system[29,30]. Most workers (Shah and Tollefsen[46], Cachin et al.[47], Vikram et al.[48] and Snow et al.[49]) agree on this issue and showed that the prognosis worsens as the number of

involved nodes increases.

It is interesting to note, however, that others could not concur with this generally accepted belief. Schuller et al.[50] demonstrated no difference in 5-year survival between patients who had one positive node versus those who had multiple positive nodes. Their conclusion was that the most important information relating the status of the lymph nodes to prognosis was whether or not tumor was present or absent in the cervical nodes, and that attributing added significance to individual features of metastatic nodes was not warranted. Likewise Sessions[51] reported no correlation between prognosis and number of positive nodes for glottic and supraglottic carcinomas.

1.7.2 Extranodal spread

The extension of squamous cell carcinoma in cervical lymph nodes has been recognized as a bad prognostic sign. As mentioned in paragraph 1.2, Martin[4], as early as 1941, concluded that whenever the tumor had transgressed the capsule of the lymph node a combination of surgery and radiotherapy was useful. Others have since confirmed the significance of extranodal spread as an independent prognostic factor for recurrence of tumor. Noone et al.[52], Shah et al.[41], Kalnins et al.[53], Zoller et al.[54], Cachin et al.[47], Johnson et al.[55], Myers and Johnson[56], Snow et al.[49], and Richard et al.[57] have reported on reduced survival or higher regional relapse rates in the presence of extranodal spread. Most workers report an overall incidence of extranodal spread just over 50 percent.

Carter et al.[58,59] were able to distinguish between microscopic and macroscopic extranodal spread; it was concluded that only macroscopic extranodal spread significantly increased the recurrence rate.

Snow et al.[49] and Cachin et al.[47] showed that whereas the incidence of extranodal spread increases with the diameter of the involved lymph node, the finding of this feature was by no means uncommon in the smaller nodes; in Snow's series 23 % of nodes less than 1 cm in diameter showed extranodal spread.

1.8 Classification of neck dissections

The development of modifications of the radical neck dissection and of less than

radical neck dissections, and their increased use, have created confusion over recent years. Therefore a great need arose for a proper classification of neck dissections[60,61]. A rational classification should primarily indicate the lymph node groups of the neck that are removed. Secondly it must take into account important anatomical structures that may be removed or preserved. Medina[18] proposed such a classification in 1989, and distinguished basically two types of neck dissection based on the lymph node regions that are cleared: comprehensive and selective (Table 1).

Comprehensive neck dissections consist of removal of all five nodal regions of the neck, according to the Memorial Sloan-Kettering Cancer Center Classification[17]. The prototype in this category is the classical radical neck dissection, in which the spinal accessory nerve, the internal jugular vein and the sternocleidomastoid muscle are removed as well. Also included in this category are the three modifications of the radical neck dissection, aiming at reducing the morbidity; i.e. Type I, in which the spinal accessory nerve is preserved[62,63,64,65,66,67]; Type II, in which, the spinal accessory nerve and the internal jugular vein are preserved; and Type III, in which all three structures are preserved. This last neck dissection corresponds to the 'functional neck dissection' as described by Bocca et al.[68].

In selective neck dissections only those lymph node groups are removed that, depending on the site of the primary tumor, are most likely to contain metastases. Examples of this category are the supraomohyoid neck dissection (removal of regions I through III)[69], the anterolateral neck dissection (removal of regions I through IV)[61], and the lateral neck dissection (removal of regions II through IV)[70,71]. Another example in this category is the posterolateral neck dissection, mostly used to remove nodal disease from cutaneous melanoma of the posterior scalp[72,73,74]. In this procedure the suboccipital lymph nodes, the retroauricular lymph nodes, and the regions II through V are removed. Depending on the clinical situation, the spinal accessory nerve, the internal jugular vein, and the sternocleidomastoid muscle can either be removed or preserved.

Neck dissections, in which one or more additional lymph node groups and/or nonlymphatic structures are removed that are not encompassed by comprehensive neck dissections, are referred to as extended neck dissections. Examples are removal of the paratracheal lymph nodes in neck dissection for glottic or subglottic carcinoma, and removal of preauricular and intraparotid lymph nodes in melanoma of the face.

Table 1. Classification of neck dissections

type of dissection	lymph node groups removed	structures preserved
A.COMPREHENSIVE		
1. radical	I-V	none
2. modified radical		
-type I	I-V	SAN
-type II	I-V	SAN,IJV
-type III	I-V	SAN,IJV,SCM
B.SELECTIVE		
1. antero-lateral	I-IV	SAN,IJV,SCM
supraomohyoid	I-III	SAN,IJV,SCM
2. lateral	II-IV	SAN,IJV,SCM
3. postero-lateral		
-radical	II-V*	none
-type I	II-V*	SAN
-type II	II-V*	SAN,IJV
-type III	II-V*	SAN,IJV,SCM
C.EXTENDED		

SAN = spinal accessory nerve, IJV = internal jugular vein,
SCM = sternocleidomastoid muscle,
* as well as the suboccipital and retroauricular nodes

Recently the framework of the above classification has been adopted by the Subcommittee for Neck Dissection Terminology and Classification of the American Academy of Otolaryngology-Head and Neck Surgery[75].

1.9 Indications

1.9.1 Therapeutic management of the neck

In patients with clinical evidence of neck node metastases (N+) from a primary tumor located in the upper respiratory and digestive tract, neck dissection is the most widely accepted treatment[76]. On the other hand, in tumors that are sensitive to radiation, such as nasopharyngeal cancers, good control of the primary tumors and neck node metastases may be obtained by radiotherapy alone[77].

The comprehensive neck dissection is the commonly used operation in most

institutions[78] for the treatment of the N+ neck. In our institution the spinal accessory nerve is preserved if the peroperative situation permits this. While metastases along the course of the nerve through the posterior cervical triangle are rare[79,80], they are far more common along the upper part of its course in the subdigastric region. It is thus, in the subdigastric region, where the nerve runs closely adjacent to the internal jugular vein, that most contraindications as to the preservation of the spinal accessory nerve arise. The feasibility of preservation of the spinal accessory nerve has to be carefully evaluated by the surgeon during the dissection. Furthermore it is to be realized that preservation of the nerve does not guarantee an unimpaired shoulder function postoperatively[81,82,83,84,85].

The other structure that may be preserved is the internal jugular vein. As the most frequently involved groups of nodes have a close anatomic relationship with the vein, and as one can never be quite certain that extranodal spread has not occurred, caution is warranted against the preservation of the internal jugular vein. In our institution the vein is preserved only in bilateral neck dissections, and then on the least involved side of the neck only, to prevent the serious sequelae of bilateral venous obstruction of the cerebral outflow[86,87,88,89].

Preservation of the sternocleidomastoid muscle makes the dissection more difficult, and possibly less radical in the upper neck, whereas the advantage of preservation, a more normal contour of the neck, probably is not of great significance in the usually elderly male patient.

1.9.2 Elective management of the neck

The issue whether to treat the neck nodes electively in the patient with a clinically negative neck (NO) remains controversial. There are two prospective randomized trials reported in the literature.

One study, by Vandenbrouck et al.[90], looked at the feasibility of a 'wait and see' policy versus elective neck dissection after interstitial radiotherapy for a T1-3NO carcinoma of the oral tongue and floor of mouth. Thirty-nine patients were entered in the elective neck dissection group, of which 19 patients had positive nodes and were postoperatively irradiated. Thirty-six patients were followed after treatment of their primary, and subsequently in 19 of these patients cervical nodes became involved. In all

except two patients neck dissection was performed. Survival for both treatment groups was comparable. This study is criticized, however, on two counts: the number of patients included was small, and at follow-up visits patients were examined exclusively by experienced head and neck surgeons.

Another study, by Fakih et al.[91] from India, described the results of an ongoing clinical trial, in which the feasibility of elective versus therapeutic neck dissection in patients with T1-2NO squamous cell carcinoma of the oral tongue was studied. The primary cancers were treated by hemiglossectomy, regardless of how small the tumor was. The overall disease-free survival (median follow-up of 22 months) was higher in the group receiving elective neck dissection (64% vs 47%). These figures, however, were not statistically significant and one has to wait for this study to mature before any conclusions can be drawn. It is to be realized that this study suffers from insufficient follow-up in an indigent rural population, and this data cannot be easily extrapolated to the western situation.

Several publications from the University of Texas MD Anderson Cancer Center[92,93,94] show, that, whereas a 'wait and see' policy for patients with a NO neck, and treating the neck if clinically positive nodes appear, may be successful at the regional level, these patients are at an increased risk of developing distant metastasis and therefore have a poorer prognosis.

The basic problem that relates to this question is the incidence of occult microscopic nodal disease for a given primary tumor. In most institutions treatment of the clinically negative neck is considered justified if the rate of occult lymph node metastases exceeds 15-20 %[95]. Most primary sites and stages of head and neck squamous cell carcinoma qualify for elective treatment of the neck nodes on this basis[21]. Furthermore elective treatment is considered in patients with necks that are difficult to assess clinically, when regular follow-up is not possible and if the neck must be entered for exposure of the primary tumor. It is likely that the rationale of elective neck dissection in case of a high incidence of occult nodal metastases, will have to be reassessed in the light of the routine use of advanced imaging techniques[25,96,97].

Opinions differ about the question of elective neck irradiation versus elective neck dissection. In general the mode of treatment should depend on the selection of treatment for the primary tumor: if the primary is treated by surgery, the neck is also treated

surgically, whereas the neck will be irradiated if the primary tumor is treated by radiotherapy[20]

The classical radical neck dissection, in which the spinal accessory nerve is routinely sacrificed, has no place in the elective treatment of the neck. The operation of choice is either a modified radical or a selective neck dissection.

Although the various types of selective neck dissections are increasingly performed, the ultimate efficacy of these procedures is not yet established. The supraomohyoid neck dissection is considered to be a sound oncological procedure for carcinoma of the oral cavity by some workers[69,98,99,100]. It may be helpful in indicating which patients require more radical treatment of the actual nodal metastases in the NO neck. It is noted, however, that most of the data supporting the concept of supraomohyoid neck dissection comes from two institutes, the Memorial Sloan-Kettering Cancer Center, New York and the University of Texas MD Anderson Cancer Center, Houston, and that many of the patients were postoperatively irradiated, which increases the overall morbidity, while the procedure was originally designed to reduce surgical morbidity.

1.10 Technique of neck dissection

1.10.1 The neck dissection

A schematic description of the (modified) radical neck dissection is outlined below, with the understanding that modifications are used depending on the particular metastatic disease in the individual patient.

In the non irradiated patient a Y-incision is used, with a lazy S-shaped 'vertical limb' (thus breaking the lines of contraction as it runs perpendicular to the relaxed skin tension lines) and a 'horizontal' limb running from the mastoid to the mentum (Fig.4). Care is taken that the trifurcation is located posteriorly to the carotid artery, so any wound problems resulting in breakdown would not prove hazardous to this vital structure. In selected cases, e.g. in the irradiated patient, a MacFee[101] incision (consisting of two slightly curved horizontal incisions in the suprahyoid region and just superior to the clavicle) is utilized, which allows for less exposure but secures a vital skin flap postoperatively covering the carotid artery, thus bearing less potential for wound

problems[102] (Fig.5). In anteriorly located midline carcinoma of the inferior oral cavity a visor flap[103] (extended with appropriate vertical limbs) is used (Fig.6) and in laryngeal carcinoma a modified Gluck Sorensen[104] apron flap is used (Fig.7).

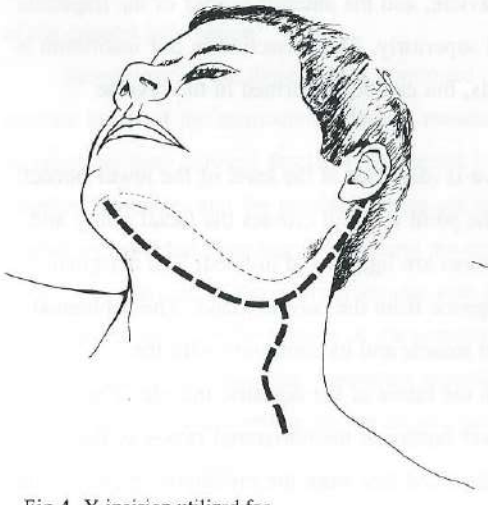

Fig.4 Y-incision utilized for comprehensive neck dissection in the previously untreated patient.

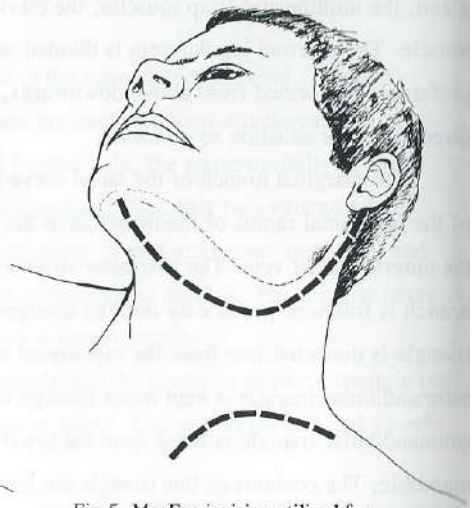

Fig.5 MacFee incision utilized for comprehensive neck dissection in the previously irradiated patient.

