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REVIEW ARTICLE

Narrow band imaging in transoral laser microsurgery (TLM) in moderately advanced (T2, T3) glottic cancer

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

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ABSTRACT:

Introduction: Treatment planning in T2, T3 laryngeal carcinoma is based on clinical assessment and radiological imaging. However, to delineate precise mucosal margins for transoral laser microsurgery (TLM), a high class, sophisticated endoscopy is indispensable. Narrow band imaging (NBI) which is an optical filter technology, seems to be a useful adjunctive tool in marking superficial margins.

Materials and Methods: A total of 98 patients diagnosed with HNSCC underwent cordectomies and were enrolled in the evaluation. T2 and T3 stage cancer was diagnosed in 90 and 8 patients, respectively. Intraoperatively, prior to the first laser shot, all anatomical sites were endoscopically evaluated by WL and NBI.

Results: In 10/98 patients (10.2%), 10 samples were taken based only on NBI findings to guarantee better delineation of superficial margins. The result of histology revealed moderate dysplasia in 4 cases (40%), severe dysplasia in 2 (20%), carcinoma in situ in 3 (30%) and hyperkeratosis in 1 (10%). Based on presented results, combined NBI/WL endoscopy reached sensitivity of 100%, specificity 98.88%, positive predictive value 90%, negative predictive value 100% and accuracy 98.98%. All patients had clear margins according to definitive histology results.

Discussion: In this paper, we aimed to assess the usefulness of NBI in intraoperative imaging of laryngeal mucosa and delineation of superficial margins in patients with selected T2 and T3 laryngeal cancer treated with TLM. We proved in our study that with the support of NBI endoscopy, it is possible to increase accuracy of superficial resection margins in patients with moderately advanced laryngeal cancer (T2, T3).

KEYWORDS: narrow band imaging, transoral laser microsurgery, glottic cancer

INTRODUCTION

Transoral CO2 laser microsurgery (TLM) has become a standard treatment for early laryngeal cancer in the recent years. There is a significant number of newly published papers on the expansion of indication criteria for TLM to also include patients suffering from moderately advanced laryngeal cancers (T2, T3) [1]. TLM in those patients has proven to be as successful as an open surgery approach and gives comparable functional and oncological outcomes [1, 2]. Nevertheless, the larger the tumour and the more extensive the TLM, the worse intraoperative exposure of the operated field and more difficult adequate delineation of margins. In this case, negative margins, one of the most important factors determining the success of TLM, have to be wider than ultra-narrow margins currently recommended for T1 tumours [3]. Thus, precise and thorough intraoperative visualization of the ‚real boundary' of unchanged mucosa during organ preservation strategy is required.

In order to improve demarcation of mucosal cancer infiltration, narrow band imaging (NBI) which enhances the visibility of vessels on mucosal surface, is used. Its usefulness in early

detection of larynx cancer has been proven in numerous papers [4–6]. Based on the vascular pattern surrounding lesions invisible in WL endoscopy, but visible in NBI, it is possible to detect small, superficial, multifocal or dispersed lesions [3]. It has been proven that any well-demarcated brownish area with thick dark spots and/or winding vessels are highly probable to be positive in final histological examination [7].

However, even though the usefulness of NBI has been proven in everyday practice in the outpatient setting, there is a scarce experience whether NBI may be a useful adjunct in TLM, especially in guiding surgery in moderately advanced glottic cancer. Thus, the aim of this paper is to assess usefulness of NBI in intraoperative imaging of the mucosa in patients with T2 and T3 glottic cancer treated by TLM. The main predictive factor was the disparity between WL and NBI in breadth of delineated resection margin. The assessment of NBI accuracy in comparison to WL endoscopy was achieved by statistical analysis of primary and secondary predictive variables and outcome variables. Primary outcome variables were: histological results of additional samples taken under the guidance of NBI and 1-year disease-free survival. Age, sex, localisation, T-stage and type of cordectomy were additional predictor variables. Additional samples taken from suspected regions in NBI examination were sent for final histological examination.

