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HEAD AND NECK

Upfront transoral robotic surgery (TORS) *versus* intensity-modulated radiation therapy (IMRT) in HPV-positive oropharyngeal cancer: real-world data from a tertiary comprehensive cancer centre

Confronto tra chirurgia transorale e radioterapia a intensità modulata nel carcinoma orofaringeo HPV-positivo

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SUMMARY

Objective. This study aims to provide real-world data on oncologic and functional outcomes of the most modern surgical and non-surgical treatments of locally advanced HPV-positive oropharyngeal cancer.

Methods. We reviewed data on patients treated for stage III and IV HPV-positive oropharyngeal squamous cell carcinoma with either endoscopic surgery (Transoral Robotic Surgery, TORS; Transoral Laser Microsurgery, TLM – group A) or intensity-modulated radiotherapy (IMRT – group B). The minimum follow-up required was 6 months. Survival outcomes and toxicities of treatments were evaluated.

Results. 30 patients in group A and 66 in group B were eligible for the analysis. 28% of patients in group A underwent a unimodal treatment, while 42% needed trimodal treatment. 90% of patients in group B underwent concurrent chemoradiation. We found no statistically significant difference in survival outcomes (group A: overall survival 97%, progression-free survival 83%; group B: OS 98%, PFS 86%) or toxicities between groups.

Conclusions. Both transoral surgery and IMRT provide excellent outcomes in HPV-positive oropharyngeal cancer. Because of the good prognosis, treatments need to be refined to reduce toxicities while preserving oncologic soundness.

KEY WORDS: oropharyngeal cancer, HPV, transoral robotic surgery (TORS), intensity-modulated radiotherapy (IMRT), minimally invasive surgery

RIASSUNTO

***Obiettivo**. Questo studio presenta dati di pratica clinica sui risultati oncologici e funzionali dei più moderni trattamenti chirurgici e non chirurgici del carcinoma orofaringeo HPV-positivo in stadio localmente avanzato.*

***Metodi**. Abbiamo revisionato i dati dei pazienti affetti da carcinoma squamocellulare dell'orofaringe HPV-positivo in stadio III e IV e trattati con chirurgia endoscopica (Chirurgia Robotica Transorale; Microchirurgia Laser Transorale – gruppo A) o radioterapia a intensità modulata (IMRT – gruppo B). Il follow-up minimo era di 6 mesi. Sono state valutate e confrontate sopravvivenze e tossicità.*

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Risultati. *Sono stati inclusi nell'analisi 30 pazienti nel gruppo A e 66 pazienti nel gruppo B. il 28% dei pazienti del gruppo A ha ricevuto un trattamento unimodale, mentre il 42% un trattamento trimodale. Nel gruppo B il 90% è stato sottoposto a chemioradioterapia concomitante. Non abbiamo rilevato differenze statisticamente significative nelle sopravvivenze (gruppo A: overall survival 97%, progression-free survival 83%; gruppo B: OS 98%, PFS 86%) e nelle tossicità.*

Conclusioni. *TORS e IMRT forniscono risultanti eccellenti nel cancro orofaringeo HPV-positivo. Alla luce della buona prognosi, i trattamenti devono essere perfezionati per ridurre le tossicità preservando l'efficacia oncologica.*

PAROLE CHIAVE: *cancro orofaringeo, HPV, chirurgia robotica transorale (TORS), radioterapia a intensità modulata (IMRT), chirurgia mini invasiva*

Introduction

The incidence of oropharyngeal squamous cell carcinoma (OPSCC) has progressively increased in the last years due to the diffusion of Human Papilloma Virus (HPV). In 2020, OPSCC was the 23rd cancer by incidence worldwide, affecting predominantly males (80%) in their 7th decade [1]. The incidence of OPSCC is expected to increase significantly, with an estimated number of 22.3 new cases per 100,000 people and a rise of 157% by 2045 compared to present data [2].

In contrast with the HPV-negative counterpart, the HPV target population is more likely to be younger with a greater survival probability and loco regional control. This is mainly due to both the longer time to relapses and the lower propensity to develop distant metastases [3,4]. This clinical profile demands less disabling therapies because of patients' life expectancy [3]. The best treatment option is still debated and is currently based on past findings and ongoing studies.

The combination of the most modern and minimally-invasive treatment approaches, such as transoral robotic surgery (TORS) and intensity modulated radiation therapy (IMRT), has been associated with satisfactory oncological outcomes and reduced long-term side effects [5]. Specifically, minimally invasive surgical approaches permit precise removal of the tumour through the mouth, thus avoiding trans-mandibular surgical access. This technique reduces complication rates as well as poor functional and cosmetic outcomes [6]. Unfortunately, it cannot spare possible shoulder impairments due to neck dissection, which should be always taken into account [7]. Similarly, before the advent of IMRT, radiation treatments were burdened by severe late toxicity, such as xerostomia and chronic dysphagia. The need for enteral feeding via percutaneous endoscopic gastrostomy (PEG) was frequent: Machtay et al. reported that 43% of patients suffered from high-grade late toxicity, while 10% were dependent on PEG [8]. Of note, swallowing defects were the most relevant determinants of patients' quality of life [9,10]. Although somehow neglected, dental caries and carotid stenosis are further long-term toxicities to consider: recent meta-analyses reported tooth decay in 29% [11] and vascular endoluminal narrowing > 50% in 25% [12] of irradiated patients, with worsening effects over time. IMRT techniques (e.g. Volumetric Modulated Arc Therapy – VMAT and Tomotherapy) allow the delivery of more conformed doses to the target volume, hence sparing healthy tissues and decreasing toxicity, especially in oropharyngeal cancer tumours [13].