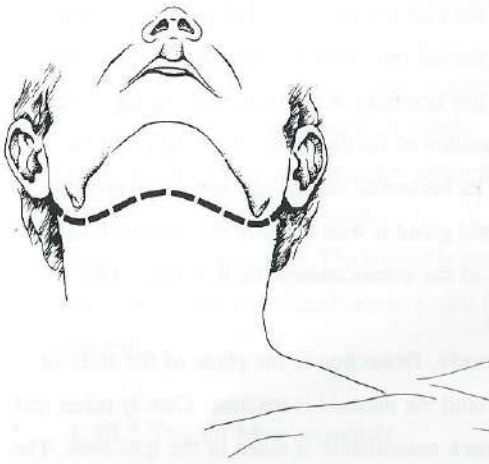

Fig.6 Visor flap utilized for excision of anteriorly localized inferior oral cavity carcinoma. This incision is extended with vertical limbs for comprehensive neck dissection.

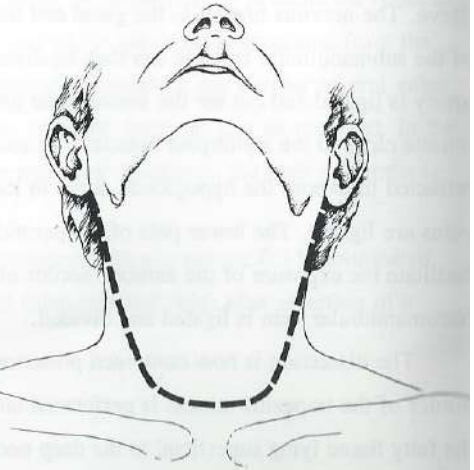

Fig.7 Modified Gluck Sorensen incision utilized in laryngeal carcinoma patients in whom a comprehensive neck dissection is performed.

The incision is carried through the skin, the subcutaneous tissue and the platysma muscle down to the investing layer of the deep cervical fascia. The flaps are elevated to expose the lower border of the horizontal ramus of the mandible and the tail of the parotid gland, the midline and strap muscles, the clavicle, and the anterior border of the trapezius muscle. The external jugular vein is divided superiorly. The dissection in our institution is preferably performed from above downwards, but can be performed in the reverse direction if the situation so demands.

The marginal branch of the facial nerve is identified at the level of the lower border of the horizontal ramus of the mandible at the point where it crosses the facial artery and the anterior facial vein. The two latter structures are ligated and divided. The marginal branch is followed posteriorly until its emergence from the parotid gland. The submental triangle is dissected free from the mylohyoid muscle and its continuity with the submandibular triangle is kept intact through the fascia of the digastric muscle. The submandibular triangle is freed from the lower border of the horizontal ramus of the mandible. The contents of this triangle are dissected free from the mylohyoid muscle from anterior to posterior. The free posterior border of the mylohyoid is retracted anteriorly exposing the lingual nerve, the duct of the submandibular gland, and the hypoglossal nerve. The nervous branch to the gland and the duct are ligated and divided. The contents of the submandibular triangle can then be dissected free from the deep layer. The facial artery is ligated and cut for the second time just cranially of the tendon of the digastric muscle close to the stylohyoid muscle. The tendon of the digastric muscle can now be retracted to expose the hypoglossal nerve in its horizontal course and several overlying veins are ligated. The lower pole of the parotid gland is then taken in the specimen to facilitate the exposure of the anterior border of the sternocleidomastoid muscle. The retromandibular vein is ligated and divided.

The dissection is now continued posteriorly. Dissection in the plane of the anterior border of the trapezius muscle is performed until the mastoid is reached. Care is taken that the fatty tissue lying superficial to the deep neck musculature is taken in the specimen. The superior attachment of the sternocleidomastoid muscle is cut from the skull exposing the posterior belly of the digastric muscle, which is retracted superiorly. The occipital artery, the internal jugular vein, the spinal accessory nerve, and the hypoglossal nerve can now be visualized. The vagus nerve and the internal carotid artery, lying posterior and medial to

the hypoglossal nerve respectively, are identified. The spinal accessory nerve (if it is safe to preserve it) is followed through the sternocleidomastoid muscle to its entrance in the trapezius muscle. The internal jugular vein is ligated and divided below the skull base. The tissue overlying the deep neck musculature is dissected from cranial to caudal to the level of the carotid bifurcation.

Subsequently, the dissection is continued at the supraclavicular level. The two inferior heads of the sternocleidomastoid muscle are cut from their attachments, after incising the deep cervical fascia. The external jugular vein, the posterior belly of the omohyoid muscle, and the brachial plexus are visualized. The first two structures are ligated and divided. The vagus nerve and the common carotid artery are identified, and then the caudal end of the internal jugular vein is ligated and divided. The phrenic nerve is identified as it lies on the surface of the anterior scalenus muscle.

The supraclavicular fat is retracted superiorly and the posterior cervical triangle is dissected carefully preserving the spinal accessory nerve. The transverse cervical vessels are ligated and divided.

The specimen is retracted anteriorly and cranially, taking care that the phrenic nerve is preserved. It can now be dissected from the carotid artery, after identifying the vagus nerve. At this stage the roots of the cervical plexus are visualized. If possible the roots to the trapezius muscle are spared. The anterior end of the specimen is separated from the pharynx, larynx and the thyroid, thereby ligating or coagulating and cutting several veins and the anterior belly of the omohyoid muscle. Now the specimen can be removed. In the situation of en bloc removal of primary tumor and neck dissection, the neck specimen is left attached at the appropriate level.

Hemostasis is achieved. The wound is irrigated with a cytotoxic 0.1% solution of sublimate and is carefully closed in two layers (platysma and skin) after insertion of a vacuum-drain.

1.10.2 The en bloc principle

Since Crile's days it has been recognized that whenever a neck dissection is indicated in the same procedure as the excision of the primary tumor, the two specimens must be excised in-continuity, thereby removing the lymphatics between the primary and the

regional nodes which can harbour tumor cells in transit[105,106]. In the management of, e.g., pharyngeal and laryngeal tumors an en bloc neck dissection adds little or nothing to the morbidity compared to the situation where the primary and the neck are treated separately. If, on the other hand the primary tumor is localized in the anterior oral cavity, an in-continuity resection of primary and neck nodes does add considerably to the morbidity in terms of impairment of function and disfigurement. In those cases all the intervening structures of the floor of the mouth have to be excised, thus, necessitating major reconstruction of tissues.

To reduce the postoperative sequelae, the en bloc principle was, in selected cases of anterior oral cavity carcinoma, defied. In 1973 Spiro and Strong[107] published their results in tongue carcinoma and concluded that in lesions suitable for transoral excision, a discontinuous neck dissection can be performed without apparent adverse effects on survival.

1.11 Combination therapy

The use of radiation therapy either as planned preoperative treatment or as adjuvant after surgical treatment has been widely accepted for several decades. As early as 1941 Martin[4] described the combination of radiation and surgery in his treatment of 'metastatic nodes that perforated the node capsule and invaded the adjacent tissues'.

Strong[108], in 1969, reported on the efficacy of preoperative X-ray therapy as an adjunct to radical neck dissection in a randomized trial. Patients who were entered in the combination arm received 5 x 4 Gy immediately preoperatively and they suffered significantly fewer regional recurrences than the surgery only arm. In this study, however, the correction for recurrence at the primary site (25%) was not mentioned. Furthermore a similar survival rate was observed in both treatment groups, but with a lower locoregional failure rate and a higher incidence of distant metastases for the combination therapy group.

In the 1960s preoperative radiotherapy was favored on the theoretical ground that radiation therapy is much more effective when the vascularization of the tumor is still intact[109]. A decade later the general policy shifted to postoperative radiotherapy mainly for three practical reasons. First, the incidence of surgical complications is high after preoperative irradiation[110]. Second, it was realized that the histopathological report of the

neck dissection specimen is much more reliable than clinical assessment with regard to the determination of risk factors for recurrence in the neck. Radiation therapy can thus be justified and planned more selectively when given postoperatively[41,42,49,47,57]. Lastly, it is important to note that radiotherapy after cancer surgery is usually better tolerated by the patient than when given before surgery[111].

The total dose administered should be in the range of 50 to 60 Gy[112] delivered to both sides of the neck and the primary site, if the neck dissection had been carried out as part of a composite resection together with the resection of the primary tumor. Patients with greater risk for recurrence should receive dosages in the higher range. There is evidence that patients who started their radiotherapy later than 6 weeks after surgery suffer significantly more neck recurrences than patients in whom radiotherapy started within 6 weeks[48].

The basic question that relates to the indication for postoperative radiotherapy is the issue of which patients should be regarded as having a high risk of failure in the neck after surgery. Most authors agree that recurrence in the neck is related to the tumor burden present at the time of the neck dissection, and postoperative radiotherapy is generally recommended if multiple positive nodes are present or if extranodal spread is reported[48,49,52,53,54,47,55,56]. Others feel that postoperative radiation therapy is needed in every patient with a histopathological positive neck node.[57]. In our institution, until 1988, patients were irradiated postoperatively if three or more positive nodes or extranodal spread were reported.

Several authors, in retrospective studies, have shown that postoperative radiotherapy diminishes the number of neck recurrences[113,114,115]. Jesse and Fletcher[116] analyzed the effect of adjuvant radiotherapy on lymph node control in the N+ neck as a function of disease stage. Patients that were not controlled at the primary site were not included. The benefit of adjuvant radiotherapy was clearly shown for each stage of disease. Mantravadi et al.[117] concluded that only in patients with more than two metastatic nodes and with extranodal spread postoperative radiotherapy was useful in terms of decreasing the ipsilateral recurrence. Vikram et al.[48] analyzed the failure in the neck following combination treatment for advanced head and neck cancer. The regional recurrence rate in their series appeared to be independent of the extent of disease in the neck and was lower than in the historic control group[108]. The value of postoperative radiotherapy as an adjuvant

to radical neck dissection was also determined by Bartelink et al.[36]. In their series patients, who received postoperative radiotherapy upon the histologic finding of high risk factors for recurrence, enjoyed a decreased neck failure rate compared to patients treated by surgery alone. Especially in patients with extranodal spread without fixation of the lymph nodes, the combined approach improved the prognosis significantly. Snow et al.[34], in taking together patients from two different time periods, were able to show the positive effect of postoperative radiotherapy on the regional recurrence rate in patients with extranodal spread. This study, however did not correct for simultaneous recurrences at the primary site.

Although our armamentarium includes the availability of postoperative radiotherapy we should always keep in mind the surgical principle put into words by Ballantyne[111]: 'no surgeon should be deluded by the siren song of postoperative radiation into doing a less than adequate surgical procedure in the hopes that gross disease left behind can be satisfactorily eradicated by the radiotherapist'.

1.12 Failure after neck dissection

(with or without postoperative radiotherapy)

Failure after neck dissection is basically a function of patient-, disease-, and treatment factors. This thesis will deal with the two latter factors. Disease (tumor) factors, most distinctly, execute their influence through the extent of nodal disease present in the neck on histopathologic examination. The surgical procedure and adjuvant radiotherapy are the two most important treatment factors.

We believe that the way to assess the efficacy of treatments that are applied locoregionally, such as surgery and radiotherapy, is to determine failure rates in the treated area and not to compare survival curves. When comparing survival curves several other factors may play a role and in particular survival curves are contaminated by the unmasking of previously hidden distant metastases as the locoregional control rates become higher. In other words revealing the natural history of head and neck squamous cell carcinoma.[15,118,119]. It must be emphasized that in determining neck control, it is of great importance to exclude a concomitant recurrence at the primary site as a cause for reseeding to the neck.

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Chapter 2

THE EFFICACY OF COMPREHENSIVE NECK DISSECTION WITH OR WITHOUT POSTOPERATIVE RADIOTHERAPY IN NODAL METASTASES OF SQUAMOUS CELL CARCINOMA OF THE UPPER RESPIRATORY AND DIGESTIVE TRACTS

Charles R. Leemans MD, Rammohan Tiwari MD, Isaac van der Waal DDS, A.B.M.F. Karim MD, Jos J.P. Nauta MSc, Gordon B. Snow MD

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Abstract

Neck recurrence-free curves corrected for local recurrence were compared for 494 patients who underwent 565 comprehensive neck dissections. In 42 dissections, no radicality could be obtained. Of the 523 histologically radical dissections, examination revealed tumour in 352 cases. Patients in whom three or more positive nodes or extranodal spread in one or more nodes were found received postoperative radiotherapy. In the histologically NO group, the incidence of neck recurrence after 5 years was 3%, in the histologically N+ group as a whole, it was 10%. Analysis of the influence of extranodal spread and the number of positive nodes showed that the group with one or two positive nodes without extranodal spread (that did not receive postoperative radiotherapy) did not statistically differ from the other groups.

This suggests that the results of the group with one or two positive nodes without extranodal spread can be improved by postoperative radiotherapy.

2.1 Introduction

In patients with squamous cell carcinoma of the upper-air and food passages who have clinical evidence of cervical node involvement, neck dissection is traditionally the treatment of choice. It has been recognized that the incidence of recurrence in the neck after neck dissection is high in patients with histological evidence of extranodal spread and/or multiple involved nodes in the neck[1,2,3,4,5,6]. A recurrence in the neck almost invariably carries a fatal prognosis[7].

