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Considerations in the Treatment of the Node-negative (N0) Neck in Glottic Carcinomas

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Treatment of lymph node negative (N0) glottic carcinoma has raised numerous controversy for decades. Prevention is one of the oldest axioms in medicine. On the other hand, overtreatment can cause unnecessary harm to patients. This retrospective study was performed in 206 patients having glottic cancers with clinically node-negative (N0) necks. The aim of this assessment is to deal with the diagnosis, predictive factors and surgical therapy of occult metastases of squamous cell cancers originating from the glottic region. The examinations were performed in three phases. Preoperative clinical, histological – and in selective cases – imaging were carried out to separate high-risk patients. Intraoperative cases of open surgery after U-shaped skin preparation up to the hyoid bone with direct inspection of jugular lymph node chain (JLNCh) where the neck was staged. The enlarged suspicious nodes were submitted for

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immediate frozen section. The types of neck dissection were based on the size, shape, number and histological diagnosis of regional nodes. The postoperative additional management was decided according to the results of definitive pathological findings from serial sections of the dissected specimen. Endolaryngeal LASER surgery was carried out in 87 patients based on clinical, histological and imaging criteria. In the course of two years follow-up 2 occult metastases became clinically apparent. At 119 cases open surgery were performed. In 51 patients we could not see enlarged lymph nodes ($N < 2$ mm) with direct examination, and thus the JLNCh remained intact. In 68 patients elective neck dissections (END) were carried out. In cases of extracapsular spread (ECS) and/or multiple nodal involvements additional radiotherapy was given. (Pathology Oncology Research Vol 8, No 4, 257–261)

Introduction

The condition of neck nodes is one of the most decisive prognostic factors of the upper aerodigestive track cancers. There are widely accepted rules how to treat the manifest metastases of neck, but the management of clinically node-negative N0 neck has raised numerous controversial questions for decades, and continues to be a therapeutic challenge.^{1,2,3} The object of this retrospective study is to deal with the diagnosis, predictive factors and surgical therapy of occult metastases of squamous cell cancers originating from the glottic region.⁴

The limited sensitivity of physical examination is well known, but there are many new methods to raise the diag-

nostic accuracy of preoperative neck condition.⁵ The aim is to find reliable predictive clinical, histopathological factors and imaging modalities to identify as many N+ nodes as possible to avoid the under or overtreatment of N0 neck.^{6,7}

Methods and materials

The examination was carried out in three phases:

1. Preoperative – to recognise the high-risk patients
2. Intraoperative – to identify the subclinical but pathologically positive (pN+) nodes
3. Postoperative definitive histological diagnosis from serial sections of dissected specimen to decide whether additional radiotherapy should be given to patients following elective neck dissection (END)

The exact staging – site, size, macroscopic aspect, mobility and histopathological grading of malignancy of glottic cancers with N0 neck nodes are evaluated to draw conclusion to the more endangered patients. For these patients the

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Table 1. Distribution of 206 glottic SCCs with N0 neck Clinical, pathological findings and imaging

T-stage	No. of patients	Histological differentiation of primary tumors			Imaging
		G ₁	G ₂	G ₃	
T _{1a}	61	39	17	5	0
T _{1b}	23	11*	7*	5*	23
T ₂	49	18*	22	9	18
T ₃	54	20	25	9	7
T ₄	19	7	4	8	4
	206	95	75	36	52

*41 patients candidates for endolaryngeal surgery

sensitivity of physical examination can be augmented with computed tomography (CT) scanning, magnetic resonance imaging (MRI), but ultrasound-guided fine needle aspiration cytology (USGFNAC) has recently found to be the most accurate preoperative staging modality of N0 nodal status patients – requiring a well trained specialist, with very expensive and sophisticated devices.^{2,8,9,10} *Table 1* details the distribution of 206 glottic tumors with N0 neck. Beside clinical characteristics of primary cancers in selected cases the histological grade of differentiation and imaging criteria were taken into consideration in the management of N0 patients.^{4,11} In cases of open surgery – entering the neck through an apron shaped skin flap prepared up to the hyoid bone – the intraoperative inspection of jugular lymph node chain (JLNCh) provides the most reliable diagnosis of regional node involvement. The choice of neck management will be based on the size, number and frozen histological finding of first draining sentinel–echelon nodes.^{12,14}

