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Benefits and drawbacks of Open Partial Horizontal Laryngectomies, Part B: intermediate and selected advanced stage laryngeal carcinoma

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3 **Benefits and drawbacks of Open Partial Horizontal**
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6 **Laryngectomies, Part B: intermediate and selected advanced**
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8 **stage laryngeal carcinoma**
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12 (presented at the 5th World Congress of International Federation of Head and Neck
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Abstract

Background. Cancer of the larynx in the intermediate/advance stage still presents a major challenge in terms of controlling the disease and preserving the organ. Among therapeutic options, open partial horizontal laryngectomy (OPHL) is proposed as function-sparing surgical technique.

Methods. We analyzed the clinical outcomes of 555 patients with laryngeal cancer staged pT3–pT4a who underwent OPHL.

Results. 5 years overall survival, disease-free survival, locoregional control, local control, laryngectomy-free survival and laryngeal function preservation rates were 84.6%, 84.2%, 86.3%, 90.6%, 93.3% and 91.2%, respectively. Disease-free survival, locoregional control and laryngeal function preservation prevalences were significantly affected by pT4a staging (68.1%, 71.7% and 78.0% respectively), while pN+ influenced only disease-free survival ($\leq 72.6\%$) and locoregional control ($\leq 79.6\%$).

Conclusions. in cases of laryngeal tumors at intermediate and selected advanced stage, also with sub-glottic extension, the choice of OPHL with a modular approach can be considered effective in terms of prognostic and functional results.

Introduction

The first and basic common step in curing laryngeal squamous cell carcinoma (SCC) is assessment of the type, extent and pattern of the neoplasm. The second step is choice of treatment that should be as conservative as possible, above all for surgical approaches. In fact, after the first total laryngectomy performed by Prof. Theodor Billroth on 31 December 1873,¹ the problems of voice preservation and airway restoration spurred surgeons towards the development of organ/function sparing, though oncologically sound, procedures. Nowadays their employment represents the common trend among therapeutic approaches,²⁻⁴ having significantly increased the survival from laryngeal SCC, although poor prognosis and loss of larynx functionality are still common features of the disease, especially in its advanced stage. Generally, open neck demolitive or “partial functional laryngectomies” represents the surgical procedure of choice, the greater part of which, above all in Europe, is represented by open partial horizontal laryngectomies (OPHL). Literature addressing this topic is rich, and a number of surgical procedures have been described coping with the different patterns of endolaryngeal tumor site and spread.⁵⁻⁹ Recently, the European Laryngological Society proposed a classification of the more commonly adopted procedures according to extent of resection,¹⁰ including three types of OPHL: Type I - supraglottic, Type II - supracricoid and Type III - supratracheal. The latter, described in 2006, is based on resection of the entire glottic and subglottic sites and of the thyroid cartilage, sparing both or at least one functioning cricoarytenoid unit.¹¹ In our practice, extending the limits of resection, OPHL Type III enlarges the indications suggested by National Comprehensive Cancer Network (NCCN) and Italian Head and Neck Society (IHNS) guidelines for the treatment of laryngeal cancer with conservative surgery (T1-T2, N0 or selected T3): some problematic glottic cT3 (i.e. sub-glottic extension

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3 and cricoarytenoid joint invasion) and some supraglottic cT3 (i.e. large transglottic
4 extension) became now manageable by OPHL, showing promising oncological and
5 functional results.^{12, 13} Even, albeit with great caution, the same practice can be considered
6 as up-front option in very restricted cT4a cases, with minimal anterior extralaryngeal
7 extension, when it is reasonable to expect an exclusive treatment.
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14 In this study, we present a multicentric retrospective outcome analysis of 555 patients with
15 supraglottic/glottic laryngeal SCC in the intermediate/advanced stage, managed by OPHL
16 type II or III. The analysis was conducted over a 16-year period, during which organ-
17 preservation protocols with chemoradiotherapy or total laryngectomy were applied as
18 conventional therapeutic options for these types of locally advanced tumors.^{2, 4}
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32 **Material and Methods**

33 *Patients*

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36 All patients were from the Hospital of Vittorio Veneto, Treviso, or the Martini Hospital of
37 Turin. Selection was based on routinely performed clinical assessment lasting 3 weeks
38 prior surgery, in order to evaluate the superficial and depth extent of the tumor, as
39 previously described.¹²
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45 Inclusion criteria were histological diagnosis of intermediate/advance stage glottic or
46 supraglottic laryngeal SCC, with Karnofsky index¹⁴ higher than 80.
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50 Exclusion criteria were severe diabetes mellitus, severe bronchopulmonary chronic
51 obstructive disease, neurological problems impairing the ability to expectorate and/or
52 swallow, or severe cardiac disease. Advanced age, an important cut-off for relative
53 surgical indication,¹⁵ has not been considered, in itself, an exclusion criterion.
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Surgery

After informed consent had been obtained, 555 patients were selected to undergo a modular function sparing surgical approach from January 1, 1995 and December 31, 2011. Ninety-six patients (17.2%) included in the present analysis had been treated previously for laryngeal carcinoma by CO₂ transoral laser surgery (38 of 96; 39.5%), (chemo)-radiation therapy (35 of 96; 36.4%), open partial laryngectomy (8 of 96; 8.3%) or cordectomy (15 of 96; 15.6%).

The tumors were glottic in 506 patients and supraglottic in 49 patients. The vocal fold mobility was: 30 cases with normal or impaired vocal cord mobility (19 supraglottic pT3 and 11 supraglottic pT4a), 443 cases with fixed vocal cord and mobile cricoarytenoid joint (15 supraglottic pT3, 4 supraglottic pT4a, 152 transglottic pT3, 207 glottic pT3, and 65 glottic pT4a) and 82 cases with fixed vocal cord and cricoarytenoid joint (48 glottic-subglottic pT3, 33 glottic pT4a, and 1 transglottic pT3).

