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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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**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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### 31 **Author Contributions**

32

33  
34 Giovanni Succo, surgeon who performed the surgical procedures, study conception and  
35 design, drafting the article, final approval of the version to be published; Erika Crosetti,  
36 surgeon who performed the surgical procedures, study conception and design, final  
37 approval of the version to be published; Andy Bertolin, study conception and design, data  
38 collection; Marco Lucioni, surgeon who performed the surgical procedures, study  
39 conception and design; Giulia Arrigoni, data collection; Valentina Panetta, data analysis,  
40 statistical analysis; Andrea E. Sprio, data analysis, statistical analysis, drafting the article;  
41 Giovanni N. Berta, drafting the article, final approval of the version to be published;  
42 Giuseppe Rizzotto, surgeon who performed the surgical procedures, study conception and  
43 design, final approval of the version to be published.  
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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,<sup>1</sup> 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,<sup>2-4</sup> 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.<sup>5-9</sup> Recently, the European Laryngological Society proposed a classification of the more commonly adopted procedures according to extent of resection,<sup>10</sup> 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.<sup>11</sup> 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.<sup>12, 13</sup> 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.<sup>2, 4</sup>  
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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.<sup>12</sup>  
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45 Inclusion criteria were histological diagnosis of intermediate/advance stage glottic or  
46 supraglottic laryngeal SCC, with Karnofsky index<sup>14</sup> 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,<sup>15</sup> 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 CO<sub>2</sub> 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.<sup>10</sup> 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.<sup>6, 7, 9,</sup>

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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.<sup>12</sup> Anyway, a further  
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In all patients, resection margins were examined intraoperatively with frozen sections: when positive, the resection was expanded until the margins were negative. As the interventions were conducted using the principles of a modular approach, the resection is always prepared in standard mode and the larynx is opened from the side less affected by disease. At this point, under visual control, the subsites involved are removed and the resection can be easily enlarged as follows: (1) Type IIa/b → Type IIa/b + ARY; (2) Type IIIa/b → Type IIIa/b + CAU; (3) Type IIa → Type IIb; (4) Type IIa/b + ARY → Type IIIa/b + CAU; (5) Type IIIa → Type IIIb.

The margins of the surgical specimen were always checked again upon definitive pathology. Neck dissection (ND), graded according to the American Academy of Otolaryngology - Head and Neck Surgery Foundation classification,<sup>17</sup> was performed in 503 patients (90.6%), and was monolateral in 324 (64.4%) and bilateral in 179 (35.6%) cases. ND was elective (ND levels II-IV) in 447 cN0 patients (88.9%) and curative (ND levels II-V + Internal Jugular Vein in one case) in 56 cN>0 patients (11.1%). In 123 patients, whole level VI or unilateral paratracheal lymph node clearance was added. No ND was performed in an additional 52 patients (9.4%) (elderly and/or cN0 disease or in previously treated neck).

#### *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.<sup>12</sup> 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.<sup>18</sup> 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  
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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/m<sup>2</sup> cisplatin on days 1, 22, and 43 of the course of radiotherapy.<sup>19</sup>  
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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.<sup>20</sup>  
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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,  
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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 system<sup>21</sup> (Table 1).  
51  
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*

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

22 Locally intermediate/advanced laryngeal carcinomas differ greatly in surgical indications  
23 and prognosis. The analyses were hence conducted on the basis of pathological staging in  
24 order to obtain homogeneous prognostic data. By stratifying the chart data, we evaluated  
25 whether pT, pN and type of surgery could affect the OS, DFS and LRC end-points in terms  
26 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;  
8  
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*