To increase the effectiveness of therapy, combined radiation therapy and surgery first described by Martin[8] in 1941 gained popularity in the 1960s. In those days preoperative radiotherapy was favored on the theoretical ground that radiation therapy is much more effective when the vascularization of the tumor is still intact.

A decade later, the general policy shifted to postoperative radiotherapy mainly for three practical reasons. First, the incidence of surgical complications is high after preoperative irradiation[9]. Second, it was realized that the histopathological report of the neck dissection specimen is much more reliable than clinical assessment in regards to the determination of risk factors for recurrence in the neck[4]. Histological evidence of extranodal spread and multiple histologically positive nodes are the most important risk factors[6]. Radiation therapy can thus be justified and planned more selectively when given postoperatively as compared to preoperative radiotherapy. Lastly, it is important to note that radiotherapy after cancer surgery is usually better tolerated by the patient than when given before surgery.

Until the late 1960s, the classical radical neck dissection as described by Crile[10] and well established by Martin[8,11], remained unchallenged. In the last two decades, however, 2 types of modifications of the neck dissection have been introduced and increasingly applied. First has been preservation of 1, 2, or all 3 structures that are sacrificed in the radical neck dissection, namely the spinal accessory nerve, the internal jugular vein, and the sternocleidomastoid muscle[11,12]. The reasons for developing these modifications were functional and cosmetic, while oncological safety was preserved. These operations have recently been defined as comprehensive neck dissections by Medina[13]. In the 1980s, the concept of selective neck dissection as opposed to

comprehensive neck dissection, for which Lindberg[14] and Skolnik[15] laid an important basis, was introduced. In selective neck dissections, only those groups of lymph nodes are removed which, depending upon the location of the primary tumor, are most likely to contain metastases. The supraomohyoid neck dissection is the most frequently carried out selective neck dissection.

In spite of the changes which have been introduced in the treatment of cervical lymph node metastases in the last 2 decades, it is not completely clear where we stand today in terms of results of treatment. Several reports are available on the efficacy of the various types of neck dissection, either alone or followed by radiotherapy, relative to the histological status of the lymph nodes of the neck. Most studies, however, do not take recurrence at the primary site into account when reporting on the results of treatment of regional disease. Local recurrence can cause regional recurrence by reseeding of the neck after surgery. The relapse rate in the neck can thus be clouded by our inability to cure the primary tumor.

The purpose of this study is to report the efficacy of treatment of metastatic neck nodes relative to the histopathological findings of the neck dissection specimens in a large series of patients treated in one center. All patients underwent comprehensive neck dissections (selective neck dissections were not carried out in the period under observation). Strict indications as to the preservation of important structures and as to postoperative radiation therapy have been maintained throughout the study.

2.2 Patients and methods

The study comprises a consecutive series of 494 patients who underwent a total of 565 comprehensive neck dissections at the department of Otolaryngology-Head and Neck Surgery of the Free University Hospital, Amsterdam, in the period from January 1973 until July 1986. There were 383 men (77.5%) and 111 women (22.5%). Their ages ranged from 26 - 85 years, with a mean age of 61 years. All primary cancers were squamous cell carcinomas of the mucosal linings of the upper respiratory and digestive tracts, excluding the paranasal cavities and nasopharynx. The majority of the patients had their primary tumors located in the oral cavity or larynx (Fig.1).

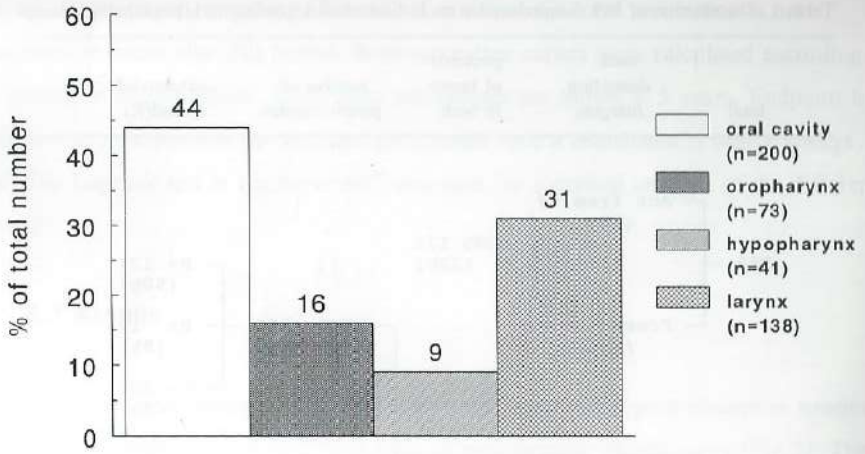

Fig.1 Distribution of primary tumors of patients who underwent a histopathologically radical neck dissection.

The dissections were performed, either simultaneously with the resection of the primary tumor or secondarily when regional lymph node involvement became apparent during follow-up. All neck dissections were comprehensive, which means removal of the regions I through V; i.e. the submental-submandibular, jugular-digastric, mid-jugular, low-jugular and posterior triangle lymph nodes (Fig.3, chapter 1). Whenever it was oncologically safe to do so, the spinal accessory nerve was preserved. The internal jugular vein, however, was left in situ only in bilateral dissections, and then only on the least-involved side of the neck. The sternocleidomastoid muscle was removed in every instance.

On pathological examination, an average number of 20 to 40 lymph nodes were retrieved from the specimen and, depending on the size, one to three sections were made of each lymph node. In the tumor containing dissections, the number of involved nodes and the presence of extranodal spread (R) were noted. Table 1 depicts the division of the total number of neck dissections (n=565) on the basis of their radicality and histopathological status of the lymph nodes.

Macroscopic radicality became evident during the surgical procedure, whereas microscopical irradicality was reported by the pathologist if there was extranodal tumor growth at the margins (e.g., towards the deep level of dissection, i.e., carotid artery, or in the supraclavicular or mastoid area). In 42 patients the resection was either macro

Table 1. Distribution of 565 comprehensive neck dissections according to histopathologic status

total	neck dissection margins	presence of tumor in neck	number of positive nodes	extranodal spread(R)
565	not free 42 (7%)			
	free 523 (93%)	pNO 171 (33%)		
		pN+ 352 (67%)	pN<3 251 (71%)	R- 127 (50%)
				Rx 19 (8%)
				R+ 105 (42%)
			pN≥3 101 (29%)	R- 30 (30%)
				Rx 4 (4%)
				R+ 67 (68%)

R indicates extranodal spread

scopically or microscopically not radical. In the remaining 523 neck dissections histopathological examination revealed no tumor in 171 cases, while tumor was found in 352 dissections. The latter group received postoperative radiotherapy when three or more positive nodes or extranodal spread were found in the specimen. All patients were treated with 4 or 6 MeV photons by two lateral ports, with daily fractions of 1.8 to 2 Gy, to a total dose ranging from 50 to 72 Gy in 5 to 8 weeks. When the neck dissection had been carried out in the same procedure as the excision of the primary tumor, radiation therapy was directed to the neck as well as to the primary site.

Patients were followed at regular intervals. At the time of analysis, all patients had at least a 2-year follow-up. Only two patients were lost to follow-up. Stomal recurrence after laryngectomy was defined as a local recurrence, and such cases were not included. Twenty-one patients with a neck recurrence who also suffered recurrence at the primary site within two months before or after the appearance of neck recurrence were excluded from further analysis. This arbitrary interval was chosen because an occult primary recurrence at the time of neck relapse would have become clinically apparent during this

interval. Furthermore, reseeding after radical excision of a local recurrence is not considered to occur after this period. Recurrence-free curves were calculated according to the method of Kaplan-Meier. Recurrence percentages are shown at 5 years. Endpoint for analysis was recurrence in the operated neck, since such a recurrence is nearly always fatal. The Logrank test or the trend test[16] was used for statistical analysis of the different curves.

2.3 Results

In the group of patients with tumor-positive margins in the neck dissection specimen (n=42), recurrence occurred in 27% in spite of postoperative radiotherapy (Fig.2). The overall incidence of recurrence on the operated side was 7.2% in cases with histopathologically free margins (Fig.3).

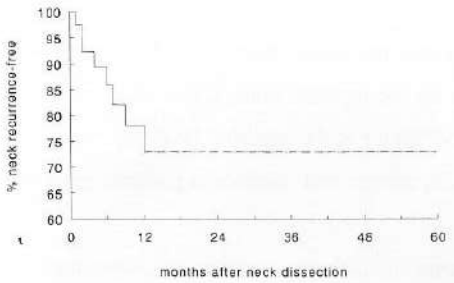

Fig.2 Proportion of necks remaining free of recurrence after comprehensive neck dissection in 42 patients with tumor at margins.

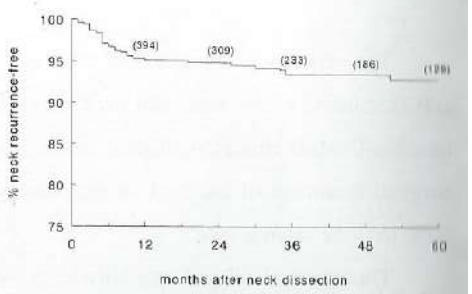

Fig.3 Proportion of necks remaining free of recurrence after comprehensive neck dissection with margins free of tumor. Numbers in parentheses indicate the number of patients at risk.

The majority of recurrences occurred within two years after neck dissection. Figure 4 shows the incidence of recurrence in histologically tumor-negative (pNO) and tumor-positive (pN+) necks. For the pN+ group, this occurred in 25 cases (9.7% recurrence)

whereas 4 were encountered in the pNO necks (2.6% recurrence). All but one patients with ipsilateral neck recurrences died within 18 months after neck relapse occurred (Fig.5). The patient who survived suffered a small low-jugular lymph node metastasis and was salvaged by radiation therapy to the neck.

Further analysis of the pN+ dissections shows that the greater the number of involved lymph nodes, the higher the possibility of recurrence ($p=0.039$; Fig.6). The recurrence rates in the pNO, $pN<3$ and $pN\geq3$ necks was respectively, 2.6%, 9.1%, and 11.3%.

In 23 necks (6.5%) the presence of extranodal spread was uncertain (Rx); and these were excluded in the final analysis of the different groups, in which both the number of positive nodes and extranodal spread was taken into account. Of the remaining 329 pN+ necks, 52.3% showed extranodal spread. There was no statistical difference between the groups $pN<3R$-, $pN<3R+$, $pN\geq3R$-, and $pN\geq3R+$ (Fig.7), which implies that patients with one or two positive nodes without extranodal spread did not do better in terms of neck recurrence than patients with more positive nodes or extranodal spread.

2.4 Discussion

The efficacy of any form of treatment of nodal metastasis in the neck of squamous cell carcinoma of the head and neck is reflected by the regional control rate after such treatment. Most studies published on the issue of failure at the regional level after surgical treatment of the neck in head and neck squamous cell carcinoma patients report a 10% to 36% relapse rate[1,2,3,4,6,19,20].

The regional relapse rate correlates well with the pathologic extent of involvement of the neck and whether surgical treatment has been followed by radiotherapy. Few of the aforementioned studies have taken into account the influence that recurrence at the primary site may have on the regional control rate. It is emphasized that the various studies are also difficult to compare because of differences in patient and tumor selection and types of neck dissection carried out.

This study shows an overall recurrence rate in the operated neck of 7.2% after comprehensive neck dissection. For the histopathologic tumour-negative neck, a small recurrence rate of 2.6% was found; and this is in accordance with others. This is

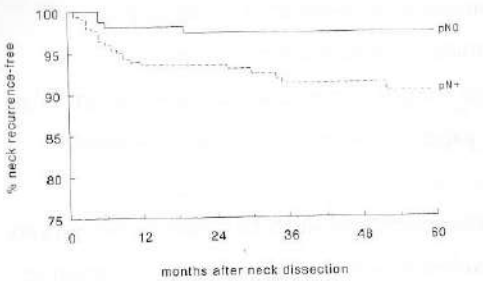

Fig.4 Proportion of necks remaining free of recurrence according to histologic absence (pNO) and presence (pN+) of metastatic tumor in the neck ($p=0.01$).

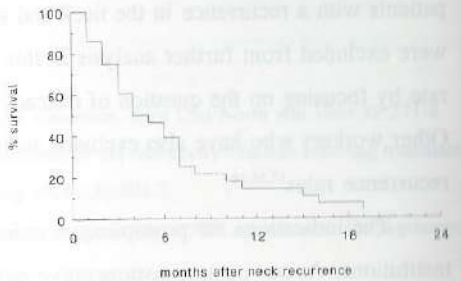

Fig.5 Survival curve of patients after an ipsilateral neck recurrence occurred.

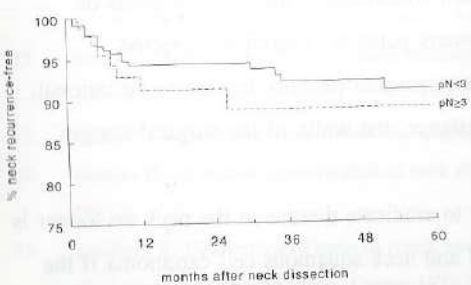

Fig.6 Proportion of necks remaining free of recurrence according to the number of histologically positive nodes ($pN<3$ and $pN\geq3$; $p=0.039$).

