Strahlenther Onkol (2019) 195:496–503
https://doi.org/10.1007/s00066-019-01451-8

ORIGINAL ARTICLE

Definitive radiochemotherapy or initial surgery for oropharyngeal cancer

To what extent can p16 expression be used in the decision process?

Anouchka Modesto[1] · Thibaut Galissier[2] · Amélie Lusque[3] · Jean-Pierre Delord[4] · Emmanuelle Uro-Coste[2] · Jérôme Sarini[5] · Frédéric Mouchet[6] · Raphaël Lopez[7] · Anne Laprie[1] · Pierre Graff[1] · Sébastien Vergez[5] · Michel Rives[1]

Received: 31 August 2018 / Accepted: 27 February 2019 / Published online: 15 March 2019

Abstract

Background The decision between definitive radio(chemo)therapy (RCT) or a surgical strategy, i.e. surgery ± adjuvant radio(chemo)therapy for optimal treatment of oropharyngeal cancer is highly debated. Human papillomavirus(HPV)-related tumours are a distinct entity associated with p16 overexpression. While this represents a major prognostic factor, its predictive significance remains unknown.

Results Among 183 consecutive unselected patients treated between 2009 and 2013 with a state-of-the-art surgical procedure ± adjuvant radio(chemo)therapy or definitive RCT including intensity-modulated radiotherapy, 3-year disease-free survival (DFS) was 74 vs. 57%, respectively ($p=0.007$). When focusing on p16+ patients (49%), there was no significant difference in tumour control rate between surgery ± radio(chemo)therapy and the definitive RCT group (3-year DFS 83 vs. 82%, respectively; $p=0.48$). However, delayed severe dysphagia was significantly lower in favour of definitive RCT: 35 vs. 4%, respectively; $p=0.0002$.

Conclusion Our results highlight distinct outcomes after definitive RCT or initial surgical treatment according to p16 status, which should thus be considered during the decision process.

Keywords Human papillomavirus · Genes, p16 · Radiotherapy · Survival · Risk factors

S. Vergez and M. Rives are co last authors.

✉ Anouchka Modesto, M.D.
modesto.anouchka@iuct-oncopole.fr

[1] Radiation Oncology Department, Institut Claudius Regaud, Institut Universitaire du Cancer de Toulouse, 1 avenue Irène Joliot-Curie, Cedex 9, 31059 Toulouse, France

[2] Pathology Department, Centre Hospitalo-Universitaire de Toulouse, Institut Universitaire du Cancer de Toulouse, 1 avenue Irène Joliot-Curie, Cedex 9, 31059 Toulouse, France

[3] Biostatistics Department, Institut Claudius Regaud, Institut Universitaire du Cancer de Toulouse, 1 avenue Irène Joliot-Curie, Cedex 9, 31059 Toulouse, France

[4] Medical Oncology Department, Institut Claudius Regaud, Institut Universitaire du Cancer de Toulouse, 1 avenue Irène Joliot-Curie, Cedex 9, 31059 Toulouse, France

[5] Head and Neck Surgery Department, Centre Hospitalo-Universitaire de Larrey, Institut Universitaire du Cancer de Toulouse, 1 avenue Irène Joliot-Curie, Cedex 9, 31059 Toulouse, France

[6] Head and Neck Surgery Department, Clinique Ambroise Paré, Toulouse, France

[7] Maxillo-facial Surgery Department, CHU Toulouse Purpan, 1 place Baylac, Toulouse, France

Definitive Radiochemotherapie oder initiale Operation beim Oropharynxkarzinom

In welchem Umfang kann die p16-Expression im Entscheidungsprozess verwendet werden?

Zusammenfassung

Hintergrund In der Erstlinie werden die radio(chemo)therapeutische und die chirurgische Strategie z. B. Operation ± adjuvante Radio(chemo)therapie (RCT) für die oropharyngeale Krebsbehandlung stark diskutiert. Humane-Papillomvirus(HPV)-induzierte Tumore sind eine eigenständige Entität, die mit einer p16-Überexpression assoziiert ist, die einen wichtigen prognostischen Faktor darstellt, deren prädiktive Bedeutung jedoch unbekannt bleibt.