Nowadays, the role of surgery and IMRT in oropharyngeal cancer is highly debated. Several trials are ongoing worldwide to assess the superiority of one strategy over the other [14]. Meanwhile, the choice between these two approaches is based primarily on the physicians' expertise, the institutions' equipment and the patient's preference.

The aim of the present study is to provide real-world data on the two most modern conservative treatment approaches (TOS +/- radiotherapy +/- chemotherapy VS concurrent chemoradiation with IMRT) for locally advanced HPV-positive OPSCC. Oncological outcomes and toxicity profiles are compared.

Materials and methods

We retrospectively reviewed patients treated for locally advanced OPSCC between January 2015 and October 2020 at the European Institute of Oncology (IEO) in Milan. All data were retrieved from a dedicated database.

Inclusion criteria were as follows: 1) age older than 18 years; 2) primary OPSCC of tonsillar lodge (TL), base of tongue (BOT), soft palate (SP), or posterior wall (PW); 3) HPV-DNA or p16 positive tumours; 4) advanced stages (clinical stage III and IV according TNM 7th edition of the American Joint Committee on Cancer -AJCC- Staging system); 5) minimum follow-up of 6 months; 6) availability of written informed consent for the anonymised use of data for scientific purposes. Consequently, patients were excluded in case of: 1) non-SCC histology; 2) early stage (I-II according AJCC 7th edition); 3) HPV-DNA or p16 negative tumours; 4) previous treatment in the head and neck region; 5) need for any open surgical procedure (transcervical, trans-mandibular) in the resection of the primary lesion; 6) treatment for any malignancy in the previous five

years, with the exception of superficial skin tumours; 7) incomplete medical records; 8) enrollment in clinical trials; 9) indication to surgical reconstruction with free or pedicled flaps; 10) radiotherapy performed with non-standard fractionation and or non-IMRT technique; 11) personalised treatment due to the COVID-19 pandemic.

Each clinical case was discussed in a weekly-scheduled Multidisciplinary Board, which included a dedicated head and neck radiologist. The indications were based on National and International guidelines, and in accordance with patients' expectations. As a general rule, upfront TransOral Surgery (TOS) was proposed to smoker patients with T1/T2 lesions. Patients were considered "smokers" in case of exposure greater than 10 pack-years, independently of the timing [4]. All other patients were referred to IMRT (+/- concurrent chemotherapy). Upfront TOS was excluded in case of bilaterally positive neck nodes, radiological evidence of extra nodal extension, unresectable neck disease, tumour extension to more than 50% of base of the tongue (BOT) and radiologically-proven infiltration of parapharyngeal fat tissue.

Pre-treatment staging

All patients were evaluated with fibre optics under white light (WL), "I-scan Chromo Endoscopy system" (Pentax Medical) and HD Video Rhino-Laryngoscope NBI (Storz). Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) were used for loco-regional staging, whereas total body 18-fluorodeoxyglucose Positron Emission Tomography (18-FDG PET) or, alternatively, total body CT scan were used for systemic staging. In case of suspicious nodal involvement which could influence the therapeutic choice (such as contralateral or bilateral lymph nodes), an ultrasound-guided fine needle aspiration was performed to rule out malignancy.

HPV positivity was defined by the detection of p16 on immunohistochemistry (IHC) of at least 70% of cells of a tumour sample or on node fine-needle aspiration cytology (FNAC). In case of p16-IHC expression lower than 70%, HPV-DNA was assessed by polymerase chain reaction (PCR).

Surgical procedure

A standardised TORS approach (en bloc removal of the primary lesion) was performed in all surgical candidates. Surgical steps were as follows: oropharynx exposure was obtained after placing either a Dingman mouth retractor (Mueller, San Diego, CA, USA) or a Feyh–Kastenbauer retractor (Gyrus ACMI, Southborough, MA, USA) or a Davis Meyer mouth gag (Karl Storz, Tuttlingen, Germany, Europe). A lateral oropharyngectomy was performed according to the surgical technique described by Holsinger et al. [15] and Weinstein et al. [16]. The incision is placed between the anterior tonsillar pillar and the pterygo-mandibular raphe; the superior constrictor muscle is sectioned and pulled medially to guide further resection on the deeper parapharyngeal fat. An additional en bloc mucosal resection was incorporated to enclose the hard palate, intermaxillary and buccal mucosa whenever a superficial mucosal involvement of the tonsillar pillars into the mobile tongue, soft palate, or posterior pharyngeal wall was suspected. Base of tongue resections were performed using a 30° three-dimensional robotic telescope with one forceps instrument and either a spatula or hook cautery instrument, as described by O'Malley et al. [17].

Reconstruction of the surgical defect was performed by direct closure or with local flap if necessary, as described by Almeida et al. [18]. However, in the majority of cases patients healed by secondary intention, possibly favoured by a protective layer made of human fibrinogen and thrombin sponge.

The Transoral Laser Microsurgery (TLM) approach adopted is the same described by Steiner et al. [19]. The exposure was obtained with either a Kleinsasser laryngoscope (Karl Storz, Tuttlingen, Germany) or a Steiner's oropharyngoscope (Karl Storz, Tuttlingen, Germany). For visualisation of the surgical field, we adopted a Zeiss OPMI PENTERO 800 (Carl Zeiss AG, Germany) with applied CO_2 laser in super pulse modality.

Surgical margins of the final specimen (superior, inferior, lateral, medial, deep) were macroscopically evaluated for residual disease and then inked by the surgeon in the operating room. Frozen sections were not used routinely, but reserved only for cases with suspicious intraoperative margins.

A therapeutic neck dissection of levels Ib to IV with preservation of submandibular gland was systematically performed at the same time of TOS but ahead of it, so that closure of either the lingual or the facial-pharyngeal arteries could provide better haemostasis during the subsequent oropharyngectomy and also prevent major post-operative bleedings.