Between 1989–1999, 587 patients were treated surgically with squamous cell cancers (SCCs) of the larynx in our department. Because of manifest metastases and previous radiotherapy, 319 patients were excluded from this assessment. Among the untreated 268 patients, 206 had glottic cancers with clinically negative (N0) necks nodes who met the criteria of this study. Our retrospective evaluation is based on these cases. The distribution of 206 patients according to the therapy of primary tumors is detailed in *Table 2*. For the 61 T_{1a} vocal cord cancers, endolaryngeal *laser surgery* was carried out. Another 26 patients were selected for endolaryngeal treatment from 23 T_{1b} and 49 T₂ glottic tumors based on histological grading and imaging (14). In 119 cases open surgery – entering of the neck – was performed. At these patients the JLNCh was explored. *Table 3* outlines the intraoperative findings of neck. The choice of neck

**Figure 1. Modified radical neck dissection**

management was decided partly on the direct inspection and palpation of neck nodes partly on the results of frozen pathological diagnosis. According to the intraoperative neck staging – 41 modified radical neck dissections (MRND) (*Figure 1* and *Figure 2*.) and 27 selective lateral neck dissections (SLND) in the II-III or II through IV levels were performed.

Histological information of definitive dissected specimens can select the patients for additional neck irradiation, taking the extracapsular spread (ECS) and/or multiple positive nodes into consideration. 8 of 68 patients (12%) received postoperative radiotherapy directed to the neck.

Results

A total of 206 patients with primary SCC of the glottis without clinical evidence of neck metastases were assessed. Treatment of the glottic tumors – in our department – included endolaryngeal laser surgery in 87 patients and open surgery in 119 patients with postoperative additional radiotherapy in 8 cases to the dissected necks. Observation of clinically negative neck nodes was most frequently used for patients with early stage (T_{1a}) primary disease. Subse-

Table 2. Treatment of 206 primary glottic tumors based on prospective examinations

Group	Endolaryngeal laser	Open surgery: 119 cases				All
		VPL	Hemi-laryngectomy	Total laryngectomy	Extended total laryngectomy	
T _{1a}	61	0	0	0	0	61
T _{1b}	14	9	0	0	0	23
T ₂	12	18	19	0	0	49
T ₃	0	0	0	54	0	54
T ₄	0	0	0	0	19	19
Total	87	27	19	54	19	206



Figure 2. Radical neck dissection

quent development of manifest metastases was 1,5% – only 1 case out of 61 patients.¹⁴ In cases of 23 T_{1b} and 49 T₂ glottic cancers the histological grading of differentiation and imaging were used to predict the probability of occult node involvement.^{11,15} Based on these criteria 26 patients from 72 were selected for endolaryngeal laser surgery. We experienced only one manifestation of subsequent metastases in 20 cases of controlled primary site tumors (5%) during two years' watchful waiting. *Table 3.* outlines the intraoperative findings of clinically N0 necks with open surgery in 119 patients. After preparing the "U" shaped skin flap the, JLNCh were explored on both sides of the neck. We would like to emphasise the diagnostic importance and simplicity of intraoperative staging of regional – satellite lymph nodes. According to the size, shape and number of suspicious, enlarged first draining echelon or sentinel nodes, completed by frozen section histology – the neck can be staged.

The intraoperative direct findings of ipsilateral necks with 119 open surgery were as follows: in 51 cases we could not see enlarged lymph nodes – cut-off diameter 2 mm (N< 2 mm). In 31 patients single enlarged lymph nodes were recognised with a diameter between 2 to 10 mm. In 14 cases the only node was larger than 10 mm. In 23 patients multiple nodes were found (Ns > 5 mm) (*Table 3*).