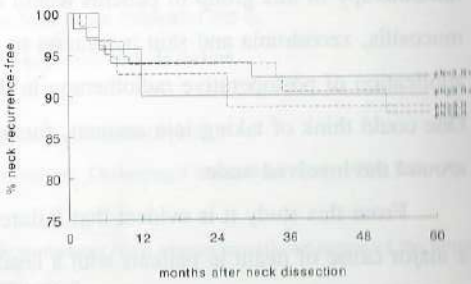

Fig.7 Proportion of necks remaining free of recurrence according to the number of histologically positive nodes and extranodal spread ($pN<3R$, $pN<3R+$, $pN\geq3R$, $pN\geq3R+$; ns).

probably to be attributed to tumor cells left behind or failure to observe microscopic amounts of tumor in the dissection specimen by the pathologist. For the histopathologic tumor-positive neck, the regional recurrence in this series is 9.7%, which is lower than the rates usually reported in the literature[1,2,4,6]. This is very likely due to the fact that patients with a recurrence in the neck and simultaneous recurrences at the primary sites were excluded from further analysis in this study to provide a more precise recurrence rate by focusing on the question of efficacy of neck dissection and radiation therapy only. Other workers who have also excluded such patients from analysis have found similar recurrence rates[17,18,19].

The indications for postoperative radiotherapy differ considerably among the various institutions. At our center, postoperative radiotherapy was applied if extranodal spread in one or more positive nodes and/or three or more tumor-positive nodes were found in the specimen at histopathological examination. The indications for postoperative radiation therapy remained unchanged during the study period. It is striking that patients with one or two histologically positive nodes without extranodal spread, who were hitherto considered to have the most favorable prognosis[6], did not do better in terms of recurrence in the neck than the other patient groups, who did receive radiotherapy.

This important observation has prompted us to consider giving postoperative radiation therapy also to patients with two or even one histologically positive node without extranodal spread, as has been suggested by others[20]. However, postoperative radiotherapy in this group of patients would add considerable morbidity in terms of mucositis, xerostomia and skin induration to many patients. Therefore, selected application of postoperative radiotherapy in this group of patients appears to be rational. One could think of taking into account, for instance, the width of the surgical margin around the involved node.

From this study it is evident that failure to eradicate disease in the neck no longer is a major cause of death in patients with a head and neck squamous cell carcinoma if the neck is treated by comprehensive neck dissection, followed in the majority of cases by radiotherapy. A strong plea is made for a uniform nomenclature and classification of neck dissections, such as proposed by Medina[16]. Also, there is a need for uniform reporting of results of treatment of neck nodes. Accurate information on the histologic status of nodes is always to be included, whereas recurrence at the primary site has to be taken into

account. Only when these conditions are met, will it be possible to compare the results of, e.g., selective neck dissections, to those of comprehensive neck dissections such as reported in this study.

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Chapter 3

DISCONTINUOUS VERSUS IN-CONTINUITY NECK DISSECTION IN CARCINOMA OF THE ORAL CAVITY

Charles R. Leemans MD, Rammohan Tiwari MD, Jos J.P. Nauta MSc,
Gordon B. Snow MD

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Abstract

We compared the results of transoral excision of the primary tumor with discontinuous neck dissection with the results of in-continuity dissection of primary tumor and neck nodes in anteriorly localized squamous cell carcinoma of the oral cavity. We analyzed 27 patients who underwent 28 discontinuous dissections and 34 patients who underwent 40 in-continuity dissections for T2 anterior tongue or floor-of-mouth carcinoma. The overall ipsilateral neck recurrence rate was 11%. The discontinuous dissection group did significantly worse than the in-continuity dissection group, with a neck recurrence of 19%. Consequently, the 5-year survival of patients who underwent a discontinuous dissection was substantially decreased (63%) compared to patients who were treated by an in-continuity dissection (80%). Discontinuous neck dissection, thus, is not to be recommended in oral cancer.

3.1 Introduction

Treatment of the regional neck nodes is an important consideration in the management of squamous cell carcinoma of the anterior tongue and floor of the mouth. All patients who have clinical evidence of nodal disease will need treatment of the regional lymphatics. Furthermore, many authors advocate surgical treatment of the neck in patients with a primary lesion larger than 2 cm because of the high incidence of occult regional metastases in these cancers[1,2,3].

The lymphatic drainage of the anterior oral cavity passes the intervening tissues of the floor of mouth before entering the neck. On theoretical grounds, therefore, the neck dissection is usually performed in continuity with the resection of the primary tumour, thereby removing the lymphatics between the primary and the regional nodes, which can harbour tumour cells in transit[4].

Since the first publications by Crile[5,6], the principle in the surgical treatment of oral carcinomas has been based on these anatomical grounds. It is recognized, however, that the sacrifice of the intervening structures in an en bloc resection adds to the morbidity in terms of function and disfigurement. To reduce these postoperative sequelae, the en bloc principle was, in selected cases, defied. In 1973, Spiro and Strong[7] published their results in tongue carcinoma and concluded that in lesions suitable for transoral excision, a discontinuous neck dissection can be performed without apparent adverse effects on survival.

The question whether a discontinuous neck dissection can be performed mainly arises in the smaller carcinomas (T2; lesion >2 cm but not >4 cm), because these usually can be excised adequately by the intraoral route. In larger lesions, it is often necessary to use extraoral approaches for exposure, thereby encroaching on the neck, and it is then good surgical practice to treat the neck nodes in the same procedure regardless of the clinical staging. We analyzed our material to obtain an answer to the issue of whether discontinuous and in-continuity neck dissection are equally effective.

3.2 Patients and methods

Sixty-one patients underwent a neck dissection for T2 carcinoma of the mobile tongue or of the floor of the mouth at the department of Otolaryngology-Head and Neck Surgery of the Free University Hospital, Amsterdam, between January 1978 and July 1988. Thirty-five (57%) anterior tongue carcinomas originated on the lateral border; of the 26 (43%) floor-of-mouth carcinomas 25% and 27% were located anteriorly in the discontinuous and in-continuity neck dissection groups respectively, the remainder being located laterally. Patients with fixed neck nodes or patients who underwent a histopathologically nonradical resection of the primary tumor or neck dissection (i.e. extranodal tumor growth at the margin of the neck dissection specimen) were excluded from this study as they represent a different population with a worse prognosis and, thus, would confuse the issue. The ages of the patients ranged from 40 to 79 years, with a mean age of 59 years. Women were 32% of the patients.

A total of 68 neck dissections were performed. Twenty-seven patients underwent 28 discontinuous neck dissections and 34 patients underwent 40 en bloc procedures. All treatment plans were discussed in a multidisciplinary head and neck oncology group, and all patients were operated on by the same five surgeons.

Table 1 gives the general characteristics of both groups as well as the clinical and histopathologic status of the neck and the percentage of occult neck nodes. It shows that both groups were comparable. All patients were staged according to the UICC-AJCC 1987 staging system[8]. The tumor stage distribution was also comparable in both groups: discontinuous group, 55% stage II, 41% stage III, and 4% stage IV; in-continuity group, 47% stage II, 47% stage III, and 6% stage IV.

All neck dissections were comprehensive, which means removal of the submental-submandibular, jugulo-digastric, midjugular, low-jugular, and posterior triangle lymph nodes. Whenever it was oncologically safe to do so, the spinal accessory nerve was preserved. Neither the sacrifice nor the preservation of the spinal accessory nerve was related to the outcome. The internal jugular vein, however, was left in situ only in bilateral dissections, and then only on the least involved side of the neck. The sternocleidomastoid muscle was removed in every case.

The pathology report was reviewed for the number of positive nodes and the

Table 1. General characteristics of patients*

	dissection group		
	in-continuity	discontinuous	total
No. of patients	34	27	61
No. of dissections	40	28	68
Age,y,range(mean)	40-75(60)	40-79(59)	40-79(59)
Neck classification %			
clinical			
NO	52	54	53
N+	48	46	47
pathologic			
NO	50	50	50
N+R-	28	32	29
N+R+	22	18	21
Postoperative RT %	28	25	26
Occult nodal disease %	29	20	25

*RT indicates radiotherapy; R extranodal spread

presence of extranodal spread. When three or more positive nodes and/or extranodal spread were reported, patients received postoperative radiotherapy. The total dose ranged from 50-66 Gy, directed to the neck as well as to the primary site.

Patients were followed up at regular intervals. When analyzed on July 1,1990, the follow-up data of all patients was available; securing a minimal follow-up of 2 years, and a 92% 3-year follow-up of the total group. Regional recurrence was defined as relapse in the side of the neck operated on without evidence of recurrence at the primary site. In those cases it was defined as locoregional and excluded from the analysis of ipsilateral (side of neck dissection) neck recurrence .

Survival and recurrence-free curves were calculated according to the Kaplan-Meier method; percentages are given at 5 years. Curves were compared using the generalized Wilcoxon test. Null hypotheses were tested one-sided against the alternative that continuous dissections prolong survival and reduce ipsilateral regional recurrence. Figures were stratified for postoperative radiation therapy, and this factor could, thus, be excluded.

Table 2. First Site of Failure

	dissection group	
	in-continuity	discontinuous
Local	2*(6%)	1 (4%)
Locoregional	1 (3%)	2 (8%)
Regional	2 (6%)	5 (21%)
Distant	2 (6%)	1 (4%)
Second primary	2 (4%)	1 (4%)

* one patient survived

3.3 Results

The overall survival rate in our group of patients was 72.5%. A total number of 15 (24.6%) of 61 patients died of disease in this series: six in the in-continuity group and nine in the discontinuous group. For the first group, the survival rate was 80.2%, and for the latter it was 62.7% (Fig.1). This difference was statistically significant (p=0.024). In both groups, the curves leveled off after 2.5 years.

The first site of failure is given in Table 2. It shows that both groups differed only in respect to regional recurrences (two vs five in the in-continuity and the discontinuous groups, respectively), whereas the number of local recurrences, distant metastases and second primary cancers were within the same range.

A total number of 10 ipsilateral regional recurrences were detected in the whole series of 68 neck dissections. All recurrences occurred within the first year after treatment. Three recurrences were locoregional rather than regional and were excluded from further analysis. Table 3 gives the number of ipsilateral neck recurrences relative to the pathologic involvement of the neck. The ipsilateral neck recurrence-free rate for all neck dissections was 89.1%. The in-continuity neck dissection group suffered significantly fewer neck recurrences than the discontinuous neck dissection group: 5.3% vs 19.1% (p=0.027; Fig.2).

Table 3. Number of ipsilateral neck recurrences relative to pathologic involvement of nodes

	in-continuity dissection group	no. of neck recurrences	discontinuous dissection group	no. of neck recurrences
pN0	16 (47%)	-	14 (51%)	1
pN1	10 (29%)	-	8 (30%)	3
pN2a	-	-	-	-
pN2b	6 (18%)	1	4 (15%)	-
pN2c	2 (6%)	1	1 (4%)	1
pN3	-	-	-	-

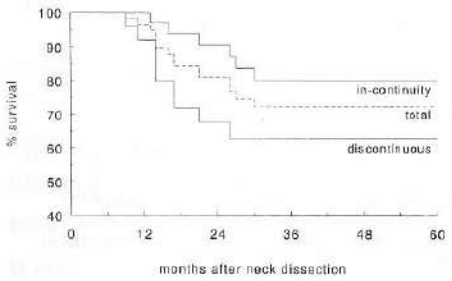

Fig.1 Survival curves for the total group, as well as for the two treatment groups: discontinuous vs in-continuity neck dissection (p=0.024).

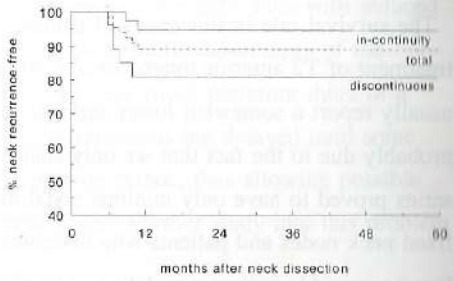

Fig.2 proportion of necks remaining free of recurrence for the total group, as well as for the two treatment groups: discontinuous vs in-continuity neck dissection (p=0.027).

3.4 Discussion

The management of small, anteriorly localized carcinomas of the oral cavity poses some controversial problems. The issue whether to treat the neck is vital, and this has been the subject of considerable debate. Many authors believe that some form of

treatment of the cervical nodes is called for because of the high incidence of occult regional metastases. Considerable literature on this subject exists, but the question whether to perform the neck dissection in continuity with the primary tumor or discontinuously is seldom addressed.

Spiro and Strong[7] published the results of a series of patients treated for tongue cancer and found no adverse effects of discontinuous procedures. In their series, however, there were significantly more less-advanced cases in the discontinuous group than in the in-continuity group, and this may have influenced their results. Ballantyne[9] reported that discontinuous dissections were the operation of choice in the University of Texas MD Anderson Cancer Center, Houston, if the lesion could be excised by the intraoral approach. Most studies on tongue or floor-of-mouth cancer, however, do not mention whether the neck was treated continuously or discontinuously.

It is, indeed, attractive to treat these patients with a less than en bloc operation, thereby reducing postoperative wound problems and minimizing sequelae like chewing and swallowing difficulties, impairment of head movements, and disfigurement. These features should not, however, outweigh the possibility of curing the patient.