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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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31 Local recurrences were observed in 35/459 (7.6%) untreated and 10/96 (10.4%) pre-  
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33 treated patients. Among them, eight had inferior paraglottic space involvement, 4 had  
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35 internal thyroid lamina involvement, 10 had transglottic extension, 3 had subglottic  
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37 extension and inclusion of a cricoarytenoid joint, 2 had surface extension as far as the  
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39 inferior edge of the cricoid ring, 15 had extralaryngeal extension (9 anterior, 6 posterior)  
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41 and 3 showed surface extension toward the posterior commissure.  
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45 In all patients with local recurrence, salvage therapy included total laryngectomy and  
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47 adjuvant radiation therapy and/or chemotherapy in 29 patients, radiation therapy and/or  
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49 chemotherapy in eleven patients and laser surgery in five cases. Totally, seventeen  
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51 patients died of laryngeal cancer from progression of disease (average 18.1 months, range  
52  
53 3–42 months), 7 patients died of other disease, while at the last follow-up, 1 patient was  
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55 alive with the disease and 20 patients were alive and disease-free; overall local control  
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57 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  $32 \pm 6$  days, which was significantly longer than that for patients  
30 without acute complications ( $21 \pm 5$  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 CO<sub>2</sub> 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  $\geq 65$  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  
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11 comparison between younger (92.6%) and older (88.5%) patients, we can appreciate a  
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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  
22  
23 (16.4%) patients, respectively, while aspiration pneumonia (AP) (Pearson's Grade III) was  
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25 recorded in 16 patients (2.9%). After the second year, a satisfactory degree of laryngeal  
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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  
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39 (547/555; 98.6%) had the NGT or gastrostomy removed. The NGT remained in place for  
40  
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  
47  
48 cases during follow-up, which required a temporary gastrostomy; for 30 of them, it was  
49  
50 removed within the first post-operative year. In 14 cases, the gastrostomy was maintained  
51  
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  
8  
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  
48  
49 disease and preserving the larynx, regardless of the therapeutic option chosen.<sup>2-4, 6, 7, 9, 22-</sup>  
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52 <sup>25</sup> 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.<sup>10</sup> 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.<sup>12, 13</sup> 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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30 In this study, we have analyzed the outcomes of 555 patients affected by III-IV staged  
31 laryngeal SCC undergoing function sparing OPHL protocols. For the sake of clarity, we  
32 report in our cohort an higher percentage of glottic tumors (91.2%) than in previously  
33 described trials or case series for the great number of transglottic cancers (27.4%), which  
34 were included and being these always considered to originate from the glottis.

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41 During the surgery, the open partial resection was tailored under visual control to obtain  
42 disease-free safe margins, which can be as close as of only 4–5 mm. It is important to  
43 note that such intra-surgery flexibility can be useful to address the heterogeneity of tumors  
44 on the base of their true extent. In our series, in fact, upstaging of cT3 to pT4a was found  
45 in 14.9% of specimens, generally due to the full thickness involvement of the thyroid  
46 lamina, and of cN0 to pN+ in 3% of cases, in spite of preoperative neck CT and/or MRI.  
47 Being aware of these, otherwise not identifiable, upstaging may represent an explanation  
48 of the differences we already reported<sup>12</sup> 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,<sup>12</sup> but highlighted great differences with literature data  
11  
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%).<sup>4, 26</sup> 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  
23  
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.<sup>4, 26</sup>  
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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  
37  
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%),<sup>12</sup> 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.,<sup>27</sup> 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.<sup>13</sup> 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.<sup>12</sup> 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.<sup>12</sup>  
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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  
46  
47 robust and repeatable. Many experiences reported in the past 20 years supports this  
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49 claim.<sup>5-9</sup> 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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## 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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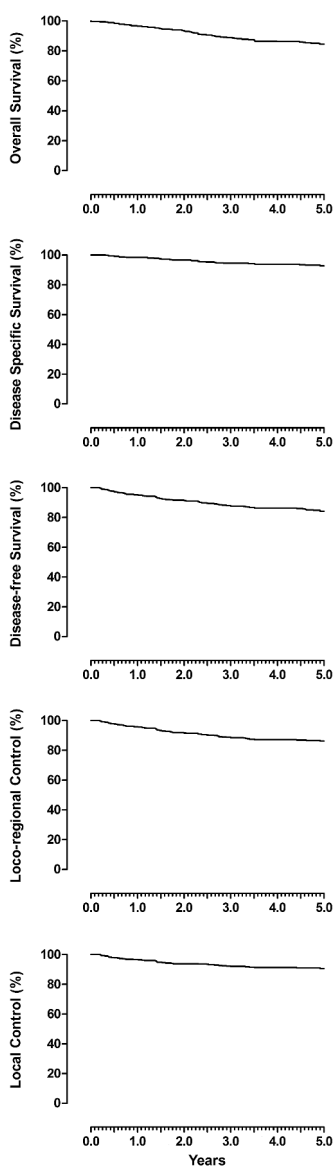


Fig. 1. End point analysis (overall survival, disease specific survival, disease-free survival, locoregional control, and local control) of the patient cohort using Kaplan–Meier curves 246x758mm (600 x 600 DPI)