In 45 patients the suspicious lymph nodes were submitted for immediate frozen section and MRND was carried out if metastasis (pN+) was diagnosed. The definitive pathological findings of 41 MRND specimens proved metastasis in 20 patients (49%).¹⁶ The pathologist could not find metastases in 36 frozen specimens, but among them three (8%) proved to be false negative on serial section of the dissected specimen. The cut-off time for our assessment of regional control in cases of glottic cancers with N0 necks was two years, excluding patients with failure at the primary site tumors. We experienced the manifestation of occult metastasis in the course of the two-year follow-up in two cases (2.3%) of the 87 patients treated by endolaryngeal laser surgery. Because of strict observation these metastases were recognised in due time (1 N₁ and 1 N_{2a}): with MRND and irradiation we were able to rescue both of them.

Among the 119 patients having open surgery the intraoperative direct findings were negative in 51 cases (N<2 mm), and therefore the JLNCh remained intact. In the course of observation 3 manifestations of subclinical metastases (6%) became apparent. Two of these patients were lost to follow-up (1 N₁ and 1 N₃). The follow-up contact with patients having open surgery was not as good as it was after the laser operation.

Regional failure in the neck of 68 therapeutic dissections – MRND and SLND – excluded patients with local

Table 3. Open surgery in 119 patients intraoperative clinical and pathological staging

N-stage	No. of patients	Frozen section		Serial section histology	All histopathology	
		Negative	(n) Positive		pN-	pN+
N<2 mm	51*					
N>2-10 mm	31	27	31 4	5 pN+ (1 fals negative)	26	5
N>10 mm	14	9	14 5	7 pN+ (2 fals negative)	7	7
Multiple nodes N>5 mm	23	Not examined		9 pN+	14	9
Total ipsilateral	119	36	45 9	12 pN+	47	21
Contralateral neck	4	3	4 1	1 pN+	3	1

51* lymph node chains remained intact

Table 4. Cumulative rates of neck control for elective dissections and observations

Management of necks	No. of patients	Suitable for analysis	Controlled necks
MRND	41-8*	33	30/33 = 91%
SLND	27-5*	22	20/22 = 91%
Observation	138-14*	124	120/124 = 96.8%
Total	206-27*	179	170/179 = 94.9%

*excluded patients having recurrences at primary sites or lost for other causes

recurrences of primary cancers or deaths from other causes that occurred in 5 of 55 patients (9%). We were able to rescue with RND and irradiation only two of 5 patients (2/5). Cumulative rates of neck control for the group treated by therapeutic neck dissection (n=68) or observation (n=138) in the course of two years follow-up of patients available for analysis decreased 55 and 124 respectively. *Table 4* shows the overall neck disease specific survival after MRND and SLND with rescue treatment is 52/55 (94%), comprising 122/124 (98%) for observation group.

Intraoperatively, enlarged contralateral nodes were observed in 4 cases of 68 dissected necks. In three cases the frozen section histology was negative and SLND in levels II-III were performed. In one case the result of intraoperative histology was positive. SLND in II through IV levels and additional radiotherapy was given to both sides of the neck. Recurrences were not observed.

Comment

The one hundred years of clinical observation has proved that the occurrence of both manifest and occult metastases of glottic cancers are significantly less than of the oral cavity or pharynx tumors, even though the histological character of these tumors is similar to other head-neck cancers. The differences are the result of anatomical and clinical peculiarities e.g. well-defined barriers, different lymphatic system and in a lot of cases early diagnosis due to changes in voice quality, hoarseness and other disorders.

According to the most recent work of Werner et al¹⁷ the incidence of lymphatic spread correlates with the density of initial lymphatic and the proximity of tumour to the laryngeal lymph collectors.^{18,19} Deeply invaded cancers get to the pre-collectors and collectors and the incidence of lymphatic spread become greater. For the advanced glottic cancers with

supra- and/or subglottic infiltration – the rate of involved nodes is nearly the same as at the primary tumors of these regions. Recently we have performed examinations looking for the first draining – sentinel – lymph nodes giving peritumoral patent blue and/or technetium labelled preparation – 1 mG ^{99m}Tc monocolloid. We want to learn the exact location of the echelon nodes of glottic origin tumors. By submitting these nodes for frozen section we hope to detect even smaller occult metastases.²⁰

The question debate for is what to do with the contralateral N₀ neck in cases of ipsilateral – N_{2a}, N_{2b} and N₃ – metastases. Selective neck dissection, irradiation or both of them are recommended.