A temporary tracheotomy was performed in case of: difficult intubation, high risk of post-operative bleeding because of anticoagulant therapy, or increased risk of post-operative upper airway oedema after prolonged surgery. In case of positive margins after definitive histopathological report, an additional resection was systematically proposed.

Radiation and systemic therapy

Radiation treatment was proposed for both curative and post-operative intent. Indication for postoperative IMRT was given for patients with pT3-pT4 tumours, pN ≥ 2a, extranodal extension, perineural/lymphovascular invasion,

or close or positive surgical margins. According to current indications from international guidelines, concurrent postoperative chemotherapy was 100 mg/m^2 three-weekly cisplatin for three courses in all eligible patients. The concurrent postoperative strategy was offered to patients younger than 70 years and with positive surgical margins and/or extra nodal extension. High-dose cisplatin was the preferred regimen even in the curative setting [20,21], in accordance with the available literature, while cetuximab was considered for patients unfit for cisplatin [22].

Radiation treatment was performed with a VMAT technique using a SIB (Simultaneous Integrated Boost) schedule. Conventional fractionation was proposed for all patients. In case of exclusive treatment, 35 fractions were administered up to a total dose of 70 Gy (2 Gy/day) on gross tumour volume, 63 Gy (1.8 Gy/day) for high risk areas and 58.1 Gy (1.66 Gy/day) for low risk volumes. In case of postoperative IMRT, a total dose of 66 Gy (2 Gy/day) was administered in case of extranodal extension (ENE) and/or positive surgical margins with 59.4 Gy (1.8Gy/day) and 56.1 Gy (1.7 Gy/day) administered to high and low risk volumes, respectively. In all other postoperative cases, 30 fractions were administered up to a total dose of 60 Gy (2 Gy/day) and 54 Gy (1.8 Gy/day) for high and low risk volumes, respectively. All patients were treated with Linear Accelerator and 6 MV energy photons. A thermoplastic head and shoulders mask was used for all positioning and setup. An image-guided technique was applied with a verification CT performed at 40-50 and 60 Gy. Clinical evaluation for toxicity assessment was performed at least once a week during the radiation course.

Follow-up

A clinical evaluation was planned every three months for the first two years after treatments. Subsequently, clinical assessment was performed 4 times/year during the subsequent two years, then 2 times/year for the fifth year. In case of curative IMRT, MRI of the head and neck region was requested 3 months after the end of treatment to assess tumour response. A total body staging was performed once a year for the entire follow-up period with either 18-FDG PET (first choice imaging modality) or CT. In case of recurrent disease, further treatment was defined during the weekly multidisciplinary discussion. Follow-up of patients was carried out in a dedicated outpatient clinic together with a radiotherapist.

Toxicities

Postoperative complications were defined as any event requiring surgical revision (e.g. bleeding or salivary fistula) and all local or systemic events with functional impairment or unforeseen prolonged hospitalisation (more than 7 days). Radiation-related toxicity was assessed immediately after treatment completion, 12 months later, and at last follow-up. Common Terminology Criteria for Adverse Event (CTCAE) scale was used for both the acute and late toxicity. Skin erythema, mucositis, xerostomia and dysphagia were considered as acute toxicity for patients treated with radiotherapy alone, while nausea, renal failure and neutropenia were also investigated in case of concurrent systemic treatments. One year later, skin erythema, xerostomia, dysphagia, laryngeal oedema, dysphonia and soft tissue fibrosis were assessed. At last follow-up, we inquired about severe laryngeal and swallowing dysfunction (defined by the presence of a tracheal tube or the need of enteral nutrition and/or oesophageal dilation) and the presence soft tissue necrosis.

Statistical analysis

We compared patients treated with surgery (group A) and IMRT (group B). For this purpose, a Chi-square test were used to compare categorical variables and Wilcoxon rank test for continuous variables. Overall survival (OS) and progression-free survival (PFS) curves were drawn using the Kaplan-Meier method and log-rank test was used to assess survival differences among curves. Overall survival was calculated from biopsy to death from any cause, or to last contact if alive. Time to progression was defined as the time from biopsy to progression or death or last contact if alive. All patients alive or free from progressions at the last follow-up date were considered right censored.

Results

Data on 196 patients were retrieved. Ninety-six met inclusion criteria and were considered as the present study cohort (Fig. 1). Group A and group B included, respectively, 30 and 66 patients. Demographic and clinical characteristics are summarised in Table I. Age and gender were not significantly different between the two groups ($p = 0.49$ and $p = 0.14$, respectively).

Staging according to both AJCC 7th and 8th editions is reported in Table I. According to AJCC 8th edition, group A had smaller primary tumours (c/pT1-2, $p = 0.002$) and lower stages (I and II, $p < 0.001$) compared to group B. In group A, tumours were located mainly in the TL ($p = 0.03$). Overall, stage IV according to the AJCC 8th edition was absent in both cohorts. About one-third of patients in group B were affected by a stage III disease, whereas patients in group A had stage I or II.

Concurrent chemotherapy was more frequently employed in patients treated in the curative setting rather than the post-operative one ($p < 0.001$).