Resections were classified according to the European Laryngological Society Classification.¹⁰ In particular, only Type II and III OPHLs were performed: Type IIa (supracricoid partial laryngectomy/crico-hyoido-epiglottopexy) = 62 (11.1%), Type IIa + ARY = 243 (43.8%), Type IIb (supracricoid partial laryngectomy/crico-hyoido-pexy) = 32 (5.8%), Type IIb + ARY = 117 (21.1%), Type IIIa (supratracheal partial laryngectomy/tracheo-hyoido-epiglottopexy) = 9 (1.6%), Type IIIa + CAU = 82 (14.8%), Type IIIb (supratracheal partial laryngectomy/tracheo-hyoido-pexy) = 4 (0.7%), Type IIIb + CAU = 6 (1.1%), where "+ARY" represents the removal of one arytenoid and "+CAU" the removal of one cricoarytenoid unit.

The indications adopted for Type II (a+b) OPHLs were the classical ones, applied according to tumor extent, now being accepted and advocated by numerous authors.^{6, 7, 9,}

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3 Although definitions for the Type III (a+b) OPHLs were only recently introduced, the
4 precise indications and contraindications adopted were those already described in our
5 previous study for tumors in the intermediate/selected T classification.¹² Anyway, a further
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14 In all patients, resection margins were examined intraoperatively with frozen sections:
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16 when positive, the resection was expanded until the margins were negative. As the
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18 interventions were conducted using the principles of a modular approach, the resection is
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20 always prepared in standard mode and the larynx is opened from the side less affected by
21
22 disease. At this point, under visual control, the subsites involved are removed and the
23
24 resection can be easily enlarged as follows: (1) Type IIa/b → Type IIa/b + ARY; (2) Type
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26 IIIa/b → Type IIIa/b + CAU; (3) Type IIa → Type IIb; (4) Type IIa/b + ARY → Type IIIa/b +
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28 CAU; (5) Type IIIa → Type IIIb.
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32 The margins of the surgical specimen were always checked again upon definitive
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34 pathology. Neck dissection (ND), graded according to the American Academy of
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36 Otolaryngology - Head and Neck Surgery Foundation classification,¹⁷ was performed in
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38 503 patients (90.6%), and was monolateral in 324 (64.4%) and bilateral in 179 (35.6%)
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40 cases. ND was elective (ND levels II-IV) in 447 cN0 patients (88.9%) and curative (ND
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42 levels II-V + Internal Jugular Vein in one case) in 56 cN>0 patients (11.1%). In 123
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44 patients, whole level VI or unilateral paratracheal lymph node clearance was added. No
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46 ND was performed in an additional 52 patients (9.4%) (elderly and/or cN0 disease or in
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48 previously treated neck).
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54 *Postoperative care and adjuvant treatments*
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3 All patients were monitored for early complications (local and general) and late sequelae.
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5 Patients underwent the same rehabilitation protocol, apart from those with serious early
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7 complications.
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10 The postoperative protocol was in accord with our previous report.¹² Briefly: (1) insertion of
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12 an uncuffed tracheal cannula and beginning of phonation (days 1 to 4); (2) intermittent
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14 occlusion of the tracheostomy with saline-soaked gauze and starting of feeding without the
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16 tracheal cannula in position (days 4 to 6); (3), nasogastric (NG) tube removal as soon as a
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18 good level of swallowing of both solids and liquids was achieved (day 6 onwards). Post-
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20 operative aspiration was graded in accordance with Pearson's scale.¹⁸ On the basis of
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22 pathological findings (pN+ and/or extracapsular spread, large extralaryngeal extent,
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24 positive margins), 72 patients (12.9%) were subjected to adjuvant radiotherapy. The
25
26 indications for adjuvant therapy were: 40 N+ (14 level VI pN+, 26 pN2), 27 cases with
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28 gross extralaryngeal extent (3 supraglottic pT4a and 24 glottic pT4a) and 5 cases with
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30 positive margins.
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34 A large volume encompassing the primary site and all draining lymph nodes was irradiated
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36 with a dose of up to 54 Gy/2 Gy. Regions at higher risk for malignant dissemination
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38 received a 12-Gy boost (total 66 Gy/2 Gy – range 62–68 Gy). Forty-two of 72 patients also
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40 received 100 mg/m² cisplatin on days 1, 22, and 43 of the course of radiotherapy.¹⁹
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45 *Larynx functional assessment*

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47 Pearson's scale evaluation was repeated and larynx functional status was evaluated with
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49 the Performance Status Scale throughout five post-operative years.²⁰
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53 *Statistical methods*

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56 Overall survival (OS), disease free survival (DFS), disease specific survival (DSS),
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58 locoregional control (LRC), local control (LC), laryngectomy free survival (LFS) and
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3 laryngeal function preservation (LFP), were assessed by means of Kaplan-Meier curves.
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5 Log-rank and Gehan-Breslow-Wilcoxon tests (for early events) were used to compare
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7 Kaplan-Meier estimates between groups (staging, clinical history of previous treatment,
8
9 type of surgery, and age). The end points considered were obtained as the length of time
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11 from the date of diagnosis to: OS) the date of death; DFS) the date of the first recurrence;
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13 DSS) the date of death from the disease; LRC) the date of the first locoregional
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15 recurrence; LC) the date of the first local recurrence; LFS) the date of total laryngectomy;
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17 LFP) the date of total laryngectomy or presence of tracheostomy, NG tube, gastrostomy
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19 feeding, or non-intelligible voice.
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23 All analyses were performed with GraphPad Prism version 5.00 (GraphPad Software, San
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25 Diego CA), with $p < .05$ as the significant cutoff.
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28 29 **Results**

30 31 *Patients*

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34 A cohort of 555 patients undergoing Type II or III OPHLs was considered (Table 1).
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36 Current or former smokers made up 93% of the cohort. Patients were followed for a mean
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38 period of 5.57 years.
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45 46 *Pathology*