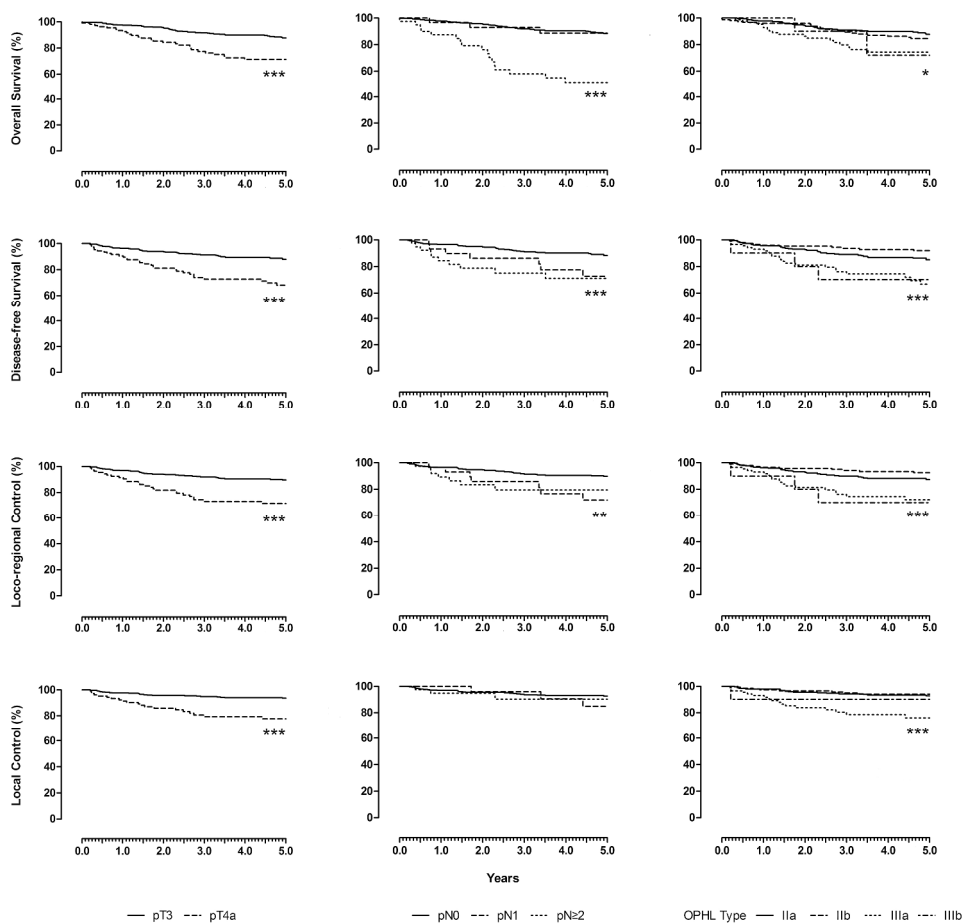


Fig. 2. Patient cohort stratification for pT classification (left column), pN classification (middle column) and type of surgery (right column) using Kaplan–Meier curves. The end points considered were (from top to bottom) overall survival, disease-free survival, loco-regional control, and local control.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

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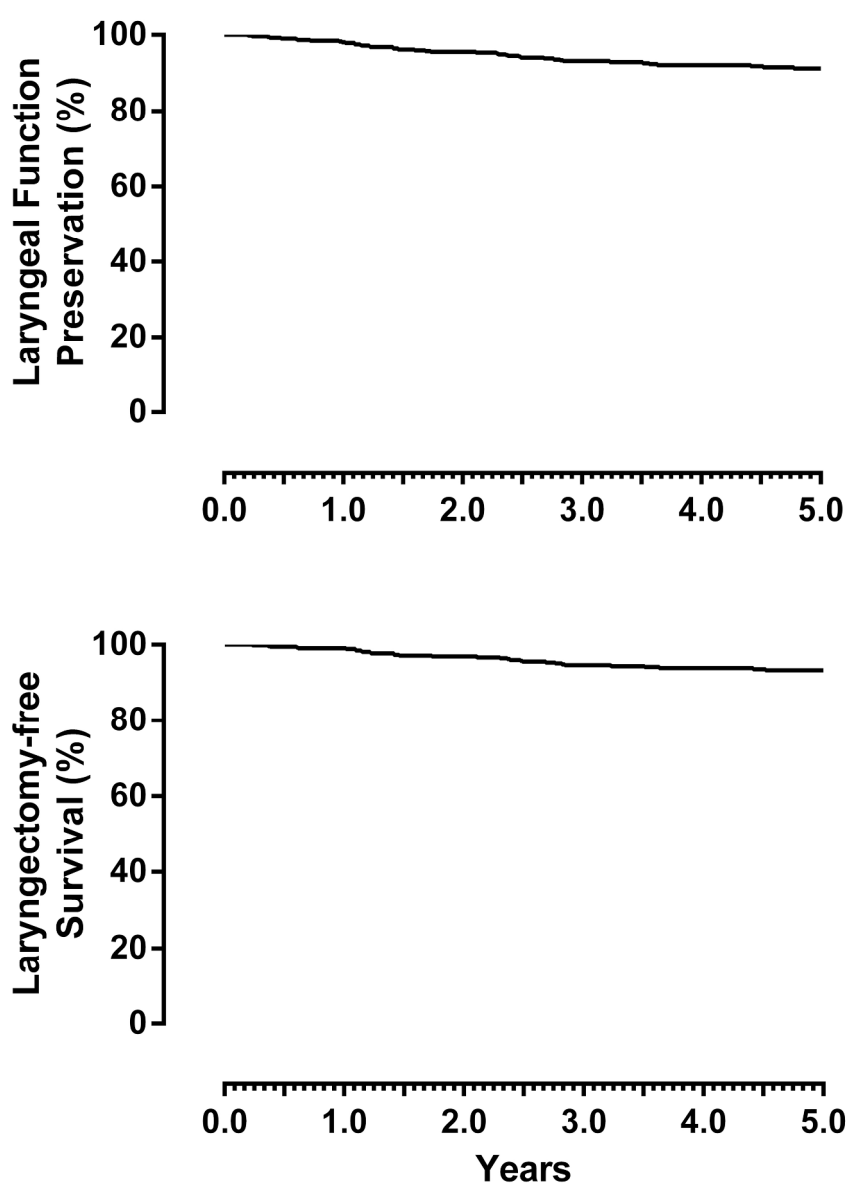