MATERIAL AND METHODS

The presented study was prospectively designed and conducted at the Poznan University of Medical sciences, Department of Otolaryngology, a tertiary referral centre, between 2012 and 2017. A total of 98 consecutive patients with glottic HNSCC, who met the inclusion criteria and underwent cordectomies, were enrolled in evaluation and analysis. Among 90 patients with stage T2 cancer, 81 (90%) were men and 9 (10%) women. In T3 stage, there were 6 (75%) men and 2 (25%) women. Cordectomies of type V and VI were performed in 59 and 31 patients, respectively.

Inclusion criteria were defined as follows: 1. glottic squamous cell carcinoma confirmed in pathology; 2. TNM evaluation according to current guidelines – tumour stage T2 or T3 [8, 9]; 3. treatment with TLM; 4. cordectomy type V–VI with curative intent. The group of enrolled T2 glottic cancer patients was selected strictly: high volume or AC infiltrating tumours or patients with impaired vocal fold mobility, previously categorised as T2b and much closer to T3 than to T2 staging. Patients with less advanced T2 tumours, treated by cordectomy I–IV, were excluded. The analysed variables were age, sex, T staging, localisation of tumour, type of cordectomy and final histology results of whole specimen and NBI guided additional samples.

All procedures performed were in accordance with the ethical standards of the institutional research committee – Bioethics Committee of the XXX - and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Research did not include clinical trials. All patients provided written informed consent prior to surgery.

PREOPERATIVE WORK-UP

Rigid endoscopic examination of the larynx, transnasal flexible endoscopy (Olympus Medical System Corporation, Tokyo, Japan) with white light (WL), NBI and a preoperative CT scan were performed. During endoscopy, tissue samples were collected and sent for histological examination.

SURGICAL TECHNIQUE

All patients underwent TLM under general anaesthesia via endotracheal intubation with Laser-Flex tube. Pre- and intraoperatively, all anatomical sites were endoscopically evaluated by WL and NBI using rigid 0° angled telescope. In all cases, types V and VI cordectomies (according to the European Laryngological Society classification) were performed. The decision regarding extension of surgery was based on imaging, pre- and intraoperative information obtained in WL endoscopy and consequently, from NBI endoscopy. The final margin was delineated with NBI guidance before the first laser shot.

In 10/98 patients, the peripheral part of the margin was suspected only in NBI, thus, 10 samples were taken based on NBI findings, beyond WL scope (Fig. 1, Fig. 2). Any well-demarcated brownish area with thick dark spots and/or winding vessels was considered as suspected in NBI. All 10 specimens were sent for intraoperative pathology.

In all patients, surgical specimens were marked with black ink at one margin and sent for definitive pathological analysis. Margins greater than 3 mm were classified as negative, less than 3 mm, as positive.

In patients with positive final margins, the study protocol included second endoscopy under general anaesthesia combined with tissue sampling. Depending on that final information obtained from the second endoscopy, followed by positive pathology, successive TLM or open partial laryngectomy were performed. All patients were enrolled into follow-up scheme in the outpatient setting. Those with free margins were assessed in videolaryngostroboscopy and transnasal flexible endoscopy with WL and NBI every 8 weeks in the first year after cordectomy and every

16 weeks in the following year. Additionally, all patients were evaluated by radiological examination (CT) every six months.

STATISTICAL ANALYSIS

Statistical analysis was performed using chi-squared test for independence and Student's t-test. The level of significance was assumed at $\alpha=0.05$. All calculations were performed with Statistica 13 and MS Excel 2010 applications.

RESULTS

The examined group consisted of 98 patients, 87 men (88.78%) and 11 women (11.22%), with mean age 64, 64.3, and 62.0 years, respectively. There was no statistically significant difference in age in relation to sex [t (96) = 0.858; p = 0.3927]. Ninety (90) patients suffered from T2 (91.84%) and 8 from T3 (8.16%) stage cancer. In 67 patients (68.37%), the tumour was located in the anterior commissure, in 31 (31.63%), in other sites (vestibular fold, posterior commissure or laryngeal ventricle).

Out of 98 patients, 35 underwent cordectomy type Va, 14 type Vb, 5 type Vc, 8 type Vd – 35.72%, 14.29%, 5.10% and 8.16%, respectively. In 5 cases, there was a need for extended cordectomy (5.10%). Thirty-one patients underwent cordectomy type VI (31.63%). There were 2 patients with cordectomy type V, who underwent extended resection, all comprising in cordectomy type Va,c,d; (1 with Va,b,c and 1 with Va,b,d and epiglottis). Eighty-four (84) patients had their first cordectomy (85.71%), 13 second (13.26%) and 1 third (1.03%). All patients had clear margins according to definitive histology results.