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48 All patients suffered of a biopsy-proven supraglottic or glottic laryngeal SCC, which it was
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50 classified as pT3 or pT4a, according to the 2002 TNM classification system²¹ (Table 1).
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52 Furthermore, pathology reports indicated close margins (<2 mm) in 13 cases (2.3%) and
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54 positive margins at the definitive histopathologic examination in 5 cases (0.9%). Four
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56 hundreds ninety-nine patients (89.9%) had been staged as cN0 by palpation and neck CT-
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58 scan or MRI. Overall, lymph node metastases were detected in 71/555 patients (12.8%), of
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3 whom 40 (7.2%) had multiple metastases. Furthermore, the comparison between clinical
4 and pathological staging showed up-staging of the primary tumor in 83 cases (14.9 %) and
5 of the lymph nodes in 15 cases (2.7%).
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10 11 *Survival and disease control*

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13 The 5-year OS, DSS, DFS, LRC and LC were 84.6%, 92.8%, 84.2%, 86.3% and 90.6%,
14 respectively (Figure 1). At the last follow-up, a total of 89 patients died, 39 of them from the
15 cancer under study and 50 for causes unrelated to laryngeal cancer (Table 2).
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20 21 *Chart data stratification*

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23 Locally intermediate/advanced laryngeal carcinomas differ greatly in surgical indications
24 and prognosis. The analyses were hence conducted on the basis of pathological staging in
25 order to obtain homogeneous prognostic data. By stratifying the chart data, we evaluated
26 whether pT, pN and type of surgery could affect the OS, DFS and LRC end-points in terms
27 of prevalence (Figure 2).
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36 After 5 years from surgery, OS was greatly affected by pT and pN classifications. In fact, it
37 was 87.8% and 71.2% in pT3 and pT4a patients, respectively, whereas it is only 51.5% in
38 pN \geq 2 patients, although similar in pN0 (88.3%) and pN1 (88.5%). Also the choice of more
39 extensive surgery (OPHL Type III) can affect OS (87.7%, 84.6%, 74.3% and 72.0% for
40 patients underwent Type IIa, Type IIb, Type IIIa and Type IIIb OPHL surgery, respectively).
41 Anyway no significant differences can be detected considering the DSS end-point (from
42 94.6% of OPHL Type IIb to 87.6% of OPHL Type IIIa, $p = .242$).
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51 DFS prevalence was greatly affected by locoregional staging and surgical approach. In
52 fact pT4a patients had 68.1% DFS if compared with 87.9% of those classified as pT3;
53 similarly also pN+ patients (72.6% pN1 and 71.1% pN \geq 2) had worse outcome with respect
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3 to pN0 (88.2%). As consequence, Type III OPHL (66.6% IIIa, 70.0% IIIb) were less
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5 effective than Type II (85.1% IIa, 91.8% IIb) in maintaining patients free from disease.
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7 The same pattern was also evident for the LRC end-point: 71.7% pT4a vs 89.7% pT3;
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9 72.0% pN1 and 79.6% pN \geq 2 vs 89.8% pN0; 72.1% OPHL Type IIIa and 70.0% IIIb vs
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11 87.6% Type IIa and 92.5% IIb.
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13 We assessed also the impact of eventual previous treatment and age \geq 65 without
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15 retrieving any significant differences (data not shown).
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18 19 20 *Patterns of failure* 21

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23 Locoregional recurrences affected 66 patients within 5 years of surgery. According to the
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25 site of pathology, they were sub-grouped as 40 local (60.6%), 5 locoregional (7.6%) and
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27 21 regional (31.8%) recurrences.
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30 Local recurrences were observed in 35/459 (7.6%) untreated and 10/96 (10.4%) pre-
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32 treated patients. Among them, eight had inferior paraglottic space involvement, 4 had
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34 internal thyroid lamina involvement, 10 had transglottic extension, 3 had subglottic
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36 extension and inclusion of a cricoarytenoid joint, 2 had surface extension as far as the
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38 inferior edge of the cricoid ring, 15 had extralaryngeal extension (9 anterior, 6 posterior)
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40 and 3 showed surface extension toward the posterior commissure.
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43 In all patients with local recurrence, salvage therapy included total laryngectomy and
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45 adjuvant radiation therapy and/or chemotherapy in 29 patients, radiation therapy and/or
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47 chemotherapy in eleven patients and laser surgery in five cases. Totally, seventeen
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49 patients died of laryngeal cancer from progression of disease (average 18.1 months, range
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51 3–42 months), 7 patients died of other disease, while at the last follow-up, 1 patient was
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53 alive with the disease and 20 patients were alive and disease-free; overall local control
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55 after salvage therapy at 5 years, was achieved in 27 of 45 patients (60.0%).
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3 Recurrence in the neck was observed in 26 cases, 19 of whom were previously classified
4 as cN0 and 7 as cN>0 patients. At the time of primary resection, 2 of these 26 received
5 unilateral neck dissection, 14 received bilateral neck dissection, and eight out of 26
6 recurrences were observed at the VI level.
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11 Four recurrences in the neck were treated with surgery alone, twenty with surgery and
12 adjuvant radiation therapy and/or chemotherapy, two recurrences with chemotherapy. 11
13 patients died due to regional recurrences (range 6–38 months, mean 16.3 months), 2
14 patients died of other disease while at the last follow-up, 3 patients were alive with disease
15 and 10 patients were alive and disease-free.
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24 25 *Postoperative course and morbidity*

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27 Overall, acute complications during hospitalization occurred in 62 out 555 patients (11.2%)
28 and there were 3 perioperative deaths. The mean hospitalization time for patients with
29 acute complications was 32 ± 6 days, which was significantly longer than that for patients
30 without acute complications (21 ± 5 days). Late sequelae following discharge were
31 observed in 85 out of 555 cases (15.3%) (Table 3). All were successfully treated with
32 transoral CO₂ laser surgery (68/85, 80%), revision of the pexy (2/85, 2.3%), injective
33 laryngoplasty using Vox-implants, which successfully treated dysphagia (5/85, 5.8%),
34 completion laryngectomy (5/85, 5.8%), or other endoscopic procedures (5/85, 5.8%).
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47 *Laryngeal function preservation*