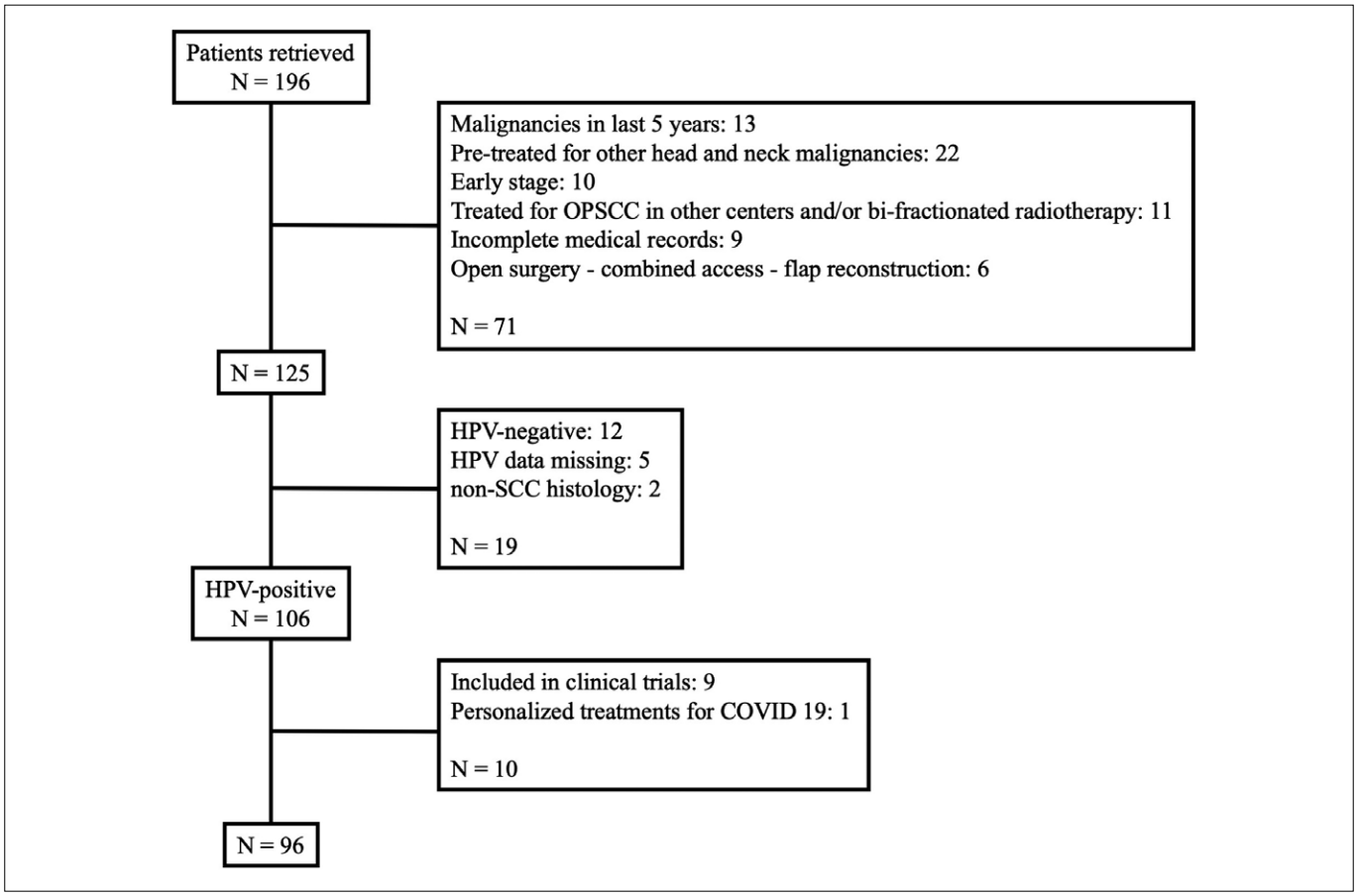

Figure 1. Selection process of patients included in the study.

Group A

Surgical procedures and pathologic characteristics are summarised in Table II.

Three patients had positive surgical margins and were referred to adjuvant chemoradiation, which was already required because of other adverse biologic features.

According to the AJCC 7th edition, the primary tumour clinical stage (cT) was confirmed by pathological examination (pT) in 48% of cases, while it was upstaged in 16/36 (44%): cT1 to pT2 in 14 cases, and to pT3 and pT4 in one case each. In 3/36 (8%) cases, a downstaging occurred (all cases from cT2 to pT1).

Table 3 provides a comparison between pathological T and N stages of the 7th and 8th AJCC editions.

Median hospital stay was 8 days. No post-operative salivary fistulas were recorded. There were no perioperative life-threatening complications and no perioperative deaths. Four patients (11%) suffered bleeding that required surgical revision (two on the primary site and two on the neck).

Ten patients (28%) were treated exclusively by surgery (unimodal treatment), while 11 (30%) received (PORT) and 15 (42%) underwent concurrent chemoradiotherapy. Despite high risk factors (microscopic ENE, see Table II), chemotherapy was omitted in five patients (5/20) because of age > 70 years (n = 3) or comorbidities (n = 2). Thirteen patients received at least 200 mg/m^2 cisplatin. Median interval time between surgery and PORT was 50 days (IQR 47-64 days). Median total dose to "high dose", "high risk" and "low risk" volumes were, respectively, 66, 59.4 and 56.1 Gy. Median treatment duration was 47.5 days (IQR 44-53 days).

During surgery, tracheotomy was performed in 35/36 cases (97%) and was kept in place until required for airway safety. No patients remained tracheotomy-dependent after TOS. Thirty-five patients (97%) resumed oral intake prior to discharge, except for one patient, who maintained a nasogastric feeding tube and needed a percutaneous gastrostomy (PEG) for worsening dysphagia during PORT. The gastrostomy tube was removed 22 months later. During PORT, two additional patients suffered dysphagia and a nasogastric feeding was temporary placed. None of the patients required a tracheotomy during the

radiation course (Supplementary Table I). One patient died 13 months after PORT (IMRT) due to a pharyngo-vertebral fistula. Of note, patients treated with exclusive surgery did not report any toxicities or dysfunction, except for a single shoulder impairment due to a radical neck dissection.

Group B

Median total dose to "high dose", "high risk" and "low risk" volumes were, respectively, 70, 63 and 58.1 Gy. Median treatment duration was 53 days (IQR 50-56 days). Six patients were treated with exclusive radiotherapy, because of age (n = 3), low-risk tumours (n = 2) and comorbidities

Table I. Demographic and clinical characteristics of the study cohort.