During follow-up, local recurrence was observed in 5/98 (5.10%) male patients, and in one of them, a second relapse developed. The age of patients with recurrence ranged from 55 to 75 years, with a mean 68 years. Four out of 5 (80%) relapses occurred in AC, 1/5 (20%) in subglottis. Four patients were classified as T2 (80%) and one as T3 (20%); 3 underwent Va-type cordectomy (60%), 1 Vb-type cordectomy (20%) and 1 extended Va,c,d cordectomy (20%). In any of those patients NBI guided endoscopy showed suspicious surgical margins and final HE pathology showed free margins.

There was no statistically significant relationship between gender and cancer stage (p=0.19775), cancer localisation (p=0.72027), type of cordectomy (p=0.58259), number of surgical procedures (p=0.84865), histology (p=0.64437), follow-up (p=0.41439) and number of additional samples taken under NBI (p=0.89700).

Fig. 1. Glottic cancer in WL endoscopy.

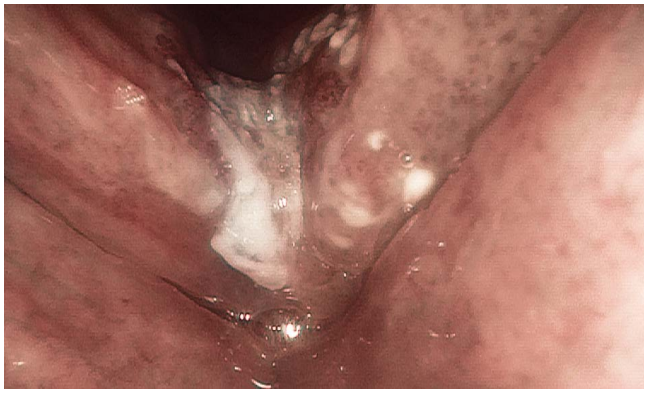

Fig. 2. Glottic cancer in NBI endoscopy.

There was a statistically significant relationship between T cancer stage and cordectomy type (p<0.00001). Stage T3 occurred only in patients who underwent Va type cordectomy (8.57%) and in all patients with extended V-type (100%) cordectomy.

In 10 patients (10.20%), additional samples were taken under NBI to delineate safe superficial margins during TLM. Suspected areas in NBI were otherwise invisible in WL endoscopy. The location of additional NBI guided samples was as follows: 5 anterior commissure, 2 right vestibular fold, 2 subglottic region and 1 left vocal fold. There was no statistically significant relationship between the number of additional samples in NBI and tumour localization or T stage (p=0.90673).

Histology results of additional samples taken under NBI are presented in Table I. Out of 10 additional NBI guided samples, in 4 patients histology revealed moderate dysplasia, in 2 severe dysplasia, in 3 carcionoma in situ, in 1 hyperkeratosis.

To calculate the specificity, negative predictive value, and accuracy, as true negatives we considered those patients where

Tab. I. Histology results of additional samples taken under NBI, otherwise invisible in WL.

ADDITIONAL SAMPLE BY NBI	DYSPLASIA MODERATE	DYSPLASIA SEVERE	CARCINOMA IN SITU	HYPERKERATOSIS	TOTAL
Anterior commissure	2 (20%)	1 (10%)	2 (20%)	0 (0%)	5 (50%)
Right vestibular fold	1 (10%)	1 (10%)	0 (0%)	0 (0%)	2 (20%)
Subglottic region	1 (10%)	0 (0%)	0 (0%)	1 (10%)	2 (20%)
Left vocal fold	0 (0%)	0 (0%)	1 (10%)	0 (0%)	1 (10%)
Total	4 (40%)	2 (20%)	3 (30%)	1 (10%)	10 (100%)

NBI did not suggest intraoperatively any additional biopsy or resection beside standard margins sampling and who had a persistently negative NBI follow-up evaluation. Based on presented result,s combined NBI/WL endoscopy reached sensitivity 100% (95% CL= 66.37% to 100%), specificity 98.88% (95% CL= 93.90% to 99.97%), positive predictive value 90% (95% CL= 56.17% to 98.44%), negative predictive value 100% and accuracy 98.98% (95% CL= 56.17% to 98.44%) [Tab. I.]