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49 At 5 years after surgery, LFP rate was 92.6% (514 out 555 patients) while LFS resulted
50 93.3% (524 out 555 patients) (Figure 3). In addition, we evaluated whether LFP could be
51 affected by local or regional staging, presence of previous treatment, or age ≥ 65 years
52 (Figure 4). Patients affected by advanced pT stage were statistically significantly more
53 prone to lose laryngeal function (78.0%) with respect to intermediate pT stage (94.2%).
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3 Otherwise, pN was not correlated with LFP: in fact, differences between pN0 (94.1%) and
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5 pN>0 (86.3% pN1 and 86.9% pN≥2) were not significant. LFP is affected by surgery
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7 (proportionally to the extent of resection) and by age, but only limited by the first years
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9 after the surgery. Although log rank test did not provide significant results in the
10
11 comparison between younger (92.6%) and older (88.5%) patients, we can appreciate a
12
13 significant difference at early times employing the Gehan-Breslow-Wilcoxon test. Finally,
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15 LFP was not biased by previous treatments (not shown).
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19 After the first post-operative month, normal swallowing (Pearson's scale Grade 0) was
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21 achieved in 333 patients (60.0%), Grade I and II were observed in 115 (20.7%) and 91
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23 (16.4%) patients, respectively, while aspiration pneumonia (AP) (Pearson's Grade III) was
24
25 recorded in 16 patients (2.9%). After the second year, a satisfactory degree of laryngeal
26
27 function (i.e. List's scale: eating in public >50, understandability of speech >50, Normalcy
28
29 of diet >70) was achieved in 460 out of 555 patients without local disease (82.9%). Out of
30
31 the 528 patients evaluated for subjective aspiration by the Pearson's scale, 227 (43%) had
32
33 no aspiration (Grade 0), 231 (43.8%) had occasional cough without clinical problems
34
35 (Grade I), 62 (11.7%) had constant cough that worsened during meals (Grade II), and 8
36
37 patients (1.4%) had frequent pulmonary complications (Grade III). Nearly all patients
38
39 (547/555; 98.6%) had the NGT or gastrostomy removed. The NGT remained in place for
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41 an average of 19.5 days (range 11–161 days).
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46 Overall, AP was observed in 41/555 cases (7.4%), 16 cases during hospitalization and 25
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48 cases during follow-up, which required a temporary gastrostomy; for 30 of them, it was
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50 removed within the first post-operative year. In 14 cases, the gastrostomy was maintained
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52 due to repeated episodes of AP and severe dysphagia for liquids. In seven cases, total
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54 laryngectomy was proposed for persistent aspiration: five patients accepted this treatment
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56 while two refused, preferring to keep the gastrostomy and maintain voice. Five patients
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3 were subjected to the endoscopic procedure for injective laryngoplasty using Vox implant,
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5 which successfully resolved the dysphagia, allowing gastrostomy removal.
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7 The mean time to intermittent occlusion of the tracheostomy was 24.6 days (range 3–406
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9 days), and the average time to tracheostomy closure was 82.4 days (range 23–489 days).
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11 In our protocol, progressive closure of the tracheostomy is preferred, and occurs
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13 spontaneously in the majority of patients following occlusion. For patients, especially in the
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15 first weeks after discharge, this leads to a sensation of greater safety concerning minor
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17 episodes of food inhalation, which are relatively frequent. When the tracheostomy has
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19 almost closed, minor plastic surgery can then be performed.
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38 Discussion

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43 Notwithstanding that the preservation of laryngeal function is one of the major advances
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45 that have been achieved over the past decades, cancer of the larynx in the
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47 intermediate/advance stage still presents a major challenge in terms of controlling the
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49 disease and preserving the larynx, regardless of the therapeutic option chosen.^{2-4, 6, 7, 9, 22-}
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52 ²⁵ In fact, many glottic cT3 tumors with sub-glottic extent (vocal cord and arytenoid fixation)
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54 often result in early pT4a for extralaryngeal extent, making them of difficult management
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56 with chemoradiotherapy or supracricoid laryngectomy.
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3 Towards the end of the 1990s, by analyzing total laryngectomy and supracricoid
4 laryngectomy specimens, in comparison with clinical data from fixed arytenoid and
5 subglottic swelling, the idea of extending the supracricoid laryngectomy downwards to
6 obtain safer margins was derived. These efforts have resulted in increased knowledge,
7 which led to the proposal of a new type of OPHL in 2006, the supratracheal laryngectomy,
8 otherwise known as OPHL Type III in the recent European Laryngological Society
9 classification.¹⁰ As recently demonstrated by Schindler et al. and Rizzotto et al., this is able
10 to spare laryngeal function without compromising locoregional control during long-term
11 follow-up.^{12, 13} As a consequence of the diffusion of supracricoid partial laryngectomies
12 (OPHL Type II), the advent of supratracheal partial laryngectomies (OPHL Type III) and
13 the consolidated role of conventional non-surgical organ sparing protocols, the role of total
14 laryngectomy in the treatment of endolaryngeal neoplasms has decreased considerably.

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In this study, we have analyzed the outcomes of 555 patients affected by III-IV staged laryngeal SCC undergoing function sparing OPHL protocols. For the sake of clarity, we report in our cohort an higher percentage of glottic tumors (91.2%) than in previously described trials or case series for the great number of transglottic cancers (27.4%), which were included and being these always considered to originate from the glottis.

During the surgery, the open partial resection was tailored under visual control to obtain disease-free safe margins, which can be as close as of only 4–5 mm. It is important to note that such intra-surgery flexibility can be useful to address the heterogeneity of tumors on the base of their true extent. In our series, in fact, upstaging of cT3 to pT4a was found in 14.9% of specimens, generally due to the full thickness involvement of the thyroid lamina, and of cN0 to pN+ in 3% of cases, in spite of preoperative neck CT and/or MRI. Being aware of these, otherwise not identifiable, upstaging may represent an explanation of the differences we already reported¹² and here further confirmed, in terms of local