	Group A N = 36 (100%)	Group B N = 60 (100%)	Overall N = 96 (100%)	p-value
Pack year (%)				
≤ 10	9 (25)	10 (17)	19 (20)	0.09
10	13 (36)	13 (22)	26 (27)	
Missing	14 (39)	37 (61)	51 (53)	
Potus* (%)				
No	33 (92)	55 (92)	88 (92)	0.11
Yes	2 (5)	0 (0)	2 (2)	
Missing	1 (3)	5 (8)	6 (6)	
Sex (n %)				
Male	30 (83)	42 (70)	72 (75)	0.22
Female	6 (17)	18 (30)	24 (25)	
Age at diagnosis				
Median [q1,q3]	62.0 [53, 68]	60.0 [55, 66]	61.0 [54, 67]	0.66
Oropharyngeal subsite (%)				
Tonsillar lodge	28 (78)	31 (51.7)	57 (62)	0.032
Base of tongue	8 (22)	27 (45.0)	35 (36)	
Soft palate	0 (0)	2 (3.3)	2 (2)	
cT AJCC 7th edition (%)				
0	0 (0)	1 (1.7)	1 (1)	< 0.001
1	26 (72)	15 (25.0)	41 (43)	
2	10 (28)	25 (41.7)	35 (36)	
3	0 (0)	6 (10.0)	6 (6)	
4	0 (0)	13 (21.7)	13 (14)	
cN AJCC 7th edition (%)				
0	0 (0)	1 (1.7)	1 (1)	0.38
1	18 (50)	20 (33.3)	38 (40)	
2	17 (47)	36 (60.0)	53 (55)	
3	1 (3)	3 (5.0)	4 (4)	
Stage for AJCC 7th edition (%)				
I	0 (0)	0 (0)	0 (0)	0.53
III	11 (31)	19 (32)	30 (30)	
IVA	25 (69)	38 (63)	60 (60)	
IVB	0 (0)	3 (5)	6 (6)	
Stage for AJCC 8th edition (%)				
I	28 (78)	33 (55)	61 (64)	0.002
II	8 (22)	10 (17)	18 (19)	
III	0 (0)	17 (28)	17 (18)	

** alcohol consumption.*

(n = 1). Fifty-four (90%) received concurrent chemotherapy, mainly cisplatin (47/54). In this subset, the majority (45/47, 98%) reached a total dose of >200 mg/m^2. Details of radiation treatment and concurrent chemotherapy (in both the postoperative and curative settings) are reported in Supplementary Table II.

During treatment, three patients needed a nasogastric feeding tube for dysphagia and two were dependent on enteral nutrition at last follow-up. One patient needed a tracheotomy and was still tube-dependent at last follow-up (see Supplementary Table I).

Recurrence and survival outcomes

The median follow-up time was 37 months in group A and 28 months in group B. The 2-year OS and PFS were 97% and 83% in the former, and 98% and 86% in the latter (Figs. 2 and 3).

Likewise, local control (LC) and locoregional control (LRC) were 94% and 94% in group A and 100% and 92% in group B, respectively. Data relating to relapses (incidence and treatment) as well as incidence of secondary tumours are reported in Table IV.

OS and PFS were not significantly different between the two groups, as were both the rate of mortality (2 patients in group A, 1 patient in group B, p 0.29) and relapses (6 *vs* 8, p = 0.61). Disease progression was not affected by smoking exposure (p = 0.93).

Toxicity

We compared toxicities between the two groups only in patients affected by stage I and stage II disease (8th edition) due to the lack of stage III in group A and missing data for patients submitted to exclusive TOS. We did not find any significant differences in the parameters investigated. Results are summarised in Table V.

Toxicity related to concurrent chemoradiation is reported

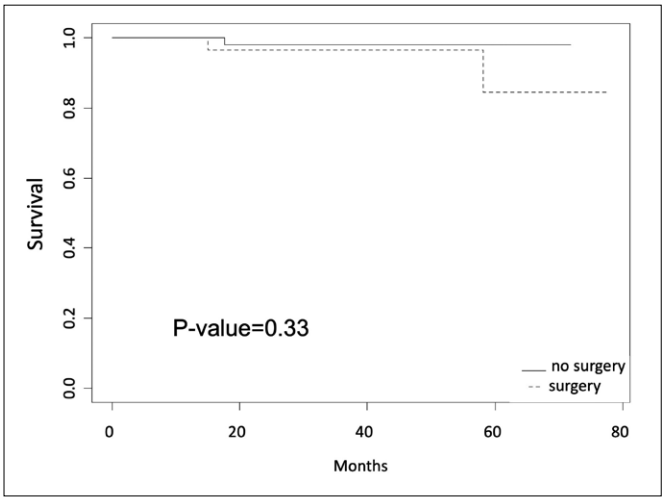

Figure 2. Overall survival by surgery.

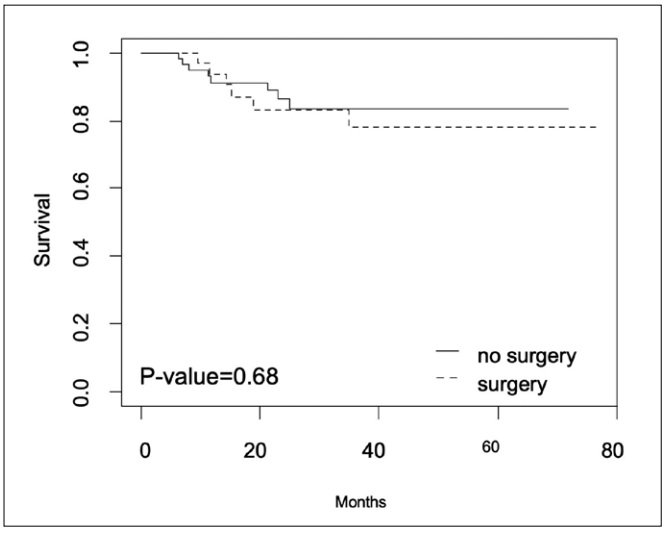

Figure 3. Progression-free survival by surgery.