The survival rate in this series of patients, who underwent a neck dissection in the treatment of T2 anterior tongue or of floor-of-mouth carcinoma,was 72.5%. Other studies usually report a somewhat lower survival for these cancers[10,11,12,13,14]. This is probably due to the fact that we only studied T2 carcinoma and that many patients in our series proved to have only minimal nodal disease. Besides, we excluded patients with fixed neck nodes and patients who underwent a histopathologically nonradical operation. In a comparable patient population, with 50% histopathologic positive nodes, Vandenbrouck et al.[15] found a similar survival rate (almost 70%) in 39 patients who underwent an elective neck dissection for oral carcinoma. Also Ferrara et al.[16] reported a 70% 5-year survival for accessible tongue carcinoma. Because of their anatomic nearness, the equal therapeutic options, and the evidence of similar behavior, reflected (for example) by a comparable nodal involvement[17,18,19,20], we considered anterior tongue and floor-of-mouth cancers as a group in this study.

A significantly better survival was noted in patients who underwent excision of the primary and in-continuity neck dissection compared with those who were treated by local excision and discontinuous neck dissection. Analysis of the reasons for this difference of

survival (17.5%) revealed that both groups could only be distinguished from each other by the regional recurrence rate, and that all other tumor related causes of death were within the same range.

The overall incidence of recurrence in the side of the neck operated on in this study was 10.9%, which is in line with our earlier findings[21]. The discontinuous dissection group, however, did significantly worse than the in-continuity dissection group, with a relapse rate that is twice as high as the rate found in head and neck squamous cell carcinoma in general.

This study clearly shows that the main drawback of discontinuous procedures lies in the higher number of neck relapses, which presumably is due to tumor cells left behind in the tissues between the primary site and the neck. This is also illustrated by the finding that almost all regional recurrences in this series were located in the submandibular area. We cannot but appreciate the wisdom and foresight of Crile, who already in the beginning of this century propagated the en bloc procedure.

We believe that since we possess an effective tool in controlling regional disease in these patients and thereby often can provide a cure, we cannot afford to jeopardize our results by performing an operation with less morbidity but at the same time with reduced potential for cure. However, it may seem possible to combine the advantages of the discontinuous dissection and maintain a better survival. One could therefore think of a staged procedure, by which the neck dissection is discontinuous but delayed until some time (e.g, 2 to 3 weeks) after the excision of the primary tumor, thus allowing possible tumor emboli in transit to reach the cervical lymph nodes. Further study into this problem is necessary.

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Chapter 4

REGIONAL LYMPH NODE INVOLVEMENT AND ITS SIGNIFICANCE IN THE DEVELOPMENT OF DISTANT METASTASES IN HEAD AND NECK CARCINOMA

Charles R. Leemans MD, Rammohan Tiwari MD, Jos J.P. Nauta MSc, Isaac van der Waal DDS, Gordon B. Snow MD

Submitted for publication

Abstract

The incidence of distant metastases in head and neck cancer patients is rising as more patients are at risk because of greater locoregional control. In view of the possible adjuvant therapy studies, the relative risks for developing distant metastases as first site of failure relative to the regional lymph node involvement were determined. The overall incidence was 10.7%, with a clear relationship between the number of involved lymph nodes and extranodal spread on the one hand, and distant spread on the other hand. The group with histopathologic N+ disease suffered twice as much distant metastases as the histopathologic NO group (6.9% vs 13.6%). Especially patients with more than three histologically positive lymph nodes were the most at risk for the development of distant metastases (46.8%). The presence of extranodal spread meant a threefold increase in the incidence of distant metastases, compared to patients without this feature (6.7% vs 19.1%).

4.1 Introduction

The advances in surgical techniques and the combination with postoperative radiotherapy have resulted in greater local and regional control in head and neck cancer patients in the last twenty years. Therefore more patients are exposed to the risk of developing distant metastases. As a result, a significant increase in long-term survival failed to materialize. This has caused an interest in the development of adjuvant therapeutic modalities (e.g. chemotherapy, immunotoxins and radio-immuno conjugates) after surgery and radiotherapy.

Several prognostic factors have been described, amongst which the histopathologic status of the neck nodes is most significant[1]. Furthermore, specific primary sites, higher T-stage and the level of neck involvement have been associated with a greater likelihood of occurrence of metastatic disease below the clavicles and, consequently, a poorer prognosis[2,3,4]. Several studies point to the fact that recurrent disease at the primary site or a regional recurrence are predictors for distant metastases[3,5].

The overall clinical incidence of distant metastases in squamous cell carcinoma of the head and neck varies from 4.3% to 26 % in different studies[1,2,6,7,8]. Autopsy studies report a much higher incidence of 40% to 57 %[3,9,10]. The commonest sites showing metastases are the lungs and the bones. Other localizations of metastatic deposits that are detected clinically are the liver, the mediastinum, the skin and the brain.

This study correlates the relative frequency of distant metastases to the histopathologic involvement of the neck nodes.

4.2 Patients and methods

During the period from January 1973 to July 1986, 519 patients underwent a neck dissection for squamous cell carcinoma of the head and neck at the department of Otolaryngology-Head and Neck Surgery of the Free University Hospital, Amsterdam. Eleven patients with tumors originating from the sinonasal tract or nasopharynx and 14 patients with neck node metastases from an unknown primary tumor were excluded, as these tumors demonstrate a distinctly higher or unknown tendency to develop distant

Table 1. Localization of primary tumors

site	total no. of patients (%)
Oral cavity	132 (47.0)
- mobile tongue	47
- floor of the mouth	42
- inferior alveolar process	10
- retromolar trigone	21
- other	12
Oropharynx	34 (12.1)
- tonsillar fossa	19
- other	15
Hypopharynx	27 (9.6)
- pyriform Sinus	22
- other	5
Larynx	88 (31.3)
- glottic	24
- transglottic	15
- supraglottic	48
- other	1

metastases. Eighty-five patients with histopathologically unsatisfactory margins (i.e. irradical excision of the primary tumor or extranodal tumor growth at the margin of the neck dissection specimen) and 120 patients, who experienced a locoregional recurrence or a second primary head and neck cancer were also excluded in this study. In these patients distant metastases cannot be properly correlated with the extent of the disease at the time of neck dissection.

This study is thus based on a total of 281 patients, who never suffered recurrent disease above the clavicles. Thirty-three patients underwent one-stage bilateral neck dissections. There were 218 men (77.6%) and 63 women (22.4%). Their ages ranged from 32 to 85 years, with a mean age of 62 years. The localizations of the primary tumors and the clinical T-stage distribution are illustrated in table 1 and 2, respectively.

The neck dissections were performed either simultaneously with the resection of the primary tumor or secondarily when neck node involvement became apparent during follow-up. All neck dissections were comprehensive, which means removal of regions I through V; i.e. the submental-submandibular, jugulo-digastric, midjugular, low-jugular and posterior triangle neck nodes. Whenever it was oncologically safe to do so, the spinal

accessory nerve was preserved. The internal jugular vein, however, was resected in all unilateral neck dissections and preserved only on the least involved side of the neck in bilateral dissections.

The pathologic report was reviewed for the number of tumor positive nodes (pN) and the presence of extranodal spread (R). Of the total group of 281 patients 171 (60.9%) had pN+ disease and 93 (54.4%) of these also showed extranodal spread. In 11 patients the presence of extranodal spread was questionable and these were excluded in the analysis in which extranodal spread was taken into account. One, two, three and more than three positive nodes were found in the neck dissection specimen of 81, 38, 12 and 40 patients, respectively. When three or more positive nodes or extranodal spread were reported, patients received postoperative radiotherapy. Some patients were postoperatively irradiated regardless of the staging of the neck, for instance large (T3-T4) pharyngeal lesions. The total dose ranged from 50-72 Gy in 5-7 weeks directed to the neck as well as to the primary site.

Table 2. Distribution according to T-stage

	Total No. of Patients	(%)
T1	50	17.8
T2	87	31.0
T3	88	31.3
T4	46	16.4
TX	10	3.5

TX = T-stage could not be assessed

Patients were followed at regular intervals for at least 5 years. Only three patients were lost to follow-up. Routine X-rays of the chest were made yearly, supplemented when necessary by a CT-scan of the thorax. Special investigations, such as bronchoscopy with sputum cytology, bone scanning, serum liver function tests, abdominal ultrasound scanning and brain scans were carried out when indicated. The endpoint of analysis was the occurrence of a clinically detected distant metastasis. Distant metastases discovered exclusively at autopsy were not included.

Recurrence-free and survival curves were calculated according to the method of Kaplan-Meier; percentages are shown at 5-years. Curves were compared using the Logrank test, either the usual one or the version to test for a trend. If possible null-hypotheses were tested against specified alternatives (e.g. the hypothesis that pN+ and R+ patients suffer more distant metastases than pNO and R- patients).

4.3 Results

Distant metastases were demonstrated clinically in 26 of the 281 patients (9.3%). Ten patients developed metastases at multiple localizations and one had metastases in four different organs. The distribution of the initial sites of metastases is illustrated in Fig.1. Twenty-two of the 26 patients with distant metastases, developed metastases in the lungs and in all but one of these patients this localization was the first manifestation of distant spread. In eight patients metastases to the bone were detected, while liver, skin, mediastinum and brain metastases were each demonstrated in 2 patients. Both mediastinal metastases were in laryngeal cancer patients. Furthermore, brain metastasis did not occur without a preceding lung metastasis. The occurrence of metastases at different sites during the follow-up and the proportion of the total number of distant metastases in time is shown in Figs 2 and 3. Survival of the patients who developed a distant metastasis is depicted in Fig.4.

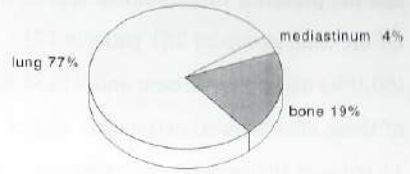

Fig.1 Distribution of initial sites of distant metastases.

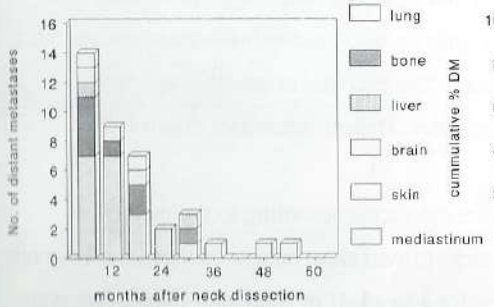

Fig.2 Occurrence of distant metastases at different sites during follow-up.

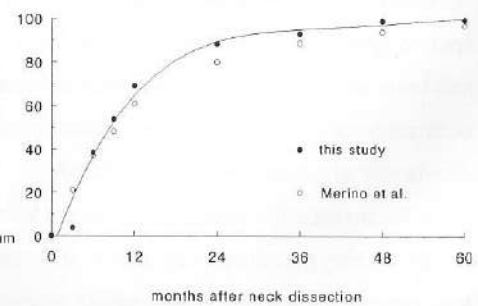

Fig.3 Proportion of total number of patients with distant metastases in time. Note similarity between this study and Merino et al.[2].

There was some, though statistically not significant, evidence that localization of the primary tumor was a prognostic factor (p=0.07); it appeared that oropharyngeal cancers resulted in a slightly higher rate of metastases than oral cancers. There was no relationship between clinical T-stage and the incidence of distant metastases.

The 5-years overall incidence of distant metastasis in our group of patients was 10.7% (Fig.5). As the number of histopathologically involved nodes and T-stage correlated, and T-stage being a potential confounding factor, we stratified for this factor when pN curves were compared. When the total group was divided according to the presence or absence of tumor positive nodes in the neck dissection specimen it was shown that this significantly affected the

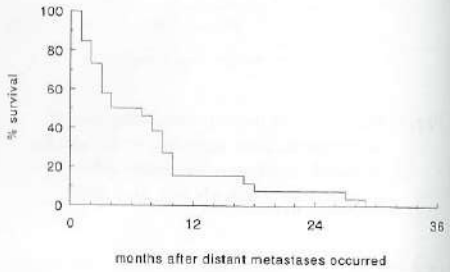

Fig.4 Survival curve of patients after distant metastases occurred.

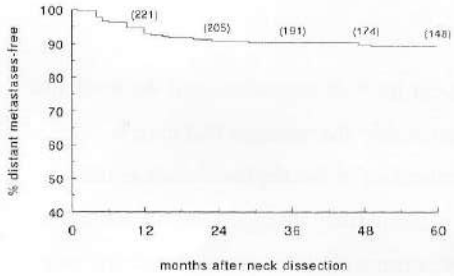

Fig.5 Proportion of patients remaining free of distant metastases. Numbers in parentheses indicate the number of patients at risk.

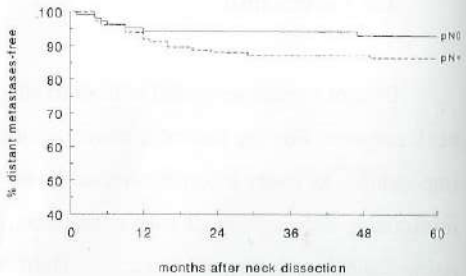

Fig.6 Proportion of patients remaining free of distant metastases according to histologic absence (pNO) and presence (pN+) of metastatic tumor in the neck (p=0.036).

