Is NBI-Guided Resection a Breakthrough for Achieving Adequate Resection Margins in Oral and Oropharyngeal Squamous Cell Carcinoma?

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Abstract

Objectives: Obtaining free resection margins is the main goal of oncological surgeons. Narrow-band imaging (NBI) has been recently used to help define resection margins in transoral laser microsurgery for laryngeal carcinoma. The aim of this study was to evaluate the effect of intraoperative NBI in defining the surgical resection margins of oral and oropharyngeal cancers.

Methods: Between January 2014 and March 2015, NBI was used intraoperatively after an initial definition of resection margins with white light in 26 patients (group A). The rate of superficial positive margins at definitive histology was compared with that of a historical cohort of 44 patients (group B) previously managed without the use of intraoperative NBI.

Results: A statistically significant reduction in the rate of positive superficial margins was observed at definitive histology in group A ($P = .028$). NBI helped to identify the presence of dysplasia and cancer around the visible tumor not otherwise detectable with visual examination alone.

Conclusions: NBI could be a useful tool for obtaining free resection margins in oral and oropharyngeal carcinoma.

Keywords

narrow-band imaging (NBI), oral cancer, oropharyngeal carcinoma, OSCC, OPSCC, adequate margins

Introduction

Oral squamous cell carcinoma (OSCC) accounts for 90% of oral malignancies and represents the sixth most common cancer worldwide.[1] The overall objective of curative surgery in oncology is the excision of the tumor mass, with macroscopically adequate surgical margins[2] as verified by the pathologist at definitive histological examination. Although the concept of margin adequacy may seem straightforward, considerable confusion surrounds its definition, with several differences in the recommended minimum extent of excision to be performed: some studies propose a macroscopic margin of 1 cm and others of 1.5 cm or 2 cm. Margin adequacy is still a matter of debate among pathologists as well.[3]

Obtaining uninvolved margins at histological examination is nonetheless the gold standard for surgeons because the presence of dysplasia or carcinoma in situ at the surgical margins has been shown to be associated with a higher incidence of local recurrence.[4] Unfortunately, this appears particularly difficult in consideration of the peculiar frequent growth pattern of OSCC and oropharyngeal squamous cell carcinoma (OPSCC), defined as the "field cancerization" phenomenon. This concept assumes that multiple, unrelated, precancerous lesions may exist adjacent to the original tumor mass, each one bearing the potential to develop into a new tumor.[5-7] Identification of this "field at risk" surrounding the tumor is very challenging by routine examination, but substantial progress has been recently made with the development and optimization of

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innovative imaging techniques allowing improved visualization of the superficial extension of the tumor.[8-10]

Among these diagnostic tools, narrow-band imaging (NBI) has widely demonstrated its effectiveness in helping detect superficial mucosal lesions of the oral and pharyngeal mucosa.[8,9] NBI is a video endoscopic system with narrow band filters that allows for the passage of only 2 specific bands of the visible spectrum that correspond to the absorption peak of hemoglobin. The filtered wavelengths enhance the microvascular abnormalities associated with the preneoplastic and neoplastic changes of the mucosal lining of the upper aerodigestive tract.[11] Its use in "biologic endoscopy"[12] has already proved its value in defining the superficial tumor extent and helping delineate resection margins.

The surgical management of OSCC and OPSCC would greatly benefit from a more accurate assessment of superficial spread of the tumor and delineation of its resection margins in order to spare patients, as far as possible, a second surgery for margin revision or adjuvant therapies (ie, radiotherapy) in the event of positive margins.

To the best of our knowledge, few studies have been carried out to investigate the impact of the intraoperative use of NBI on the incidence of positive superficial surgical margins in the treatment of OSCC and OPSCC, and none of them has focused on the evaluation of margin status at definitive histological examination. The aim of this prospective study with historic comparison was to verify the impact of intraoperative NBI on reducing positive superficial resection margins at definitive histological examination in the resection of OSCC and OPSCC.