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3 control between concomitant chemoradiation and OPHLs in the management of laryngeal
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5 cancer at the intermediate stage.
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8 In fact, data concerning survival and disease control do not display significant differences
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10 with respect to our previous analysis,¹² but highlighted great differences with literature data
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12 concerning non-surgical approaches. In the present study, the 5-year OS was 84.6% and
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14 results better than what previously reported for both concomitant chemoradiotherapy or
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16 induction chemotherapy and radiotherapy (~60%).^{4, 26} More advanced pT4a tumors
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18 displayed a 5-year DFS of 68.1%, a result in line with that of the most demolitive surgical
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20 approach, although it must be admitted that in these cases the extralaryngeal extension
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22 was minimal. These data show that a careful selection can render eligible for the partial
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24 modular surgical approach a good number of patients, even in some, very well selected
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26 “extreme cases”. However, the DFS for pT4a cancer (68.2%) was significantly lower than
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28 that for pT3 classification (87.9%), but higher than that obtained by management with
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30 radiotherapy and/or chemoradiotherapy, which ranged from 26% to 38%, respectively.^{4, 26}
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32 Finally, the number of patients which were subjected to total laryngectomy for either
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34 functional or oncological purposes was significantly low (6.2%) and there were only three
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36 perioperative deaths. The high laryngectomy-free survival rate here achieved deposed to
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38 the great potentiality of OPHL approaches in preserving the larynx. In summary,
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40 “everybody loses a piece, but few lose all”.
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46 Otherwise, larynx function preservation takes great advantages by tailoring surgery on the
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48 real extent of tumor, and significant differences ($p < .001$) are found after 5 years from
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50 surgery between OPHL type II (94.4%) and Type III (74.5%) patients. Here is important to
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52 note that the latter is consistent with our previous report (78.5%),¹² which was itself in line
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54 with that achievable with concomitant chemoradiation. As a consequence, maintenance of
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56 laryngeal function was more critical in patients affected by pT4a cancer (78.0%) and in
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3 those older than 65 (87.3%), although only if we consider early events as more severe
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5 than late ones.
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8 The real Achilles heel of OPHLs is represented by a greater proportion of functional
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10 problems compared to non-surgical treatment options. As already reported by Benito et
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12 al.,²⁷ persistent slight dysphagia and aspiration pneumonia still represent major
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14 complications in patients undergoing OPHLs, especially Type III, while voice was
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16 significantly deteriorated, and generally quite hoarse and breathy.¹³ Despite the
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18 employment of the less extended OPHL Type II, no differences in terms of acute
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20 complication and late sequelae were highlighted with respect to our previous analysis.¹² In
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22 fact, 19 out of 41 cases of aspiration pneumonia occurred in elderly patients, in whom
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24 gastrostomy was maintained in two patients owing to repeated episodes of aspiration
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26 pneumonia, and one was subjected to total laryngectomy. Fortunately these phenomena
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28 are not frequent, tend to self-restraint and to be well tolerated by patients. On the other
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30 hand, a significant reduction ($p < .01$) in hospitalization time can be achieved by better
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32 tailoring the surgery on tumor extent. Indeed it is here reported a mean hospitalization of
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34 32 and 21 days in presence or without acute complications, respectively, which were
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36 opposed to the 38 and 24 days achieved by Rizzotto et al. employing only OPHL Type III
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38 procedure.¹²
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43 Aiming these surgical options at carefully selected patients suffering from laryngeal SCC in
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45 well-defined intermediate/advanced stages, the oncological and functional results are very
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47 robust and repeatable. Many experiences reported in the past 20 years supports this
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49 claim.⁵⁻⁹ The gold standard indications are: supraglottic cT3 (OPHL Type IIb ± ARY), glottic
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51 cT3 with vocal cord fixation (OPHL Type IIa ± ARY), glottic cT3 with vocal cord fixation ±
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53 arytenoid fixation and also sub-glottic extension (OPHL Type IIIa ± CAU). In the latter case
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55 the option of a supracricoid partial laryngectomy would be very much at risk of leaving
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57 positive margins as the section line passes through a cricoarytenoid joint. A different and
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3 more cautious reasoning is required for anterior cT4a tumors with full-thickness
4 involvement of the thyroid lamina and/or minimal extralaryngeal extension: by adopting
5 OPHL, the radicality is the same as for the more demolitive interventions, but the selection
6 of patients must be made very carefully because, at the end of the work-up, the surgeon
7 must be able to ensure safe margins with sufficient certainty, thus avoiding an upfront total
8 laryngectomy.
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11 In all cases in which the extent of the tumor determines the indication for a more extreme
12 Type III partial laryngectomy (and this occurs for most tumors with sub-glottic extension or
13 extension towards the posterior commissure), this imposes a serious ethical consideration.
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16 In fact, in many specialized centers, these cases are considered to be "amenable with total
17 laryngectomy" and therefore, up-front directed to non-surgical treatment in order to spare
18 the larynx. When discussing a conservative surgical option with the patient, it must be
19 explained clearly that if the resection margins are positive in frozen sections, the option
20 immediately following that is total laryngectomy, thus "jumping" the option of concomitant
21 chemoradiotherapy, which has a degree of recommendation IA. For these reasons,
22 especially when the tumor clearly extends beyond the limits of the larynx, both the severity
23 of the intervention and the necessity for adjuvant radiotherapy demand that extreme
24 caution be taken when considering the indications.
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28 In conclusion, here we demonstrate that, in cases of supraglottic tumors with glottic
29 involvement, any subtype of glottic cT3 and finally some well-studied glottic tumors with
30 sub-glottic extension, the choice of OPHL with a modular approach versus chemoradiation
31 protocols can be considered to be viable not only in prognostic terms (above all for the
32 possibility to identify upstaging and the reduction in recurrence prevalence) but also in
33 terms of functional results (similar of what obtained by non-surgical options) such as a
34 reduction of total laryngectomies, even at the expense of voice quality and rare
35 occurrences of sequelae (aspiration pneumonia).
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References

1. Gussenbauer C. Über die erste durch Th. Billroth am Menschen ausgeführte Kehlkopf-Exstirpation und die Anwendung eines künstlichen Kehlkopfes *Arch Klin Chir* 1874;17:343-356.
2. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. *N Engl J Med* 1991;324:1685-90.
3. Chen AY, Schrag N, Hao Y, et al. Changes in treatment of advanced laryngeal cancer 1985-2001. *Otolaryngol Head Neck Surg* 2006;135:831-7.
4. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med* 2003;349:2091-8.
5. de Vincentiis M, Minni A, Gallo A, Di Nardo A. Supracricoid partial laryngectomies: oncologic and functional results. *Head Neck* 1998;20:504-9.
6. Laccourreye O, Brasnu D, Biacabe B, Hans S, Seckin S, Weinstein G. Neo-adjuvant chemotherapy and supracricoid partial laryngectomy with cricohyoidopexy for advanced endolaryngeal carcinoma classified as T3-T4: 5-year oncologic results. *Head Neck* 1998;20:595-9.
7. Lima RA, Freitas EQ, Dias FL, et al. Supracricoid laryngectomy with cricohyoidoepiglottopexy for advanced glottic cancer. *Head Neck* 2006;28:481-6.