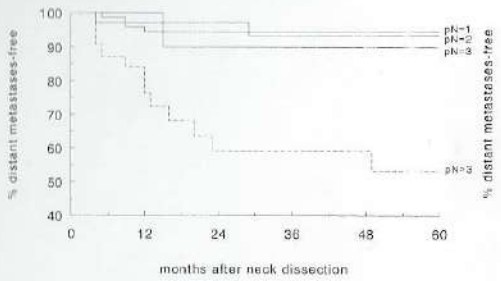

Fig.7 Proportion of patients remaining free of distant metastases according to the number of histologically positive nodes (pN=1, pN=2, pN=3 and pN>3; p=0.0027).

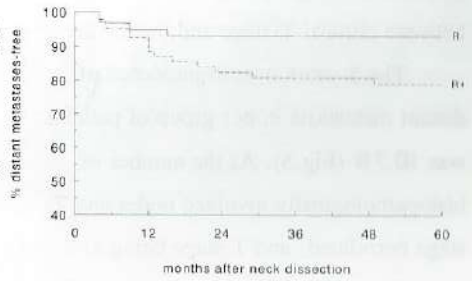

Fig.8 Proportion of patients remaining free of distant metastases according to absence (R-) and presence (R+) of extranodal spread in the pN+ group (p=0.017).

occurrence of subsequent distant metastasis (6.9% vs 13.6% for the pNO and pN+ cases (p=0.036; Fig.6). When the pN+ group was broken down according to the number of tumor positive nodes, it became clear that the number of involved nodes was prognostically significant (p=0.0027; Fig.7). Furthermore, the presence of extranodal spread in the pN+ group was associated with a much higher incidence of distant metastases (6.7% vs 19.1% for the R- and the R+ group respectively, p=0.017; Fig.8).

4.4 Discussion

Distant metastases entail a discouraging event for both the patient and the head and neck surgeon. For the patient it carries almost invariably the message that cure is impossible. As every effort is directed to the eradication of locoregional disease and minimizing the sequelae of such a treatment, it is particularly disappointing to witness a rising incidence in distant metastases. Until now, when a distant metastasis occurs, our main effort has been directed to palliative support. Only recently, an interest in the research of influencing the metastatic deposits and of how to prevent distant spread in high risk groups is developing.

A strong relation exists between initial tumor control, especially control of the neck,

and the incidence of metastatic spread below the clavicles. Recurrent disease at the locoregional site is associated with at least a doubling of the incidence of metastases[2,5]. In spite of the progress that has been made at the locoregional level, it is not completely clear where we stand today regarding the incidence of distant metastases relative to the involvement of the neck.

The incidence of distant metastases as first site of failure in our series of patients was 10.7%. Other authors report a wide range of incidences in distant metastatic spread. However, comparison between studies is difficult because of different populations, methods and statistics. The often cited study of Merino et al.[2] states an overall proportion of 10.9% of patients who developed distant metastases in the course of their disease, but this was regardless of the locoregional status. Lindberg[6] analyzed the occurrence and first sites of failure in head and neck cancer. He found a 7.2% incidence of distant metastases with locoregional control, but his series also included paranasal sinus and nasopharynx tumors. The only other study based on histopathologic data, by Vikram et al.[1], which also excluded patients who experienced a locoregional recurrence, reports an overall incidence of 20%. This difference could be explained by the fact that patients in this series presented with a substantially higher nodal stage than patients in our series. Furthermore, less patients were at risk in this study during follow-up compared to our study (e.g. at 4-years 14% vs 60%).

When the histopathologic status of the neck nodes is analyzed it appears that patients staged pN+ demonstrate a metastatic rate that is twice as high as the pNO group of patients. When the pN+ group was analyzed further, according to the number of histopathologically positive nodes, it was shown that the greater the number of nodes involved, the higher the risk for developing distant metastases. Whereas the incidences in the groups of patients with three or less positive nodes are within the same range, the group with more than three histologically positive nodes clearly is the most at risk (46.8%). Patients with a higher pathologic N-stage demonstrate not only a higher incidence of distant metastases but also a higher neck recurrence rate[11]. The exclusion of the patients with a locoregional recurrence in our series could thus have influenced the actual incidences in the groups with a high pN-stage. In spite of this, a clear relationship between involvement of the neck and the incidence of distant metastases could be established.

The presence of extranodal spread meant a threefold increase in the incidence of

distant metastases (19.1% vs 6.7%). Nine out of ten patients who eventually developed a distant metastasis did so in the first 2 years after neck dissection. However, in a small percentage of patients distant metastases occurred even after 4 years. Fifty percent of these patients died within 4 months, whereas all patients died within 2.5 years after diagnosing distant spread of their disease.

From this study it is evident that the overall incidence of distant metastases as first site of failure does not justify adjuvant systemic therapy for all head and neck cancer patients. Nevertheless some patients groups with a high incidence for developing such a fatal course can be identified. It may be worthwhile to select these patients for adjuvant therapy protocols.

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Chapter 5

RECURRENCE AT THE PRIMARY SITE IN HEAD AND NECK CANCER AND THE SIGNIFICANCE OF NECK NODE METASTASES AS A PROGNOSTIC FACTOR

Charles R. Leemans MD, Rammohan Tiwari MD, Jos J.P. Nauta MSc, Isaac van der Waal DDS, Gordon B. Snow MD

Submitted for publication

Abstract

Biologic aggressiveness of head and neck carcinoma is reflected by its capability to metastasize to regional lymph nodes and its propensity to recur after treatment. We report on 244 patients treated at the department of Otolaryngology-Head and Neck Surgery of the Free University Hospital, Amsterdam, with excision of primary tumor with in-continuity neck dissection with or without postoperative radiotherapy between January 1973 and July 1986. All patients had surgical margins free of tumor. The overall recurrence rate was 12.3%. Stages T3-4 and the presence of more than three positive nodes on histopathological examination were associated with a 16.2% and 26.2% incidence in recurrence at the primary site, respectively. No prognostic influence arose from primary tumor localization, three or less positive nodes, extranodal spread and postoperative radiotherapy. Adjuvant treatment for stages T3-4 and patients with more than three histopathologically positive nodes is indicated.

5.1 Introduction

The predictive value of neck node involvement on recurrence and survival in head and neck cancer is well known. It has been shown that the incidence in both neck recurrences and distant metastases is related to the number of tumor positive nodes and the presence of extranodal spread[1,2,3,4]. The basis for this relationship is probably the extent disease present in the neck, which is responsible for further spread. On the other hand a tumor that metastasizes to the regional nodes is a biologically more aggressive tumor than a tumor that does not spread beyond its anatomic limits, and because of this biological characteristic results in a propensity to recur after treatment[5]. If the latter concept is correct, a relationship between neck nodes and recurrence at the primary site would seem logic.

Furthermore, recurrence at the primary site is correlated with the T-stage and the histopathologic assessment of the margins[5,7]. According to some authors, both factors lose their prognostic value to some extent, if adjuvant radiotherapy is given[8].

This study reports on recurrences at the primary site in head and neck cancer relative to the involvement of the neck.

5.2 Patients and methods

Between January 1973 and July 1986, 289 previously untreated patients with squamous cell carcinoma of the head and neck were treated at the department of Otolaryngology-Head and Neck Surgery of the Free University Hospital, Amsterdam with resection of the primary tumor and in-continuity neck dissection. The primary tumor sites and clinical T-stage distribution are shown in table 1 and 2, respectively. The surgical procedures depended on the localizations of the primary tumors and included composite resection for oral cancers, partial pharyngectomy, laryngectomy (either partial or total) and laryngopharyngectomy. All neck dissections were comprehensive, which means removal of regions I through V; i.e. the submental-submandibular, jugulo-digastric, midjugular, low-jugular and posterior triangle neck nodes. Whenever it was oncologically safe to do so, the spinal accessory nerve was preserved. The internal jugular vein,

Table 1. Localization of primary tumors

site	total no. of patients (%)
Oral cavity	116 (47.5)
- mobile tongue	37
- floor of the mouth	40
- inferior alveolar process	11
- retromolar trigone	23
- other	5
Oropharynx	32 (13.1)
- tonsillar fossa	20
- other	12
Hypopharynx	26 (10.7)
- pyriform Sinus	22
- other	4
Larynx	70 (28.7)
-supraglottic	50
-(trans)glottic	20

however, was left in situ only on the least involved side in bilateral neck dissections.

The pathologic report was reviewed for the assessment of the surgical margins, the number of involved nodes (pN) and the presence of extranodal spread (R). Forty-five patients with histopathologically unsatisfactory margins were excluded regardless of the institution of postoperative radiotherapy, because the recurrence rate at the primary site is higher in these patients. Of the remaining 244 patients 153 (62.7%) had pN+ disease, of which 69 (45.1%) showed extranodal spread. In 14 patients the presence of extranodal spread was questionable and these were excluded in the analysis in which this factor was taken into account. One, two, three and more than three positive nodes were found in the neck dissection specimen of 63, 35, 14 and 41 patients, respectively.

When three or more positive nodes or extranodal spread were reported, patients received postoperative radiotherapy. Some patients were irradiated postoperatively regardless of the staging of the neck, in particular large (T3 and T4) pharyngeal lesions. Thus 95 patients were treated with a total dose ranging from 50-72 Gy in 5-7 weeks directed to the neck as well as to the primary site.

Patients were followed at regular intervals for at least 5 years. Endpoint of analysis was a recurrence at the primary site as first site of failure. Recurrence-free curves were

calculated according to the method of Kaplan-Meier; percentages are shown at 5-years. Curves were compared using the Logrank test. If possible null-hypotheses were tested against specified alternatives (e.g. the hypothesis that a higher pathologic N-stage increased the incidence of recurrences at the primary site).

Table 2. Distribution according to T-stage

	Total No. of Patients	(%)
T1	18	7.4
T2	65	26.6
T3	104	42.6
T4	52	21.3
TX	5	2.1

TX = T-stage could not be assessed

5.3 Results

Recurrences at the primary site were demonstrated in 26 of the 244 patients; 65.4% occurring within the first year after treatment and only 11.5% of the recurrences occurred after 2 years. The overall 5-years incidence of recurrence was 12.3% (Fig.1). Clinical T-stage was shown to be an independent prognostic factor. The incidence of recurrences at the primary site in patients staged T1 and T2 was 5.3%, whereas patients staged T3 and T4 suffered such a failure in 16.2% (p=0.015; Fig.2).

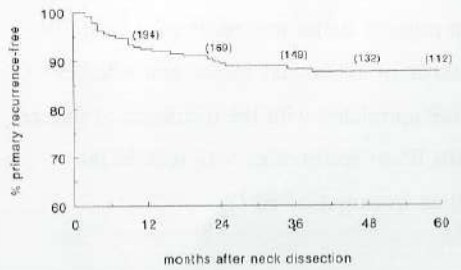

Fig.1 Proportion of patients remaining free of recurrence at the primary site. Numbers in parentheses indicate the number of patients at risk.

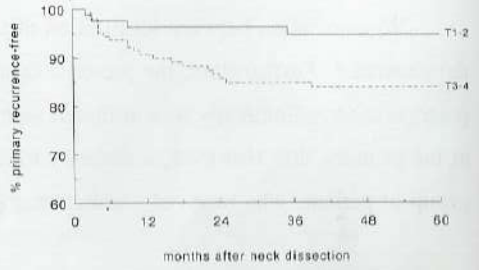

Fig.2 Proportion of patients remaining free of recurrence at the primary site for the stages T1-2 and T3-4 (p=0.015).

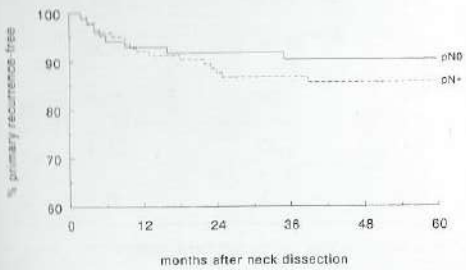

Fig.3 Proportion of patients remaining free of recurrence at the primary site according to histological absence (pNO) and presence (pN+) of metastatic tumor in the neck (ns).

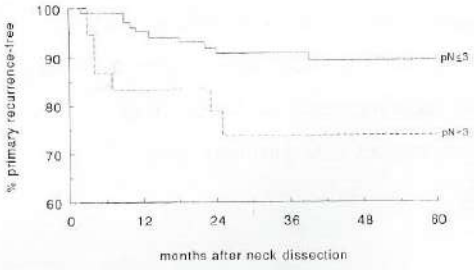

Fig.4 Proportion of patients remaining free of recurrence at the primary site according to the number of histologically positive nodes ($pN \leq 3$ and $pN > 3$; $p = 0.018$).

The difference in failures at the primary site in the groups of patients with (pN+) and without (pNO) histologically proven tumor in their dissection specimen was not statistically significant (Fig.3). When, however, the pN+ group was broken down according to the number of involved nodes it became clear that the presence of more than three positive nodes was a strong independent predictor of recurrence at the primary site (26.2%), whereas patients with three or less positive nodes experienced only a slightly higher recurrence rate (10.6%) compared to the pNO patients (9.5%) ($p=0.018$; Fig.4).

No association between localization of the primary tumor and recurrence could be demonstrated. Furthermore, the presence or absence of extranodal spread and whether postoperative radiotherapy was instituted were not correlated with the incidence of failure at the primary site. However, a tendency towards fewer recurrences was seen in the group of patients who received a radiotherapy dose in excess of 60 Gy.