Fig.3. End point analysis of laryngeal function preservation and laryngectomy-free survival in the patient cohort using Kaplan-Meier curves  
107x144mm (600 x 600 DPI)

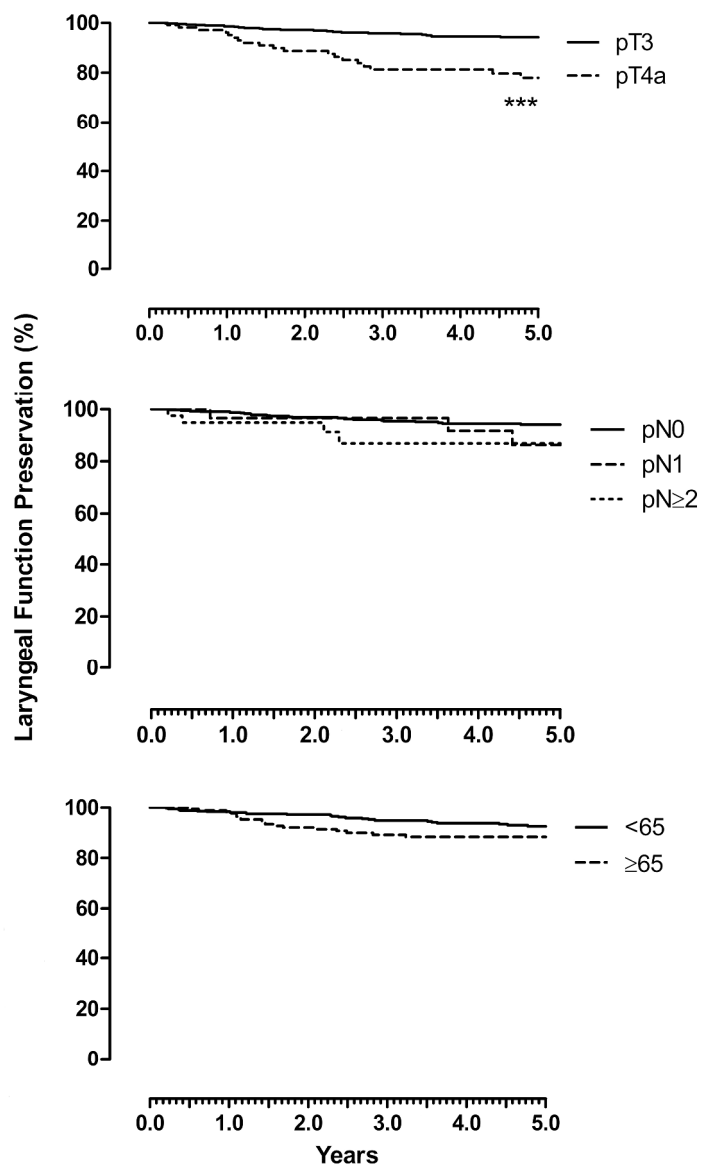


Fig. 4. Evaluation of laryngeal function preservation in the patient cohort stratified for pT classification (top), pN classification (middle) and age (bottom) using Kaplan-Meier curves. \*\*\* =  $p < .001$   
134x212mm (600 x 600 DPI)

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 (%)	
<b>Age, y</b>		
Mean	59.9±9.4	
Range	16-83	
<b>Sex</b>		
Male	512/555 (92.3%)	
Female	43/555 (7.7%)	
<b>Karnofsky Performance Status</b>		
100	326/555 (58.7%)	
90	158/555 (28.5%)	
80	71/555 (12.8%)	
<b>Pathological Grade</b>		
	<b>Supraglottic</b>	<b>Glottic</b>
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%)

For Peer Review

Table 3. Acute postoperative complications and late sequelae

	No. of Patients (%)
<b>Acute complications</b>	
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%)
<b>Late sequelae</b>	
Laryngeal soft tissue stenosis	54/555 (9.7%)
Aspiration pneumonia	25/555 (4.5%)
Dyspnea	6/555 (1.1%)