Table II. Details on surgical procedures and tumour biological characteristics.

Characteristics		N = 36
Surgical approach	Transoral robotic surgery	34 (94)
	Transoral laser microsurgery	2 (6)
Lymph node neck dissection	Functional neck dissection	34 (94)
	Radical neck dissection	1 (3)
	Modified radical neck dissection	1 (3)
Surgical margins	Positive margins	3 (8)
	Negative margins	33(92)
High-risk pathologic features	Extra nodal extension	20 (55)
	Perineural invasion	2 (6)
	Vascular invasion	1 (3)

Table III. Pathological T and N stage in the surgical cohort according to AJCC 7th and 8th editions.

pT_7th edition (%)		pT_8th edition (%)	
pT1	13 (36)	pT1	13 (36)
pT2	21 (58)	pT2	21 (58)
pT3	1 (3)	pT3	1 (3)
pT4	1 (3)	pT4	1 (3)
Missing	0	Missing	0
pN_7th edition (%)		**pN_8th edition (%)**	
pN0	1 (3)	pN0	1 (3)
pN1	10 (28)	pN1	30 (83)
pN2a	8 (22)	pN2	5 (14)
pN2b	15 (42)		
pN3	2 (6)	pN3	0
Missing	0	Missing	0

Table IV. Tumour relapses (incidence and treatment) and secondary tumours.

	Group A N = 36	Group B N = 60	Total N = 96
Overall recurrences (%)	6 (18)	8 (13)	14 (14)
Local	2 (6)	0	2 (2)
Locoregional	2 (6)	5 (8)	7 (7)
Distant metastases	2 (6)	3 (5)	5 (5)
Treatment of recurrences (%)	6 (18)	8 (13)	14 (14)
Surgery	2 (6)	4 (7)	6 (6)
Surgery + postoperative chemoradiation	1 (3)	0	1 (1)
Chemotherapy	1 (3)	2 (3)	3 (3)
Concurrent chemoradiotherapy	1 (3)	0	1 (1)
Missing	1 (3)	2 (3)	3 (3)
Secondary tumours (%)	2 (6)	3 (5)	5 (5)
Kidney	1 (3)	0	1 (1)
Lung	0	1 (2)	1 (1)
Head and Neck	0	2 (3)	2 (2)
Skin	1 (3)	0	1 (1)

in Supplementary Table III. Nausea/vomiting, neutropenia and renal failure occurred only in patients treated with concurrent chemotherapy.

Discussion

The present study presents real-world data on clinical outcomes and side effects of two modern strategies (minimally invasive surgery and highly conformed RT+/- systemic treatment) to treat locally-advanced HPV-related OPSCC. Both approaches achieved good oncologic outcomes with a favourable toxicity profile, without significant differences between the two groups. Literature data show that results of upfront TORS and curative IMRT are similar in this clinical setting [5,23,24]. Our analysis confirms this finding, as no differences in OS and PFS were found between the two cohorts of patients. Admittedly, comparison between different approaches may be burdened by several biases. Firstly, patients who underwent curative IMRT had only clinical disease staging, while surgical patients had complete pathological assessment. In this latter cohort, an upstage of the primary tumour following surgery occurred in 44% of cases. Historical series show that T3 and T4 tumours are more frequent in non-surgical cohorts compared to surgical ones [23]. Similarly, in the present study stage III was absent in group A, whereas it represented 28% of tumours in group B. Secondly, the absence

Table V. Toxicity at the end of radiotherapy and after one year for the curative and postoperative settings. ST systemic treatment, TOS transoral surgery.

	TOS followed by postoperative radiotherapy (N = 26)	Curative radiotherapy (+/- ST) (N = 43)	Overall (N = 69)	p-value
Early toxicity (%)				
Skin				
G0-G1	12 (46.2)	27 (62.8)	39 (56.5)	0.45
G2-G3	12 (46.2)	16 (37.2)	28 (40.6)	
Missing	2 (7.7)	0 (0)	2 (2.9)	
Mucositis				
G0-G1	14 (53.8)	25 (58.1)	39 (56.5)	0.99
G2-G3	10 (38.5)	18 (41.9)	28 (40.6)	
Missing	2 (7.7)	0 (0)	2 (2.9)	
Dysphagia				
G0-G1	15 (57.7)	28 (65.1)	43 (62.3)	0.99
G2-G3	9 (34.6)	15 (34.9)	24 (34.8)	
Missing	2 (7.7)	0 (0)	2 (2.9)	
Xerostomia				
G0-G1	21 (80.8)	38 (88.4)	59 (85.5)	0.70
G2-G3	3 (11.5)	4 (9.3)	7 (10.1)	
Missing	2 (7.7)	1 (2.3)	3 (4.3)	
Weight loss				
15 ≤ (sample median)	11 (42.3)	24 (55.8)	35 (50.7)	0.70
15 > sample median)	15 (57.7)	19 (44.2)	34 (49.3)	
Late toxicity (%)				
Skin				
G0-G1	15 (57.7)	32 (74.4)	47 (68.1)	0.33
G2	1 (3.8)	0 (0)	1 (1.4)	
Missing	10 (38.5)	11 (25.6)	21 (30.4)	
Mucositis				
G0	13 (50.0)	21 (48.8)	34 (49.3)	0.45
G1	2 (7.7)	8 (18.6)	10 (14.5)	
Missing	11 (42.3)	14 (32.6)	25 (36.2)	
Dysphagia				
G0-G1	15 (57.7)	33 (76.7)	48 (69.6)	0.33
G2	1 (3.8)	0 (0)	1 (1.4)	
Missing	10 (38.5)	10 (23.3)	20 (29.0)	
Xerostomia				
G0-G1	16 (61.5)	24 (55.8)	40 (58.0)	0.10
G2	0 (0)	7 (16.3)	7 (10.1)	
Missing	10 (38.5)	12 (27.9)	22 (31.9)	
Laryngeal dysfunction				
G0	14 (53.8)	28 (65.1)	42 (60.9)	0.60
G1	2 (7.7)	2 (4.7)	4 (5.8)	
Missing	10 (38.5)	13 (30.2)	23 (33.3)	
Soft tissue fibrosis				
G0-G1	16 (61.5)	31 (72.1)	47 (68.1)	0.99
G2	0 (0)	1 (2.3)	1 (1.4)	
Missing	10 (38.5)	11 (25.6)	21 (30.4)	
Pain				
No	0 (0)	13 (30.2)	13 (18.8)	0.13
Yes	1 (3.8)	1 (2.3)	2 (2.9)	
Missing	25 (96.2)	29 (67.4)	54 (78.3)	