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2
3 8. Mercante G, Grammatica A, Battaglia P, Cristalli G, Pellini R, Spriano G. Supracricoid
4
5 partial laryngectomy in the management of t3 laryngeal cancer. *Otolaryngol Head Neck Surg*
6
7 2013;149:714-20.
8
- 9
10 9. Rizzotto G, Crosetti E, Lucioni M, Succo G. Subtotal laryngectomy: outcomes of 469
11
12 patients and proposal of a comprehensive and simplified classification of surgical procedures.
13
14 *Eur Arch Otorhinolaryngol* 2012;269:1635-46.
15
- 16
17 10. Succo G, Peretti G, Piazza C, et al. Open partial horizontal laryngectomies: a proposal
18
19 for classification by the working committee on nomenclature of the European Laryngological
20
21 Society. *Eur Arch Otorhinolaryngol* 2014.
22
- 23
24 11. Rizzotto G, Succo G, Lucioni M, Pazziaia T. Subtotal laryngectomy with
25
26 tracheohyoidopexy: a possible alternative to total laryngectomy. *Laryngoscope*
27
28 2006;116:1907-17.
29
- 30
31 12. Rizzotto G, Crosetti E, Lucioni M, et al. Oncological outcomes of supratracheal
32
33 laryngectomy: A critical analysis. *Head Neck* 2014.
34
- 35
36 13. Schindler A, Fantini M, Pizzorni N, et al. Swallowing, voice, and quality of life after
37
38 supratracheal laryngectomy: Preliminary long-term results. *Head Neck* 2014.
39
- 40
41 14. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in
42
43 cancer. In: MacLeod CM, editor. Evaluation of chemotherapeutic agents. New York: Columbia
44
45 University Press; 1949. p. 191–205.
46
- 47
48 15. Schindler A, Favero E, Capaccio P, Albera R, Cavalot AL, Ottaviani F. Supracricoid
49
50 laryngectomy: age influence on long-term functional results. *Laryngoscope* 2009;119:1218-25.
51
- 52
53 16. Pinar E, Imre A, Calli C, Oncel S, Katilmis H. Supracricoid partial laryngectomy: analyses
54
55 of oncologic and functional outcomes. *Otolaryngol Head Neck Surg* 2012;147:1093-8.
56
57
58
59
60

17. Robbins KT, Clayman G, Levine PA, et al. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. *Arch Otolaryngol Head Neck Surg* 2002;128:751-8.
18. Pearson BW. Subtotal laryngectomy. *Laryngoscope* 1981;91:1904-12.
19. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004;350:1945-52.
20. List MA, Ritter-Sterr C, Lansky SB. A performance status scale for head and neck cancer patients. *Cancer* 1990;66:564-9.
21. TNM Classification of Malignant Tumours. Sixth ed. New York: Wiley-Liss; 2002.
22. Lefebvre JL. Surgery for Laryngopharyngeal SCC in the Era of Organ Preservation. *Clin Exp Otorhinolaryngol* 2009;2:159-63.
23. Wolf GT. Reexamining the treatment of advanced laryngeal cancer: the VA laryngeal cancer study revisited. *Head Neck* 2010;32:7-14.
24. Forastiere AA. Larynx preservation and survival trends: should there be concern? *Head Neck* 2010;32:14-7.
25. Denaro N, Russi EG, Lefebvre JL, Merlano MC. A systematic review of current and emerging approaches in the field of larynx preservation. *Radiother Oncol* 2013.
26. Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol* 2013;31:845-52.
27. Benito J, Holsinger FC, Perez-Martin A, Garcia D, Weinstein GS, Laccourreye O. Aspiration after supracricoid partial laryngectomy: Incidence, risk factors, management, and outcomes. *Head Neck* 2011;33:679-85.

Figure legends

Fig. 1. End point analysis (overall survival, disease specific survival, disease-free survival, locoregional control, and local control) of the patient cohort using Kaplan–Meier curves.

Fig. 2. Patient cohort stratification for pT classification (left column), pN classification (middle column) and type of surgery (right column) using Kaplan–Meier curves. The end points considered were (from top to bottom) overall survival, disease-free survival, locoregional control, and local control. * = $p < .05$; ** = $p < .01$; *** = $p < .001$

Fig.3. End point analysis of laryngeal function preservation and laryngectomy-free survival in the patient cohort using Kaplan–Meier curves.