5.4 Discussion

It is generally accepted that the presence of neck node metastases in head and neck cancer roughly reduces survival by half. This is due in large part to the correlation

between number of involved nodes and extranodal spread on the one hand, and the incidence of regional and distant relapse rates on the other. The possible role played by recurrence at the primary site has seldom been addressed in this respect. Gilbert and Kagan[5] stated in a review of the literature on recurrences in head and neck cancer, that they felt that the biological significance of clinically positive neck nodes (initially or at a later stage) reflects to a large degree the aggressiveness of the primary tumor and its propensity to recur after either surgery or irradiation. Other authors have also expressed the prognostic significance of the extent of nodal metastasis in the neck relative to recurrence at the primary site[9,10].

In this series a 12% incidence of recurrences at the primary site was found. Recurrence rates for stages T3 and T4 are higher than for the less advanced stages. Others have found comparable results[8]. The significance of the number of tumor-positive nodes only becomes evident for the patients with more than three positive nodes. This group represents extensive regional metastatic spread. The presence or absence of extranodal spread is of no significance in this regard. As biologic aggressiveness of the primary lesion is reflected by the extent of disease initially present in the neck, this quality is thus of less significance when tumor cells have arrived in the fertile soil of the lymph node.

No fewer recurrences were demonstrated when postoperative radiotherapy was given. This is probably due to the fact that this adjuvant treatment modality is instituted exactly on the basis of bad prognostic factors derived from the neck dissection specimen.

Patients staged T3 or T4 and especially those with more than three positive nodes are at high risk for developing a recurrence at the primary site. Adjuvant treatment modalities could be beneficial for these patients.

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Chapter 6

GENERAL DISCUSSION

6.1 Introduction

Failure to achieve tumor control above the clavicles has traditionally been regarded as the major cause of death in patients with advanced head and neck squamous cell carcinoma. The advent of modern reconstruction techniques have made wider excisions possible, and especially when combined with present day radiotherapy, locoregional control has increased. It is to be expected that some gain at the locoregional level will still be possible when wider margins will be taken and advanced reconstruction techniques will be applied, particularly in tumors of moderate size. Also further improvement is to be expected from sophisticated techniques of tailoring radiation therapy to the individual tumor[1]. Consequently the pattern of failure is changing[2,3,4], because more patients are at risk of developing distant metastases, and second malignant neoplasms. The overall cure rate for patients with head and neck cancer has, thus, remained stationary. Actually, the incidence of distant metastases in patients with advanced disease has not substantially increased compared to earlier data[3]. However, distant metastases in the past were almost always preceded by recurrence at the locoregional level, whereas nowadays this is no longer the case. Systemic failure has increasingly become an important cause of initial failure in patients with head and neck squamous cell carcinoma.

While the pattern of failure seems to be changing, accurate data relating to the magnitude of the problem of failure at the local, regional, and distant level in patients with head and neck cancer is lacking[5]. Accurate evaluation of the magnitude of the problem at each level is essential for estimating the potential for gain and for establishing priorities for clinical research.

6.2 Efficacy of treatment of neck nodes

The data presented in chapter 2 show that the efficacy of comprehensive neck

dissection, when indicated followed by adjuvant radiotherapy, is high. The actuarial recurrence rate in the dissected neck, for all stages combined, is 7.2%. For the histopathologically tumor-negative neck a recurrence of 2.6% was found, whereas the recurrence in the neck for the tumor-positive necks was 9.7%. These figures are on the lower end of the range, normally reported in the literature[6,7,8,9,10]. However, many of these studies did not correct for tumor recurrence at the primary site.

All patients were treated in a period, in which the surgical technique and indications for postoperative radiotherapy remained unchanged. All neck dissections were comprehensive; i.e. removal of lymph node regions I through V - according to the Memorial Sloan-Kettering Cancer Center classification. Patients with three or more positive nodes or extranodal spread were postoperatively irradiated.

An increasing number of surgeons are performing selective neck dissections, in patients who are clinically staged NO or even N1, in order to reduce morbidity. Because these selective neck dissections are used in patients with only minimal nodal disease, they should yield results at least comparable to comprehensive neck dissections, which are used also in patients with more extensive nodal disease.

When the recurrence rates of, e.g., supraomohyoid neck dissections are analyzed in comparison to our recurrence rates, it becomes clear that the recurrence rates after these selective procedures are higher. Byers[11] and Medina et al.[12] reported on a series of patients who were treated at MD Anderson Cancer Center, Houston, for squamous cell carcinoma of the oral cavity and oropharynx. They found a recurrence in the neck as first site of failure in 12 of the 80 (15.0%) histopathologic N+ necks, and 9 of the 154 (5.8%) histopathologic NO necks. Spiro et al.[13], from Memorial Sloan-Kettering Cancer Center, reported a recurrence in the side of the neck operated on, in 9 of the 43 (20.9%) necks with tumor, and 3 of the 64 (4.7%) necks without tumor on histopathologic examination. These authors compared their results to earlier failure rates and concluded that supraomohyoid neck dissections are equally effective in eradicating nodal disease in NO and N1 patients. If, however, these figures are compared to the present study, they appear to be almost twice as high (e.g. 15.0%-20.9% vs 9.7% for the tumor positive necks). From these data it is evident that, even for patients with clinically minimal nodal disease, these selective neck dissections are less effective. Caution, therefore, is warranted against these procedures, particularly as the surgical technique of these procedures is not well

standardized.

Our results show that patients with histopathologic minimal nodal disease (i.e. one or two nodes without extranodal spread), who were hitherto considered to have a more favorable prognosis and consequently were not irradiated, did not do better in terms of recurrence in the dissected neck than the other groups of patients with more extensive nodal disease and who did receive postoperative radiotherapy. The question then arose whether the results of the first group of patients could be improved by the addition of postoperative radiotherapy. In view of the fact that a recurrence in the neck almost invariably proves fatal, these results have prompted us to give postoperative radiotherapy also to the group of patients with two tumor-positive nodes without extranodal spread. One must, however, take into consideration that only a limited fraction of patients would really benefit from this adjuvant therapy, whereas a certain amount of morbidity would be inflicted to all patients of this group.

Much effort is directed currently to adapting fractionation schemes and improvement of radiation techniques resulting in higher doses to the target area and at the same time reducing normal tissue dose.

The data of chapter 3 shows that the traditional principle, that nodal disease should be removed in-continuity with the primary tumor, in order not to leave tumor cells behind, still appears to be valid. For patients with a primary tumor originating in the anterior oral cavity, in whom a discontinuous procedure would theoretically be beneficial, it was proven that the results of discontinuous neck dissection were worse with a recurrence rate in the neck of 19% (which is twice as high as the overall recurrence rate reported in chapter 2) and a lower survival. It must be assumed that tumor cells, which were in-transit from the primary to the neck and were left in the patient, are responsible for this failure. Simultaneous excision of primary tumor and discontinuous neck dissection must therefore be discouraged. It may be possible to combine the advantages of the discontinuous procedure and maintain a better survival. One could think of a procedure, in which the neck dissection is delayed until some time (e.g. 2 to 3 weeks) after the excision of the primary tumor, thus allowing possible tumor emboli to reach the cervical lymph nodes. Further study into this problem is currently going on at our institution.

6.3 Prognostic significance of neck node metastases

Failure to eradicate disease in the neck no longer is a major cause of death in patients with a head and neck squamous cell carcinoma. Nevertheless, it is of great importance to know the exact histopathologic involvement of the neck dissection specimen so as to be able to define risk factors for tumor-recurrence in the neck and, thus, to indicate when adjuvant radiotherapy is needed. Besides, the neck dissection is a staging procedure with respect to failure at distant sites and possibly also with respect to failure at the primary site.

The magnitude of the failure problem at the primary, regional, and distant site as well as the total failure is shown in table 1. In chapters 2, 4 and 5 the significance of histopathologic parameters of lymph node metastases has been described for failure in the ipsilateral neck, at distant sites, and at the primary site, respectively. In order to exclude confounding factors, the various recurrence rates were determined in a carefully selected patient population. Major factors that must be excluded are unsatisfactory surgical margins and a concomitant recurrence at a higher level; e.g. a locoregional recurrence while determining the incidence of distant metastases. Figures relating to failure at the primary and distant sites were directly derived from the corresponding chapters. The overall regional relapse rate (ipsilateral and contralateral) was calculated on the basis of the data presented in chapter 2. When patients with pN≤3 and pN>3 disease were compared, no statistical difference was noted in relation to regional relapse. For this and several other features no prognostic influence could be established and in such cases the combined figure was taken (e.g., the pN+ rate for both the pN≤3 and the pN>3 group, with respect to regional relapse).

Thus, accurate independent risk factors for failure at the three sites could be established. Several independent risk factors (such as presence of tumor in the neck and number of involved nodes) influence two or all three failure-incidences and thus have a major impact on the overall failure. It should be realized that the recurrence rates apply for the majority of patients, but that patients, who underwent histopathologic nonradical excisions, were excluded. In those cases the involvement of the neck cannot be properly correlated with tumor-recurrence.

For the whole group, the primary site is still the leading cause of failure, and

Table 1. Contribution of the different sites of first failure to the total recurrence in head and neck cancer (% at 5-years)

	Primary		Regional		Distant		Overall
Total	12.3	(39.8)	7.9	(25.6)	10.7	(34.6)	30.9
pNO	9.5	(49.3)	2.9	(14.9)	6.9	(35.8)	19.3
pN+	14.3	(36.8)	11.0	(28.2)	13.6	(35.0)	38.9
pN≤3	10.6	(38.3)	11.0	(39.6)	6.1	(22.1)	27.7
pN>3	26.2	(31.2)	11.0	(13.1)	46.8	(55.7)	84.0
T1-2	5.3	(22.2)	7.9	(33.1)	10.7	(44.7)	23.9
T3-4	16.2	(46.6)	7.9	(22.7)	10.7	(30.7)	34.8
R-	14.3	(44.7)	11.0	(34.4)	6.7	(20.9)	32.0
R+	14.3	(32.2)	11.0	(24.8)	19.1	(43.0)	44.4

Relative percentages of the overall failure for the different sites are shown in parentheses.

accounts for 40% of the total failure. Distant metastases are in second place, with 34% and recurrence in the neck accounts for 26 % of the overall failure. These figures confirm the conclusion of most authors who reported on recurrence rates after neck dissection relative to the histological involvement of the neck; i.e. patients with large tumors and multiple histologically positive nodes with extranodal spread are at high risk for developing a recurrence at one or more sites after surgery followed by radiotherapy[14,15,16,17,18,19,20].

It is evident that among these factors the presence of three or more positive nodes is an extremely bad prognostic sign. This is due to an increased incidence of recurrences at the primary site and especially the much greater risk of developing distant metastases. The parameter of extranodal spread still has an important influence on the prognosis, but its significance regarding recurrence in the neck has been undone by the strict application of postoperative radiotherapy in these cases.

As all patients with high risk factors for recurrence of their tumor already received adjuvant radiotherapy, the question arises: can we do more for these patients? We must therefore think of systemic treatments with chemotherapy and immunotherapy[2]

As to the application of (neo)adjuvant chemotherapy, almost all studies have failed to show any improvement in survival[5,21,22,23,24]. Stell and Rawson[25] reported an overview of 23 trials of neoadjuvant chemotherapy. Meta-analysis failed to show a significant overall improvement in cancer mortality. No single agent nor combination chemotherapy produced a significant reduction of cancer deaths. The rate of locoregional failure, however, was significantly lower in the treated arm. It is to be realized, however, that most of the studies were done in patients with very high risk factors for tumor recurrence and consequently the potential benefit of chemotherapy could have been overshadowed by intrinsic tumor factors. For theoretic reasons, it seems attractive to give the chemotherapy after the conventional therapy. The traditional adjuvant chemotherapy (or immunotherapy for that matter) has several advantages, e.g.,: 1) the generally accepted treatment options are not delayed and not interfered with, and 2) the patients with high risk of recurrence of their tumor can be identified on the basis of the previous surgical procedure. There are, however also disadvantages, e.g.: 1) the treatment of distant micrometastases is delayed until after the conventional treatment, and 2) because of the earlier treatment it is difficult to monitor the effectiveness, and also the uptake of drugs in the original tumor sites can be interfered with.

It remains to be seen whether the application of adjuvant systemic therapy in certain high risk patients is effective in increasing survival. On theoretical grounds, however, it may have potential for certain subgroups of patients and deserves investigation in well designed studies.

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SUMMARY

Since the first publication by Crile in 1906 there has been no doubt about the therapeutic value of radical neck dissection in squamous cell carcinoma of the mucous membranes of the head and neck. In recent years, numerous modifications of the radical neck dissection and combination treatment of surgery and radiotherapy have been increasingly applied. It is therefore not clear where we stand today in terms of management of neck node metastases.

Besides being of therapeutic value, neck dissection is of significance as a staging procedure, not only with respect to subsequent recurrence in the treated neck, but also with respect to recurrence at distant sites and, possibly at the primary site as well. However, accurate data on the prognostic significance of histopathologic parameters of neck node metastases is lacking.

The aims of this thesis are twofold. First, to determine the efficacy of the current management of nodal metastases in the neck, on the basis of a large series of patients who were treated at the department of Otolaryngology-Head and Neck Surgery of the Free University Hospital Amsterdam, the Netherlands. Second, to obtain accurate data on the prognostic value of the histopathologic involvement of the neck nodes with respect to recurrence at the different sites.