of pathological features (extra nodal extension, perineural and lymphovascular invasion and tumour grading) in the non-surgical cohort does not allow analyses on either prognostic or predictive factors.

Overall, our results confirm that the main advantage of surgery over RT is comprehensive pathologic assessment. Whether this advantage justifies a trimodal approach (surgery + radiotherapy +/- chemotherapy) in up to 40% of patients remains a matter of debate. Ideally, trimodal therapy should be offered to high-risk subjects who may benefit from more intense treatment. In this scenario, stratification granted by surgery is key to refine the treatment strategy. Current studies investigating the role of de-intensified PORT after minimally-invasive surgery may provide further clinical information and potentially allow a more personalised approach.

Thanks to technological improvements, toxicity rates in this clinical setting are becoming progressively more acceptable. To date, upfront TOS, and in particular TORS, seems effective in reaching good functional outcomes in the treatment of stage III-IV OPSCC [25-29]. Compared to open surgical approaches, TOS shows significant lower complication rates without jeopardising clinical results [6]. Similarly, the introduction of IMRT in daily clinical practice has allowed us to improve the long-term toxicity profile (e.g. xerostomia, mucositis, weight loss, oesophageal stenosis and osteonecrosis) thanks to the higher conformity of radiation doses around target volumes [13,30-32]. However, data on the comparison between these two approaches (TOS vs IMRT) are not homogenous. Superior functional outcomes of patients treated by TORS were frequently reported in retrospective analyses [8,9,33,34]. On the contrary, the prospective randomised clinical trial ORATOR showed equivalence in oncologic and functional outcomes between TOS and CRT, with a trend towards better outcomes in terms of swallowing in patients treated with IMRT [35,36]. The present analysis clearly showed a favourable and comparable toxicity profile with both approaches. Interestingly, patients submitted to trimodal treatment suffered side effects similar to those treated with chemoradiation only, for most of the parameters considered. The expected higher toxicity of an intensified approach might be balanced by highly selective treatments (i.e. minimally invasive surgery and postoperative IMRT). Nevertheless, the presence of more advanced stages and more frequent use of concurrent chemoradiation could have worsened the toxicity profile in the non-surgical cohort.

Overall, 11% of patients suffered surgical-related complications, and in particular only 2 cases (5.5%) of oral bleeding were recorded. This data is in line with other experiences [37]. No life-threatening events occurred among patients submitted to surgery. These encouraging results suggest that candidates for minimally-invasive surgical procedures should be referred to high-volume centres with dedicated equipment and medical expertise. Although toxicities are multifactorial, the employment of highly selective strategies can undoubtedly help in minimising both surgical and radiation-related side effects.

An advocated advantage of surgical over non-surgical approaches is the possibility of unimodal treatment in about one-third of patients. Of note, in this cohort, swallowing is recovered immediately after treatment and remains stable over time [38]. In their 4-year-long surgical series (2014-2018), Huang et al. reported that 70% of patients had received adjuvant treatment, and concurrent chemoradiation in almost half of cases [5]. Other authors showed that upfront TOS proved successful in sparing RT in 9-27% of cases and CRT in 34-45% [34,39,40]. Our results agree with literature data, since about 30% of patients were treated with surgery only, because of the lack of pathological risk factors.

An et al. showed that a trimodal approach, required in about 48% of advanced OPSCC, was mainly due to the presence of ENE and an advanced pN stage [41]. According to a recent review by Dhanireddy et al., the addition of concurrent chemotherapy in patients with ENE does not provide clear benefit in terms of survival, while it is associated with additional costs and increased toxicity [34]. Therefore, whether extra nodal extension demands an intensified approach (higher radiation doses and concurrent chemotherapy) is currently being investigated in ongoing trials [41]. In our cohort, only 3 patients were referred to postoperative chemoradiation with positive resection margins, because further excision would have delayed the adjuvant treatment, without sparing any part of it. Once again, this data agrees with similar reports in the literature [5,40].