It is known that the lymphatic stream becomes irregular due to blockage of the pathway on the invaded side of neck, carrying the danger of contralateral metastases. The U-shaped skin preparation over the superficial cervical fascia explores the JLNCh on both sides. With the help of direct inspection and frozen histological finding the surgeon can decide on the treatment strategy during the operation.

We have carried out SLND in the level II-III, and occasionally in level II through IV for five years in patients with clinically negative N₀ necks as part of the open surgery of the primary tumor. Based on opinions from the literature and our own experiences, we have recently performed this type of elective dissection with increased frequency even in cases in which single occult metastases have been found with frozen section histology. In comparison with the MRND the oncological result proved that selective lateral neck dissection is a similarly reliable and effective procedure with better quality of life.

Discussion

The most important requirement of a surgeon is adequate assessment and appropriate management of primary tumors and their regional metastases. The clinical criteria alone could result understaging and consequent under treatment of occult regional lymph node involvement of upper aerodigestive tract.²¹ The rate of clinically false-negative necks analysed in our 206 patients having glottic origin SCCs with N₀ neck based on pathological

Table 5. False negative rates of preoperative clinical examination in 206 patients with N₀ necks based on T-stage of primary glottic cancers

T-stage	No. of patients	Histological diagnosis		Late manifestation	All	Rates %
		Positive	Negative			
T _{1a}	61	–	–	1	1	1.6%
T _{1b} + T ₂	72	6	66	2	8	11.1%
T ₃	54	9	45	–	9	16.6%
T ₄	19	9	10	–	9	47.3%
Total	206	24	121	3	27	13.1%

examination and for two years follow-up, proved to be 1.6% at T_{1a}, 11.1% at T_{1b}+T₂, 16.6% at T₃ and 47.3% in cases of T₄ cancers. Individual additional factors have to be estimated to predict possible subclinical nodal involvement (Table 5). The decision whether endolaryngeal interference or more radical open surgery is necessary to explore the JLNCh is based on clinical, histopathological and, in selected cases, imaging factors. Among the clinical criteria the extent and location of primary tumors are decisive, but the mobility of the vocal cord and the macroscopic aspect of cancers should be taken into consideration as well. Independent from other factors, T_{1a} cancers of the vocal fold uncommonly metastasizes that is why only exact endoscopic examination is required.

In contrast, in cases of advanced T₃-T₄ glottic origin cancers, both manifest and occult lymph node metastases are more frequent. Open surgery is necessary to access to the primary tumor through a wide U-shaped skin incision exploring the jugular lymph chain too. The neck can be staged according to the intraoperative findings – size shape, and numbers of first draining echelon-sentinel lymph nodes, but the frozen section diagnosis provides the main criterion for choice of neck treatment.

In cases of intermediate staged T_{1b} and T₂ glottic cancers with node-negative N0 neck, histological grading of malignancy and additional preoperative examinations with modern devices can only augment the neck staging, and help to recognize the “high-risk” patients, who need more radical treatment. In selected cases of T_{1b} and T₂ glottic cancers, endolaryngeal surgery can be performing, followed by careful observation of primary site and the neck.^{15,22}

It would be relevant to know the biological behaviour of cancer cells, the immune defensive capacity and killer cell activity of the host.¹⁷ Postoperative additional treatment depends on definitive histopathological examination with serial section of the dissected specimen. Patients with multiple metastatic nodes and/or extracapsular spread of tumor receive adjuvant irradiation to the dissected neck.¹⁵ Finally, we hope that in the nearest future, molecular biology, gene research and tumour markers will provide reliable parameters to identify „high risk“ patients to decide on the necessity of elective treatment.

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