Materials and Methods

This study was conducted in accordance with the Declaration of Helsinki and approved by the Cattinara Hospital ethics committee (Report No. 58). All patients gave their written informed consent.

Between January 2014 and March 2015, 26 patients (group A) affected by a biopsy-proven OSCC (n = 12) or OPSCC (n = 14) were selected among candidates for surgery established by a multidisciplinary panel. Inclusion criteria were as follows: age between 18 and 90 years; no previous surgery, radiotherapy, or chemotherapy for head and neck cancers; and no cancers located in the lip, hypopharynx, or larynx. Clinical staging (cTNM) was obtained after clinical examination with computed tomography (CT) and magnetic resonance imaging (MRI), in accordance with the NCCN guidelines (National Comprehensive Cancer Network). There were 11 women and 15 men; their age ranged from 44 to 85 (mean = 66 years).

The protocol followed was the same as previously reported.[13] Prior to surgery, the primary tumors were visualized under high-definition white light (HD WL) and NBI (Visera Elite system OTV-S190 video processor and

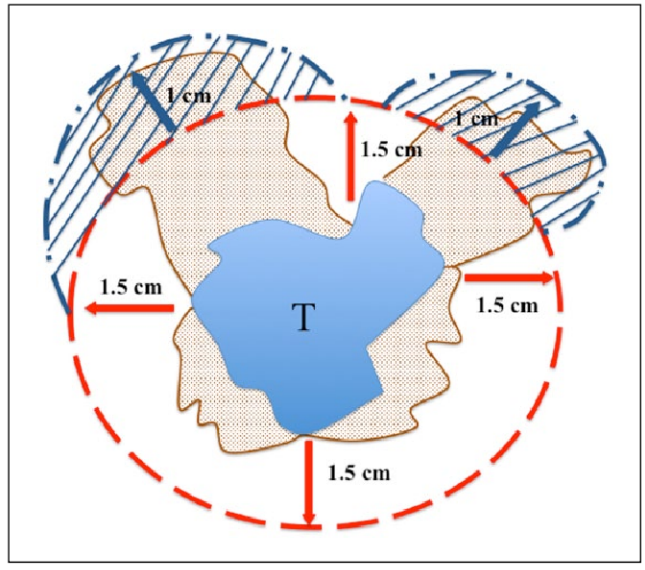

Figure 1. T indicates the tumour bulk. The (red) dashed line is the white light (WL) drawing at 1.5 cm from the macroscopic margin defined both by visualization and palpation. The (brown) dotted area is the area with intrapapillary capillary loop (IPCL) alterations visualized with narrow-band imaging (NBI). The (blue) dashed-dotted line is the NBI-guided drawing, in this example placed at 1 cm from the WL drawing. Between the (red) dashed and (blue) dashed-dotted lines, there is the NBI-guided enlargement (oblique blue lines).

CLV-190 light source, OTV-S7Pro-10E HDTV camera; Olympus Medical Systems Corp, Tokyo, Japan) with rigid endoscopes with a viewing angle of 70° for the oropharynx or an angle of 0° for the oral cavity. On the day of surgery, after general anesthesia and preparation of the surgical field, a first definition of the resection margins was obtained with an electric scalpel, using a ruler to help maintain a distance of 1.5 cm from the macroscopic lesion boundaries defined visually and by palpation. Then, NBI was used to assess the superficial extension of the lesion for the known alterations of the intrapapillary capillary loop (IPCL) (dilatation and crossing, elongation and meandering, or pattern destruction and angiogenesis[14-16]) and for the presence of brown dots,[8,9] which can underlie histological changes. This evaluation increased the operating time by an average of 5 minutes. The different steps were video recorded.