There was no statistically significant relationship between the results of final histology of additional samples in NBI-guided samples and age, gender tumour localisation, stage T cordectomy type local recurrence, number of surgical procedures.

DISCUSSION

One of the most important factors determining success of oncological surgery is achieving negative margins, and therefore precise and thorough intraoperative visualisation of lesion during non-surgical organ preservation strategy is required to obtain them [10]. Several former studies have emphasised the importance of adequate resection margin for recurrence-free survival and prognosis of patients with head and neck squamous cell carcinomas [11, 12]. The surgical margin is defined as a non- tumourous tissue separating tumour tissue from the cutting line. Width of the surgical margin depends on the primary tumour site and primary T-stage [8]. The most important factor determining the extent of resection is intraoperative microscopic assessment of the surgical margins. Depending on the localisation of the margin, we categorise them as mucosal, superficial and deep margins. It is widely accepted to classify margins as clear (more than 5 mm), close (1–5 mm), involved (less than 1 mm) [9].

Transoral CO2 microsurgery (TLM) has become a standard treatment for early laryngeal cancer in the recent years. Compared to external open surgery approach, TLM enables the surgeon to preserve more healthy tissue [13]. Thus, it results in better functional outcomes with comparable oncological results. Even though TLM is not widely recommended for intermediate-advanced laryngeal cancer, a review of the literature [1, 14, 15] shows encouraging conclusions that oncological outcomes are comparable with the standard external approach or RT and the majority of patients achieve better functional results such as faster recovery and avoidance of tracheostomy [16].

However, TLM may result in difficult specimen assessment as a consequence of thermal damage to excised tissues [17]. Therefore, close cooperation of the pathologist and surgeon is necessary. According to available literature, the accuracy of margin may be increased by intraoperative use of NBI. It facilitates identification of superficial capillaries and neoangiogenesis in abnormal mucosa [18]. NBI enhances visibility of pathological vessels in precancerous and cancerous lesions by improving the contrast of mucosal and submucosal vessel loops. Thus, by means of NBI, it is easier to visualise cancer foci around the main lesion invisible in WL endoscopy, due to their isochromatic and flat shape nature.

To our knowledge, this is the first paper that assesses intraoperative use of NBI to improve achieving negative margins in moderate advanced laryngeal cancer (T2–T3). There are three papers proving superiority of NBI over WL endoscopy alone, but only in early-stage glottic cancers [10, 19, 20]. Plaat et al. [19] proved that intraoperative use of NBI resulted in significantly lower rate of recurrences, whereas Grafollo et al. [10] showed that NBI increases the accuracy of neoplastic superficial spreading evaluation during TLM. Klimza et al. [20] confirmed these findings in a group of 44 patients showing that NBI seems to be even more useful in patients with T2 stage cancers.

In this paper, we compared the number of samples taken during TLM from suspected regions in NBI examination, which were beyond the scope of white light (WL) endoscopy and correlated these findings with those of surgical margins' histological examination . We proved that NBI supports the decision--making process during surgery, as in 9 out of 10 NBI-guided cases presented in this study, histology proved to be positive.

Our study has a number of limitations. One of them is a single institution setting. There was a significant heterogeneity

in relation to sex of enrolled patients (nearly 90% being men). Another limitation of NBI in moderate advanced tumours is the potential of the method to assess superficial margins, although deep margins are also crucial in this group of patients. Another restriction is lack of control group treated only by assistance of WL alone. Due to the fact that the prognosis of moderate advanced laryngeal cancer is serious, we did not divide the group into such with or without NBI as to not decrease chance eradication, based on proofs in the available medical literature [10, 19, 20]. The potential retrospective collected group would be of little value anyway. Although performing TLM in patients with moderate advanced laryngeal cancer (T2, T3) still remains controversial, we proved in our study that with the support of NBI endoscopy, it is possible to increase the accuracy of superficial resection margins. A negative margin status influences the overall survival of treated patients and reduces risk of second-look surgeries due to positive margins in initial surgery.

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