Fig. 4. Evaluation of laryngeal function preservation in the patient cohort stratified for pT classification (top), pN classification (middle) and age (bottom) using Kaplan–Meier curves. *** = $p < .001$

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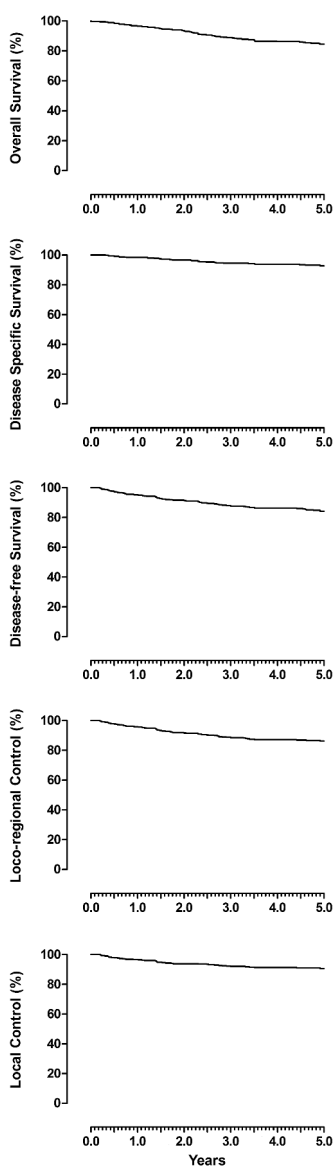


Fig. 1. End point analysis (overall survival, disease specific survival, disease-free survival, locoregional control, and local control) of the patient cohort using Kaplan–Meier curves 246x758mm (600 x 600 DPI)

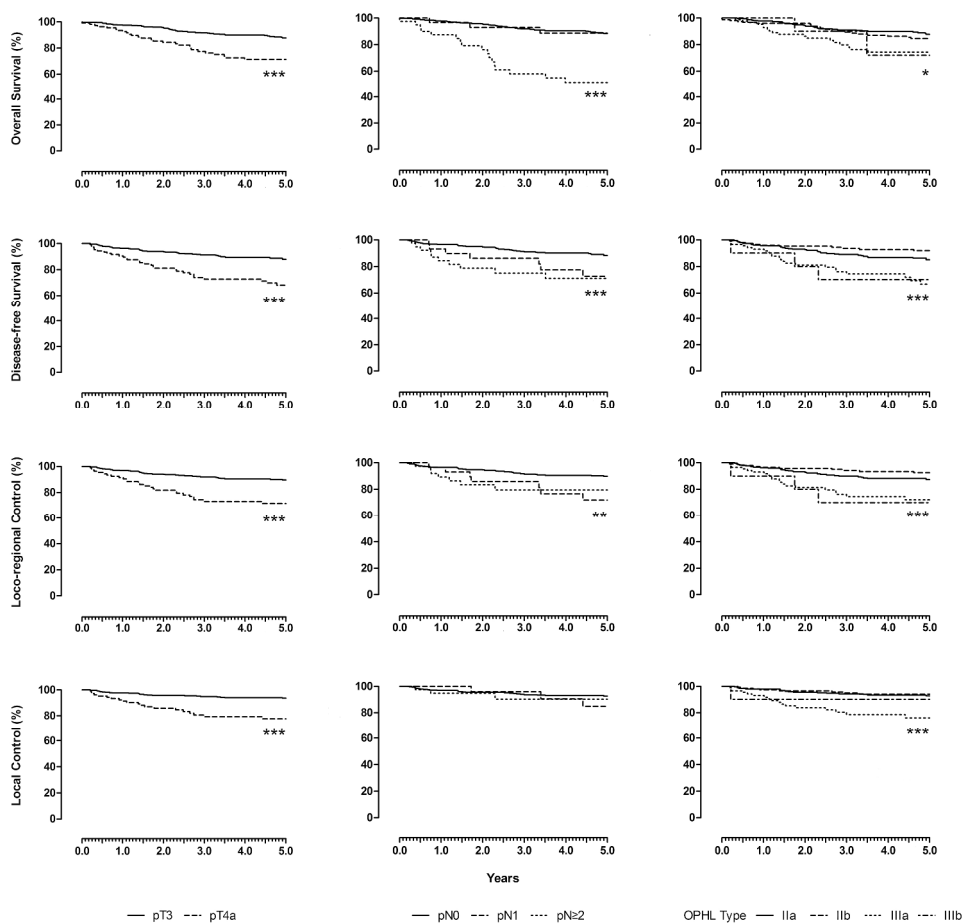


Fig. 2. Patient cohort stratification for pT classification (left column), pN classification (middle column) and type of surgery (right column) using Kaplan–Meier curves. The end points considered were (from top to bottom) overall survival, disease-free survival, loco-regional control, and local control. * = $p < .05$; ** = $p < .01$; *** = $p < .001$
172x164mm (600 x 600 DPI)

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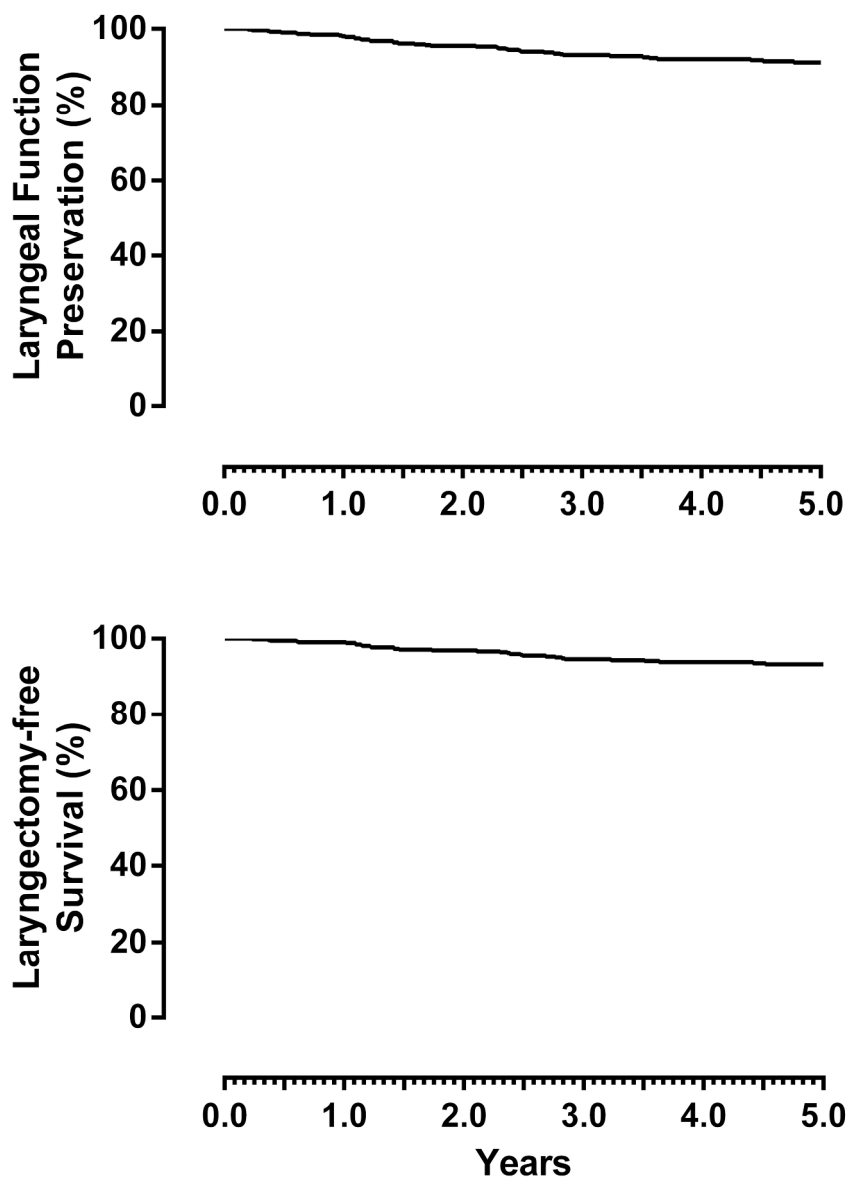