Ergebnisse Unter unseren 183 konsekutiven nichtselektionierten Patienten, die zwischen 2009 und 2013 mit Resektion mit adjuvanter Therapie oder moderner definitiver RCT einschließlich intensitätsmodulierter Strahlentherapie (IMRT) behandelt wurden, beträgt das krankheitsfreie 3-Jahres-Überleben (DFS) jeweils 74 vs. 57 % ($p = 0{,}007$). Bei der Fokussierung auf Patienten mit p16+ (49 %) ergab der chirurgische vs. radiotherapeutische Ansatz eine ähnliche Tumorkontrollrate (3-Jahres-DFS 83 vs. 82 %; $p = 0{,}48$), jedoch führte die Resektion gefolgt von adjuvanter Therapie zu einer signifikant höheren Rate an verzögerter schwerer Dysphagie (35 vs. 4 %; $p = 0{,}0002$).

Schlussfolgerung Unsere Resultate heben die unterschiedlichen Ergebnisse nach definitiver RCT oder initialer chirurgischer Behandlung gemäß p16-Status hervor, die im Entscheidungsprozess berücksichtigt werden sollten.

Schlüsselwörter Humanes Papillomvirus · Gene, p16 · Strahlentherapie · Überleben · Risikofaktoren

Over the past decades, the epidemiology of oropharyngeal squamous cell carcinoma (OSCC) has been characterised by an increased incidence attributed to human papillomavirus (HPV) infection [1, 2]. HPV-related (HPV+) OSCCs differ from other head and neck squamous cell carcinomas commonly associated with chronic smoking and drinking intoxication. They occur in healthier individuals with little or no tobacco consumption, and despite a high rate of nodal extension at diagnosis, locoregional recurrence rates decrease and survival improves irrespective of disease stage or treatment option when compared to HPV-unrelated (HPV–) OSCC patients [3]. One of the hallmarks of HPV+ OSCC is overexpression of p16, a cell cycle regulator protein whose positivity in immunochemistry is considered to be a reliable surrogate marker of an HPV-driven oncogenic process [4]. This has resulted in the development and validation of a specific staging system for HPV-related OSCC based on p16 status [5]. In OSCC, treatment options consist of either surgery followed by adjuvant radio(chemo)therapy (surgical treatment) or definitive radio(chemo)therapy (RCT) [6]. Although HPV-related OSCCs are a distinct entity and p16 overexpression represents a major prognostic factor, limited data are available on its predictive significance. No strategy has been identified as more effective and no predictive factors guide the treatment decision; nevertheless, further evidence on this issue is required. To assess the effect and the late toxicity profile of each strategy based on p16 expression, we retrospectively reviewed all consecutive patients treated for OSCC with curative intent between January 2009 and December 2013 at our tertiary cancer centre.

Patients and methods

As part of an institutional board-approved study, all consecutive patients treated with curative intent for OSCC between January 2009 and December 2013 were identified from a prospective departmental database ($N = 278$). Clinical records were retrospectively reviewed to verify patient and tumour characteristics, treatment details and clinical outcomes. Ninety-five patients were excluded from analyses for the following reasons: metastatic disease at diagnosis ($N = 4$), multiple synchronous tumour sites ($N = 22$), history of prior head and neck carcinoma ($N = 20$), three-dimensional conformal radiotherapy ($N = 26$) or material not available for p16 review ($N = 23$).

Pretherapeutic evaluation included:

- physical examination of the head and neck by a surgeon and radiation oncologist,
- triple endoscopy under general anaesthesia,
- biopsies and biological tests,
- cervical and thoracic CT scan (fluorodeoxyglucose positron-emission tomography [FDG PET] was optional),
- orthopantomogram and a dedicated dental consultation,
- nutritional assessment by a dietitian,
- vocal and swallowing evaluation by a dedicated speech and swallowing therapist.