The impact of smoking in HPV-related tumours is still debated [38]. As a general rule, smoking has a negative impact on patients diagnosed with OPSCC HPV-positive cancers. Ang et al. observed that the mortality risk for OPSCC smoker patients is similar, regardless of the HPV status [4]. Not only may smoking act as an independent negative prognostic factor, but HPV-positive OPSCC smoker patients have worse prognosis compared to non-smokers diagnosed with the same disease [42]. However, the mechanism behind the detrimental effect of smoke on outcomes remains unclear. A few hypotheses are currently under evaluation: the increased prevalence of comorbidities among smokers; their higher risk of second primaries; the lower effectiveness of RT due to smoke-related hypoxia; the lower compliance due to the increased RT-related toxicity, and possible interplays with tumour biology [5]. In our cohort, surgery was more frequently proposed in heavy smokers (> 10 pack-

year) and smoking exposure was not clearly associated with clinical outcomes, although the results are inconclusive because of missing data in terms of pack-years. This finding may derive from the alleged mitigating effect granted by a combined approach (surgery followed by RT +/- concurrent chemotherapy). This hypothesis is supported by some literature data. In 404 patients undergoing exclusive chemoradiation, Liu et al. observed that smokers had shorter OS and PFS than non-smokers [43]. However, Roden et al. studied 258 patients submitted to TORS and found no differences in recurrence-free survival according to smoking exposure (pack-year) [25]. We can arguably state that the negative impact of smoke on prognosis could be balanced by more intensive treatment, which includes surgery.

Of course, our study has some limitations, mainly its retrospective nature, the presence of unbalanced cohorts and the lack of a systematic data collection of surgery-related toxicity (e.g. scar fibrosis, functional shoulder impairment). Nevertheless, the strengths of this analysis are represented by the prospective data collection of radiotherapy-related toxicities, homogeneity of surgical procedures and radiation technique, and accurate pre-treatment staging and follow-up procedures. Moreover, these real-world data demonstrate the feasibility, efficacy and the favourable toxicity profile of TORS and IMRT in HPV-related OPSCC. Further efforts are required to define the best treatment options according to the clinical and pathological characteristics in this subpopulation with good prognosis.

Conclusions

The incidence of HPV-positive OPSCC has been growing constantly in last decade. The disease typically affects young subjects with longer life expectancy compared to classic head and neck patients. Fortunately, the tumour may be treated surgically and non-surgically with equally favourable outcomes even in intermediate and advanced stages. In this scenario, reduction of treatment-related toxicities has become of utmost importance, particularly in the long term. On one hand, de-escalation of radiation and chemotherapy is currently being investigated and results are soon expected. On the other hand, minimally-invasive transoral surgery, and mainly TORS, has already been shown to be effective in reducing complications and hospitalisations, while granting oncologic safety and function preservation. In this scenario, are all treatments really equal or is it time to re-think and tailor our approach? Our impression, based on our experience and current literature data, is that, pending the results of important ongoing prospective randomised trials, minimally-invasive surgery should be offered primarily to patients with low-risk HPV-related oropharyngeal cancer, who can be treated unimodally, whereas chemoradiation should be the first option in high-risk patients. Instead, de-intensification protocols should be proposed to intermediate-risk patients.

Accurate pre-treatment staging and patient selection, together with referral to high-volume centres, are key in providing patients with the best chance of survival and preserved quality of life.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Conceptualisation: MA, SZ, DA . Data and material acquisition: GA, FCh, MT, FR, GM, FCo. Data Analysis: SG, AG. Writing and editing: SZ, GC, DA, MCR, GP. Reviewing: MA, DA, SV.

Ethical consideration

This study was approved by the Ethics Committee of the European Institute of Oncology (approval number 3016). The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from each patient for study participation and data publication.

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Supplementary Table I. Need for nutritional and respiratory support in the three cohorts of patients.

	NGT	PEG	Tracheotomy
TOS (N 36)	Elective 36/36 (100%) Removed 35/36 (97%)*	0	Elective 35/36 Removed 35/35 (100%)
IMRT +/- ST post op (N 26)	3/26 (11%)	1/26 (4%)*	0
IMRT +/- ST curative (N 60)	3/60 (5%)	2/60 (3%) Removed 0	1/60 Removed 0

**PEG was performed in the single patient (1/36) who was not able to resume oral intake after TOS. The device was removed 22 months after placement. TOS: transoral surgery; IMRT: intensity-modulated radiotherapy; ST: systemic treatment.*

Supplementary Table II. Technical characteristics of the radiation and systemic treatment.

Postoperative radiotherapy (26 patients)	
Radiotherapy alone	11/26 (42%)
VMAT	10/26 (38%)
IMRT fixed-fields	0
Tomotherapy	1/26 (4%)
Postoperative concurrent chemoradiotherapy	15/26 (58%)
VMAT	13/26 (50%)
IMRT fixed-fields	1/26 (4%)
Tomotherapy	1/26 (4%)
Chemotherapy schedule	
Three-weekly cisplatin	14/15 (93%)
Weekly cisplatin	1/15 (7%)
Curative radiotherapy (60 patients)	
Radiotherapy alone	6/60 (10%)
IMRT	0
VMAT	6/60 (10%)
IMRT fixed-field	0
Tomotherapy	0
Concurrent chemoradiotherapy	54/60 (90%)
VMAT	54/60 (90%)
IMRT fixed-field	0
Tomotherapy	0
Chemotherapy schedule	
Three-weekly cisplatin	45/54 (83%)
Weekly cisplatin	2/54 (4%)
Cetuximab	5/54 (9%)
Miscellaneous	2/54 (4%)

VMAT: Volumetric Modulated Arc Therapy.

Supplementary Table III. Adverse effects related to concurrent chemoradiation.

	TOS + Postoperative CT/RT 15 patients	Curative CT/RT 54 patients
Nausea and vomiting		
G0	5/15 (33%)	31/54 (57%)
G1	10/15 (67%)	11/54 (20%)
G2	0	10/54 (19%)
G3	0	2/54 (4%)
Neutropenia		
G0	0	34/54 (63%)
G1	6/15 (40%)	2/54 (4%)
G2	8/15 (53%)	11/54 (20%)
G3	1/15 (7%)	7/54(13%)
Renal failure		
G0	14/15 (93%)	43/54(80%)
G1	1/15 (7%)	7/54 (13%)
G2	0	5/54 (7%)
G3	0	0

CT/RT: chemoradiation; G: grade.