If the use of NBI revealed 1 or more areas displaying IPCL alterations or brown dots not included within the previously drawn WL tattoo, these were outlined and included in the resection. The distance between the macroscopic lesion boundaries and the NBI-guided tattoo was measured (Figure 1, Figure 2). Resections were always performed transorally using a Ligasure® device, both for oral and oropharyngeal cancers. The resected specimen was fixed onto a piece of cork with insulin needles to minimize shrinkage[17-19]; sutures of different lengths were placed for correct

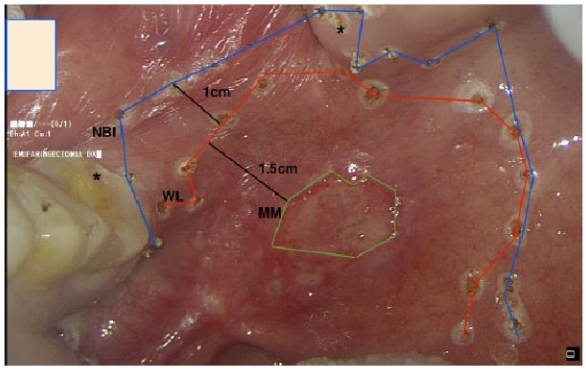

Figure 2. An intraoperative photo of a squamous cell carcinoma of the right soft palate. The inferior and superior dental arches are indicated (*). The green line indicates the gross tumor edge; the red line is the first drawing obtained with white light (WL) by visual inspection and palpation 1.5 cm from the macroscopic margins (MM); the blue line is the narrow-band imaging (NBI)–driven drawing, in this case 1 cm from the one obtained with WL.

orientation and to indicate the NBI-guided enlargement; an explanatory drawing with specific notes was prepared, and the specimen was then sent to a dedicated pathologist for histological evaluation. The pathologist's response was supplied with a drawing to indicate any definitive margin involved by cancer or dysplasia (mild, moderate, and high grade) and to signal the presence of dysplastic areas around the main tumor. All the surgical margins (superficial and deep) were assessed, and the distance between the tumor and the margins was measured. Margins were defined as "clear" when >3 mm, "close" when 0.1 to 3 mm, and "involved" only when clearly infiltrated by neoplastic cells.

This group of patients was compared with a historical group of 44 patients (group B) with the same inclusion criteria (ie, biopsy-proven diagnosis of OSCC or OPSCC, not previously treated), operated at our institution between December 2011 and December 2013 without the intraoperative use of NBI to guide the tumor resection, and therefore maintaining a 1.5 cm margin from the macroscopic lesion boundaries defined visually and by palpation.

The main endpoints of our study were: (1) to compare the rate of positive superficial margins at extemporaneous examination in the 2 groups and (2) to compare the rate of positive superficial surgical margins at definitive histology in the 2 groups so as to assess the value of NBI in achieving clear margins in the resection of OSCC and OPSCC.

The 2 groups were compared for age, gender, tumor location, and pT category: *t* test or no parametric tests were used for continuous variables; the chi-square test for independence or the Fisher exact test was used for categorical variables. The Fisher exact test was used to compare the rate of positive margins between the 2 groups, both at extemporaneous and definitive histology. The threshold of statistical significance was set at a *P* value of .05. Statistical analysis was performed with Graph Pad In Stat 3 Ink.

Results

Patient demographics, pT category, tumor location, and histological details of groups A and B are summarized in Table 1. The 2 groups were treated by the same surgeon who used the same surgical approach (transoral). The 2 groups were comparable in terms of tumor location and T dimension (T1-T4), even though there was a greater proportion of T1 and T2 cases in group B (77.3%) than in group A (50%) since group B was a historical comparison group and the patients were not selected to avoid selection bias. Despite the greater proportion of early lesions in group B, for which obtaining adequate surgical margins should be simpler, the use of NBI resulted in a statistically significant reduction of positive margins in group A.

In group A, 19 (73.1%) patients had all (superficial and deep) negative margins, 3 (11.5%) showed superficial positive margins (2 dysplasia and 1 carcinoma), and 4 patients (15.4%) had positive/close deep margins, which cannot be detected by NBI and were therefore excluded from the analysis. In group B, 25 (56.8%) patients had all (superficial and deep) negative margins, and 16 patients (36.4%) presented positive superficial margins (7 dysplasia and 9 carcinoma). Fisher's exact test revealed a statistically significant difference in the rate of positive superficial margins between groups A and B at definitive histology ($P = .028$); no statistically difference in terms of superficial positive margins was found at extemporaneous examination ($P = ns$).