Fig.3. End point analysis of laryngeal function preservation and laryngectomy-free survival in the patient cohort using Kaplan-Meier curves
107x144mm (600 x 600 DPI)

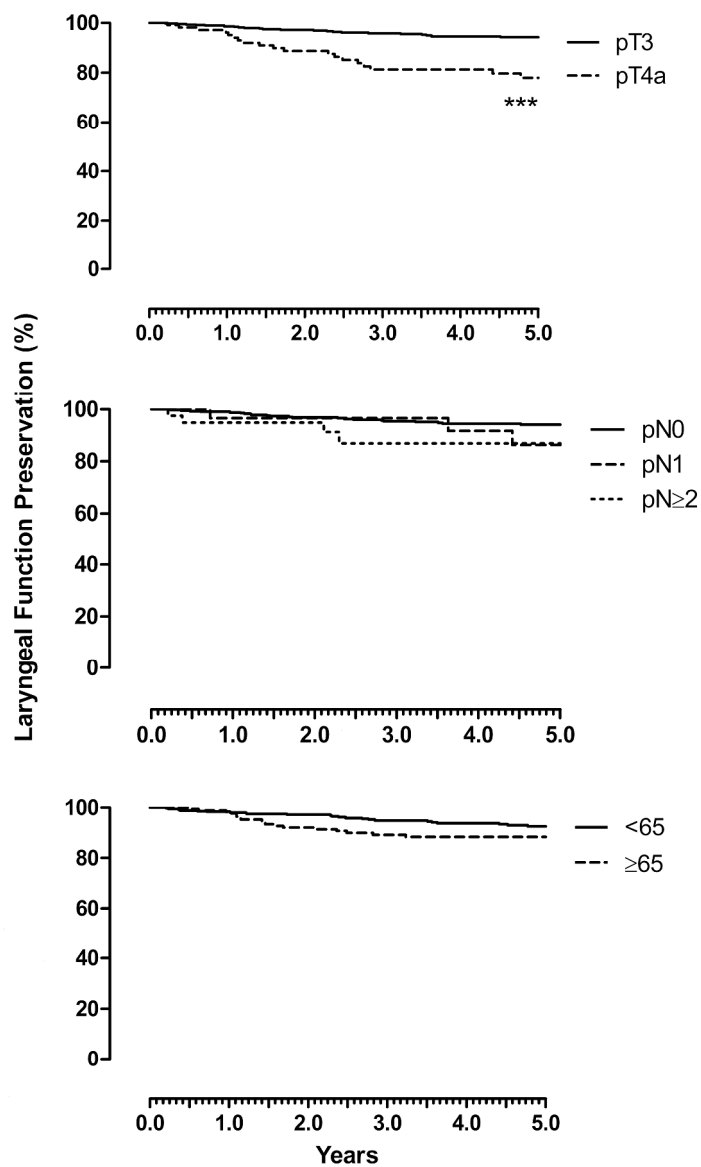


Fig. 4. Evaluation of laryngeal function preservation in the patient cohort stratified for pT classification (top), pN classification (middle) and age (bottom) using Kaplan-Meier curves. *** = $p < .001$
134x212mm (600 x 600 DPI)

Table 1. Characteristics of the 555 patients undergoing open partial horizontal laryngectomies according to age, sex, Karnofsky performance status, and pathological grade

	No. of Patients (%)	
Age, y		
Mean	59.9±9.4	
Range	16-83	
Sex		
Male	512/555 (92.3%)	
Female	43/555 (7.7%)	
Karnofsky Performance Status		
100	326/555 (58.7%)	
90	158/555 (28.5%)	
80	71/555 (12.8%)	
Pathological Grade		
	Supraglottic	Glottic
pT3	34/49 (69.4%)	408/506 (80.6%)
pT4a	15/49 (30.6%)	98/506 (19.4%)
pN0	37/49 (75.5%)	406/454 (89.4%)
pN1	7/49 (14.3%)	27/454 (6.0%)
pN2	5/49 (10.2%)	21/454 (4.6%)
Level VI pN+	14/123 (11.4%)	

Table 2: Cause of death

	No. of Patients (%)
Laryngeal cancer	39/555 (7.0%)
Post-operative death	3/555 (0.5%)
II Primary	31/555 (5.6%)
Others causes	16/555 (2.9%)
Total deaths	89/555 (16.0%)

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Table 3. Acute postoperative complications and late sequelae

	No. of Patients (%)
Acute complications	
Cervical bleeding	18/555 (3.2%)
Aspiration pneumonia	16/555 (2.9%)
Wound infection	14/555 (2.5%)
Post-operative death	3/555 (0.5%)
Others	10/555 (1.8%)
Late sequelae	
Laryngeal soft tissue stenosis	54/555 (9.7%)
Aspiration pneumonia	25/555 (4.5%)
Dyspnea	6/555 (1.1%)