Chapter 1 serves as an overview on the various aspects of neck node metastases and their treatment.

In chapter 2 the efficacy of 'comprehensive' neck dissection, with or without postoperative radiotherapy is discussed. The recurrence rate in the tumor-positive neck, after a histopathologically radical operation and corrected for recurrence at the primary site, is 9.7%. The number of involved nodes is of prognostic value with respect to ipsilateral neck recurrence; i.e. 2.6%, 9.1%, and 11.3% in the histopathologically tumor-negative neck, in the neck with one or two positive nodes, and in the neck with three or more positive nodes respectively. Provided postoperative radiotherapy is applied on indications derived from the pathology report, the presence of extranodal spread has no prognostic significance in this respect.

In chapter 3 the feasibility of the neck dissection as a discontinuous, as opposed to an en bloc procedure is addressed. The results of these two procedures are discussed for

carcinoma of the anterior oral cavity. Following excision of the primary tumor and a discontinuous neck dissection a higher rate of regional recurrences, and consequently a lower survival rate were observed than after an en bloc removal of neck nodes and primary tumor.

In chapter 4 the significance of histopathologic lymph node involvement, with respect to the development of distant metastases, is reported. The overall incidence in patients, who underwent a histopathologically radical operation and who never suffered a recurrence above the clavicles, was 10.7%. The risk for distant metastases in patients with tumor-positive nodes was twice as high as compared to patients with a tumor-negative neck (13.6% versus 6.9%). A correlation was established between number of involved nodes and distant metastases. Especially patients with three or more positive nodes had a high incidence of distant metastases (46.8%). Patients in whom extranodal spread was reported suffered a threefold incidence of distant metastases as compared to patients without this feature (19.1% versus 6.7%).

In chapter 5 the relationship between regional lymph node involvement and recurrence at the primary site is discussed. In the group of patients, who underwent a histopathologically radical operation, a recurrence at the primary site was observed in 12.3%. T-stages 3 and 4 and the presence of more than three tumor-positive nodes were associated with significantly more recurrences at the primary site (16.2% and 26.2%, respectively).

In conclusion, the general discussion is presented in chapter 6. The efficacy of treatment of neck nodes, as described in this thesis, is high. Caution is warranted against selective neck dissections in which not all lymph node regions are cleared. In general, it should be discouraged to perform the neck dissection discontinuously from the primary tumor. Postoperative radiotherapy is recommended in patients with two or more positive nodes, or extranodal spread on histopathologic examination. It could be considered to give postoperative radiotherapy to every patient with a tumor-positive neck.

The magnitude of the problem of tumor recurrence, as first site of failure, at the three different sites is presented. For the group of patients, as described in chapters 2, 4 and 5 recurrence at the primary site ranks highest with 40% of the total failure. Second are distant metastases with 34% and recurrence in the neck accounts for 26%. The incidence of tumor recurrence in certain groups of patients, such as those with more than three

positive nodes or with extranodal spread, remains high in spite of postoperative radiotherapy. It is, therefore, to be considered to apply a systemic therapy after the conventional treatment on the basis of the risk factors as described in this thesis.

SAMENVATTING

Sinds de eerste publicatie van Crile in 1906 over de "radicale" halsklierdissectie, bestaat geen twijfel over de therapeutische waarde daarvan bij het plaveiselcelcarcinoom uitgaande van de slijmvliezen van het hoofd-halsgebied. De laatste jaren worden echter, talloze modificaties van de "radicale" halsklierdissectie en combinatiebehandelingen van chirurgie met radiotherapie in toenemende mate toegepast. Het is daarom onduidelijk wat op dit moment de stand van zaken is met betrekking tot de behandeling van halskliermetastasen.

Naast de therapeutische waarde is halsklierdissectie van belang als stadiërende ingreep, niet alleen met het oog op de kans op recidief in de behandelde hals, maar ook ten aanzien van de kans op metastasering op afstand en mogelijk zelfs op recidief van de primaire tumor. Er zijn echter geen nauwkeurige gegevens over de prognostische betekenis van histopathologische parameters van halskliermetastasen beschikbaar.

De doelstellingen van dit proefschrift zijn tweeledig. Ten eerste het bepalen van de effectiviteit van de huidige behandeling van halskliermetastasen, aan de hand van een grote serie patiënten die op de afdeling keel-, neus- en oorheelkunde van het Academisch Ziekenhuis Vrije Universiteit werden behandeld. Ten tweede het verkrijgen van nauwkeurige gegevens betreffende de kans op tumorrecidief op de verschillende niveau's, gerelateerd aan de histopathologische betrokkenheid van de halsklieren.

In hoofdstuk 1 wordt een overzicht gegeven van de verschillende aspecten van halskliermetastasen en hun behandeling.

In hoofdstuk 2 wordt de effectiviteit van de volledige "comprehensive" halsklierdissectie, al dan niet gevolgd door radiotherapie, besproken. De incidentie van het recidief in de tumorpositieve hals, na een histopathologisch radicale operatie en gecorrigeerd voor een eventueel recidief van de primaire tumor, is 9,7%. Het aantal aangedane klieren is van prognostische betekenis voor het ipsilaterale halsrecidief; dit treedt op in 2,6%, 9,1% en 11,3% in respectievelijk de tumornegatieve hals, de hals met één of twee positieve klieren en de hals met drie of meer positieve klieren bij histopathologisch onderzoek. Indien postoperatief radiotherapie wordt gegeven op indicaties welke zijn afgeleid van het patholoog-anatomische verslag, heeft kapseldoorbraak geen prognostische waarde voor dit recidief.

In hoofdstuk 3 wordt de uitvoerbaarheid van de halsklierdissectie als discontinue ingreep, tegenover de "en bloc" procedure aan de orde gesteld. De resultaten van deze twee operaties werden vergeleken voor het carcinoom van de voorste mondholte. Na excisie van de primaire tumor en een discontinue halsklierdissectie werd een hoger percentage halsrecidieven gevonden en derhalve een lager overlevingspercentage, dan na een en bloc verwijdering van halsklieren en primaire tumor.

In hoofdstuk 4 wordt ingegaan op het belang van de mate van histopathologische betrokkenheid van de halsklieren in relatie tot het optreden van metastasen op afstand. In de groep patiënten die een histopathologisch radicale operatie onderging en bij wie zich geen locoregionair recidief voordeed, bedroeg de incidentie van metastasen op afstand 10,7%. Patiënten met een tumorpositieve hals hadden een tweemaal zo grote kans op het krijgen van metastasen op afstand in vergelijking tot patiënten met een tumornegatieve hals (13,6% versus 6,9%). Er werd een duidelijke correlatie gevonden tussen het aantal positieve lymfeklieren en het optreden van metastasen op afstand. Met name in de groep patiënten met drie of meer positieve klieren werd een sterk verhoogde incidentie gevonden (46,8%). Patiënten met kapseldoorbraak hadden een driemaal zo grote kans op metastasen op afstand dan patiënten die dit kenmerk niet vertoonden (19,1% versus 6,7%).

In hoofdstuk 5 wordt de relatie besproken tussen de mate van betrokkenheid van de halsklieren en het optreden van recidief van de primaire tumor. In de groep patiënten die een histopathologisch radicale operatie onderging werd bij 12,3% een recidief van de primaire tumor gevonden. T-stadia 3 en 4 en de aanwezigheid van meer dan drie positieve klieren waren gecorreleerd met significant meer recidieven van de primaire tumor (16,2% en 26,2%, respectievelijk).

Hoofdstuk 6 bevat de slotdiscussie. De effectiviteit van de in dit proefschrift beschreven behandeling van de hals is groot. Voorzichtigheid is dan ook geboden met betrekking tot selectieve halsklierdissecties, waarbij niet alle lymfekliergroepen worden verwijderd. In het algemeen is het af te raden de halsklierdissectie discontinu van de primaire tumor te verrichten. Het is aan te bevelen patiënten met twee of meer positieve klieren of kapseldoorbraak postoperatief te bestralen. Mogelijk is dit zelfs te overwegen bij iedere patiënt met een tumorpositieve hals.

De omvang van het probleem van hernieuwde tumormanifestatie, als eerste teken van recidief, wordt berekend voor de drie niveau's afzonderlijk. In de groep patiënten

zoals besproken in de hoofdstukken 2, 4 en 5, komt recidief van de primaire tumor het meest frequent voor, namelijk 40% van het totaal recidief. Op de tweede plaats staan metastasen op afstand met 34% en het halsrecidief neemt 26% voor zijn rekening. Ondanks postoperatieve bestraling blijft het percentage tumorrecidief in bepaalde patiëntengroepen - zoals de groep met meer dan drie tumorpositieve klieren of met kapseldoorbraak- hoog. Het valt daarom te overwegen deze patiënten een aanvullende systemische therapie na de conventionele behandeling te geven, op basis van de risicofaktoren welke in dit proefschrift werden gevonden.

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Velen hebben een bijdrage geleverd aan het tot stand komen van dit proefschrift. Speciale dank gaat uit naar:

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Tot slot wil ik Let bedanken voor haar onmisbare steun bij het belangrijkste deel van dit proefschrift.

CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 21 augustus 1959 te Rotterdam. In 1978 behaalde hij het eindexamen Atheneum aan de scholengemeenschap "Professor Casimir" te Vlaardingen. In datzelfde jaar werd begonnen met de studie geneeskunde aan de Erasmus Universiteit te Rotterdam. Het artsexamen werd behaald op 15 januari 1985.

Hierna was de auteur tot 1 januari 1987 werkzaam als arts-assistent op de afdeling algemene heelkunde van het Andreas Ziekenhuis in Amsterdam. Vanaf die datum is hij werkzaam op de afdeling Keel-, Neus- en Oorheelkunde van het Academisch Ziekenhuis van de Vrije Universiteit te Amsterdam: gedurende het eerste half jaar werd een geautomatiseerd bestand ontwikkeld van oncologische patiëntengegevens en vervolgens was hij een jaar als werkzaam als AGNIO. Vanaf 1 Juli 1988 is hij in opleiding tot keel-, neus- en oorarts (opleider: Prof.dr G.B.Snow). Van 1 juli 1990 tot 1 januari 1991 werd een deel van deze opleiding volbracht in het Westeinde Ziekenhuis in Den Haag (opleider: Dr I.B.Tan).

Vanaf 1 juli 1992 zal hij verder worden opgeleid in de hoofd-halschirurgie. Voor de periode van twee jaar is hem een klinisch fellowship toegekend door de Nederlandse Kankerbestrijding.

Stellingen

behorend bij het proefschrift:

The value of neck dissection in head and neck cancer
-a therapeutic and staging procedure-

1. De volledige ('comprehensive') halsklierdissectie, eventueel gevolgd door radiotherapie is een effectieve behandeling van halskliermetastasen bij patiënten met een plaveiselcelcarcinoom uitgaande van de slijmvliezen van het hoofd-halsgebied.

2. Het is uit oncologisch oogpunt onjuist de halsklierdissectie, bij patiënten met een carcinoom van de mobiele tong of voorste mondbodem, in dezelfde operatie discontinu van de primaire tumor te verrichten.

3. Bij patiënten met kapseldoorbraak van halskliermetastasen van plaveiselcelcarcinomen uitgaande van de slijmvliezen van het hoofd-halsgebied, is de kans op metastasen op afstand driemaal zo groot als bij patiënten zonder kapseldoorbraak.

4. De eerste manifestatie van metastasen op afstand, van plaveiselcelcarcinomen uitgaande van de slijmvliezen van het hoofd-halsgebied, is nagenoeg altijd gelocaliseerd in de longen, de botten of het mediastinum.

5. De aanwezigheid van halskliermetastasen is niet alleen van prognostische waarde voor het optreden van recidief in de behandelde hals en van metastasen op afstand, doch ook voor het optreden van recidief van de primaire tumor.

6. Het verdient aanbeveling een onderzoek in te stellen naar het nut van adjuvante systemische therapie bij patiënten met een hoog risico op tumorrecidief (zoals patiënten met drie of meer halskliermetastasen en kapseldoorbraak) na behandeling voor een mucosaal plaveiselcelcarcinoom van het hoofd-halsgebied.

7. Het routinematig gebruik van gerevasculariseerde transplantaten bij de reconstructie van defecten in het hoofd-halsgebied zal in de toekomst sterk toenemen.

8. Bij de toepassing van amiodarone, bij patiënten met cardiale aritmie, dient een uitgangslongfunctieonderzoek te worden verricht, ten einde de pulmonale bijwerking tijdens het gebruik van dit middel in een vroeg stadium op het spoor te komen.

9. Het verwijderen van de larynx bij de behandeling van patiënten met een sinus piriformiscarcinoom dient te worden heroverwogen, gezien het ontbreken van duidelijke voordelen met betrekking tot de overleving na een dergelijke ingreep.

10. Het belangrijkste voordeel van kernspintomografie boven echografie bij de stadiëring van patiënten met een hoofd-halscarcinoom is gelegen in de betere afbeelding van de primaire tumor en niet in de betere detectie van halskliermetastasen.

11. Door bij doorlopend krediet het maximaal rentetarief te baseren op de kredietlimiet en niet op het uitstaand saldo, wordt de strekking van de wet met voeten getreden.

12. Oort en Simons kunnen worden gezien als ambtelijke "smaakmakers".

Ch.R.Leemans