In group A, 23 patients underwent a NBI resection enlargement because of the presence of NBI positive areas around the WL drawing; this enlargement was confirmed to contain histological alterations in 19 cases (2 mild, 2 moderate, 3 high grade dysplasia, and 12 carcinoma); 4 cases were considered false positive because hyperplasia and parakeratosis were seen at histology.

The areas displaying an IPCL alteration on NBI were located no more than 11 ± 3 mm from the first margin drawn with WL, so this measurement (11 ± 3 mm) corresponded to the mean NBI resection enlargement. Consequently, in certain areas the resection was performed at 25 ± 4 mm from the macroscopic edge of the tumor.

Discussion

Although the impact on local recurrence of margin status in OSCC and OPSCC is still a matter of debate,[20-26] the vast majority of studies correlating local recurrence rate with margin status in OSCC found a strong and independent correlation between the 2 parameters.[20-24,27] Thus, the main goal in oncology remains to achieve complete excision of

Table 1. Patients' Demographic Characteristics, Tumor Location, pT Category, and Margin Status of Groups A and B.

	Group A (N = 26)	Group B (N = 44)	Difference Between Group (*P* Value)
Age, mean (range), y	66 (44-85)	67 (48-85)	*ns*
Sex, No. (%)			*ns*
Male	15 (57.7)	30 (68.2)	
Female	11 (42.3)	14 (31.8)	
Tumor location, No. (%)			*ns*
Oral cavity	12 (46.2)	30 (68.2)	
Oropharynx	14 (53.8)	14 (31.8)	
pT category, No. (%)			*ns*
T1	4 (15.4)	17 (38.6)	
T2	9 (34.6)	17 (38.6)	
T3	10 (38.5)	8 (18.2)	
T4a	3 (11.5)	2 (4.6)	
Margin status, No. (%)			
Extemporaneous superficial margins +	3 (11.5)	11 (25)	*ns*
Definitive superficial margins +	3 (11.5)	16 (36.4)	.0282

Abbreviation: *ns* = nonsignificant.

the cancer because the presence of residual tumor may lead to a higher rate of local recurrences.[27] There seems to be little consensus on the treatment of positive margins; if a surgical enlargement is possible thanks to the accessibility of the sites, many surgeons will opt to re-excise tissue, especially if this would abrogate the need for adjuvant radiotherapy[2] (in the cases in which radiotherapy is not mandatory for advanced stage), which negatively impacts the patients' quality of life.[28]

Furthermore, there is no international consensus in considering the presence of carcinoma in situ or dysplasia as a positive margin, as underlined in a survey by Meier et al.[29] At our institution, we consider a margin to be positive in the presence of either carcinoma or dysplasia, and in both cases we carry out a surgical enlargement, if possible.

Different methods have been suggested for achieving adequate resection margins in OSCC and OPSCC, from staining with Lugol's iodine solution[30-32] to the use of intraoperative touch imprint cytology.[33] Optical coherence tomography has been reported as feasible in differentiating between positive and negative surgical margins.[34] However, all these techniques still remain investigational and not widely accepted.

In our experience, the use of NBI pre- and intraoperatively proved to be a useful and easy-to- handle diagnostic tool enabling better definition of the superficial extension of OSCC and OPSCC. It helped to detect a larger area around the visible tumor involved by histological alterations (dysplasia or cancer), resulting in a resection enlargement of 11 ± 3 mm. The comparison between the rates of positive superficial margins between patients treated without and with NBI showed a statistically significant reduction from 36.4% to 11.5% ($P = .028$) in the latter group. However, it should be emphasized that even though the 2 groups in our study were statistically comparable for tumor location and for tumor size (T1-T4), group B comprised more early tumors (T1 and T2). This is due to the choice of a historical cohort as a control group, which was considered as a whole without extracting specific cases so as to avoid selection bias. Although intuitively one could think that obtaining free resection margins is simpler for smaller tumors, in our study we obtained a significant reduction in positive resection margins in group A despite it containing proportionally larger tumors than those in group B.

Similar results on the effectiveness of NBI have been reported for the larynx in a study comparing 2 groups of patients affected by Tis and T1a glottic cancers treated with transoral laser microsurgery (TLM) with or without NBI[35]: the possibility of precisely delineating the peripheral resection margins in laryngeal tumors had been previously underlined.[12]

OPSCC has been addressed in 2 different case series. Patsias et al[36] showed that the use of high-resolution microendoscopy imaging during transoral robotic surgery (TORS) might provide real-time histological assessment of tumor margins, while Tateya et al[37] evaluated the feasibility and efficacy of NBI in determining the extent of OPSCC resection by TORS and found that it enabled an estimation of the horizontal extent of the superficial lesion and detection of surrounding superficial lesions normally not identified without NBI.

Vicini et al[38] demonstrated a statistically significant difference in the rate of negative surgical margins at frozen section analysis in 2 groups of patients treated with TORS with or without the intraoperative use of NBI. In our study, the difference was not statistically significant at extemporaneous examination even though the proportion of negative margins at frozen section analysis was similar (88.5%) to that of

Vicini et al's[38] study (87.9%). By contrast, the difference between the 2 groups in our study was significant if we consider definitive histology of the surgical margins. Consistent with the international literature,[39,40] we believe final histology to be more reliable than frozen section and the only parameter having therapeutic and prognostic implications.

Molecular evidence has recently been provided that surgical margin definition using NBI resulted in more complete OSCC excision than conventional WL panendoscopy, and proponents advocate greater NBI uptake for establishing surgical margins in OSCC resections in order to leave less dysplastic and malignant residual tissue and increase surgical success rates.[41]

As reported by Hinni et al,[2] surgeons are more likely to encounter difficulties in achieving adequate margins in deep connective tissue planes as compared with mucosal margins. It should be kept in mind that the wavelengths used by NBI are effective in enhancing the visualization of the mucosal and submucosal vasculature only, thus allowing a more precise definition of only the superficial margins, with no adjunctive information of the adequacy of deep margins.[42]

The use of NBI has some organizational implications: a dedicated team should be created because the presence of a learning curve in the application of NBI has been reported,[42] and the surgeon should take this into account before basing surgical resections on NBI appearance; there should be a close relation between the surgeon and a dedicated pathologist; a preoperative NBI evaluation should be obtained for an initial assessment of tumor extent so as to limit the increase in operating time to only 5 minutes on average.

The presence of blood in the surgical field prevents NBI evaluation, so care should be taken to avoid bleeding, which is why we recommend to perform NBI before any surgical action that can alter mucosal vascularization.

NBI appears to be an effective diagnostic tool for optimizing the assessment of superficial tumor spread by helping to detect pre-cancerous areas (dysplasias) and/or cancer around the clinically visible tumor bulk intraoperatively and thus to achieve adequate resection of both and maximize the number of free resection margins at definitive histological examination. In our experience, we detected the presence of NBI positive areas around the first drawn tattoo in 23 of the 26 patients considered; even though in 4 cases these areas presented no histological alterations and might thus be considered unnecessary resection enlargements, we believe that the possibility to discover and resect dysplastic or cancerous areas not otherwise detectable in 19 cases is worthy of greater emphasis.

Albeit preliminary and obtained from a small patient sample, our results challenge the dogma that maintaining a resection margin of 1.5 cm from the macroscopic front of the tumor always represents the best compromise to obtain oncological radicality.[43] By contrast, our study shows that areas displaying histological changes may be present beyond 1.5 cm from the macroscopic front of the tumor and that these areas can be identified and removed in real time by using NBI. We consider NBI to be a first valuable attempt to surgically address the problem of the field cancerization.

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Declaration of Conflicting Interests

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