Tumours were staged according to the American Joint Committee on Cancer (AJCC; 7th edition) and each case was discussed by an institutional multidisciplinary head and neck cancer board before treatment was initiated.

Treatment decisions were made at the discretion of the institutional multidisciplinary head and neck tumour board.

Definitive radio(chemo)therapy was indicated in cases of unresectable tumours, when general anaesthesia was contraindicated due to medical conditions or in some cases of small primary cancer of the tonsil or base of the tongue. Surgery consisted of en bloc resection of the lateral wall of the oropharynx, the close portion of the soft palate, partial glossectomy and mandibulectomy in case of bone extension. When the primary tumour did not extend over the midline, a unilateral I to V dissection was performed. In cases of significant resection leading to expected functional impairment, free flap reconstruction was provided for. Detailed operative approaches are depicted in Table 2. In some cases of small tumours with bulky nodal extension (≥3 cm), an initial neck dissection was performed before definitive radio(chemo)therapy as previously reported [7]. During radiotherapy (RT), all patients were immobilised in a supine position using a five-point thermoplastic mask. A contrast-enhanced CT scan was obtained for treatment planning. All available diagnostic MRI and/or PET scans were fused to the treatment planning CTs. RT was delivered using intensity modulated RT (IMRT): step and shoot, volumetric-modulated arc therapy (VMAT) or Tomotherapy® (Accuray Incorporated, Sunnyvale, CA, US) using the integrated boost technique as previously reported [8]. In the definitive setting, patients were prescribed a dose of 66–70 Gy in 30–35 fractions to a high-risk planning target volume (PTV) and 54–56 Gy in 30–35 fractions to low-risk PTV. Adjuvant RT was indicated in cases of T3–T4 tumours or large nodal extension (>2 involved nodes or diameter >15 mm). In the postoperative setting, the prescription dose was 54–63 Gy in 27–30 fractions to the high-risk PTV and 54 Gy in 30 fractions to the low-risk PTV. Concurrent platin-based chemotherapy was added to adjuvant radiotherapy in cases of extra-capsular spreading or involved final resection margin. Follow-up consisted of three-monthly physical examinations, which included direct fibreoptic nasopharyngeal laryngoscopy by a radiation oncologist or a head and neck surgeon. Contrast-enhanced CT evaluation was performed 3 months after treatment completion and annually thereafter, or if failure was suspected. All patients were seen by a dedicated dentist and a speech and swallowing therapist twice a year for the first year after RT completion and annually thereafter. Salivary and swallowing functions were closely monitored during follow-up and were classified as "normal" function, "moderate" or "severe impairment or feeding tube dependency", and were retrospectively scored according to the Common Terminology Criteria for Adverse Events (CTCAE) scale (version 4.3) at last follow-up or before any locoregional failure within a minimum of 6 months after RT and/or surgery completion. Delayed severe toxicities were defined as grade 3 or higher dysphagia, xerostomia or osteoradionecrosis.

Immunostaining of p16INK4A was performed on 3 µm thick formaldehyde-fixed paraffin-embedded tissue sections, which were deparaffinised using high-pH solution. As a primary p16INK4A antibody, clone E6H4 (mouse monoclonal, 1:30 dilution; Roche, Almere, the Netherlands) was used and detected using Powervision (DAKO A/S, Glostrup, Denmark) and peroxidase-DAB visualisation [4]. Two independent dedicated head and neck pathologists (TG or EUC) performed evaluations of the immunostained samples and a consensus was reached on the scores. Positive p16 status was defined by continuous strong nuclear p16INK4A positivity with or without cytoplasmic staining observed in all tumour cells. In each analysis, negative and positive controls were included. The data were summarised as frequency and percentage for categorical variables and by median, range (min.–max.) and interquartile range (Q1–Q3) for continuous variables. The chi-squared or Fisher's exact test was used to compare categorical variables, and the Kruskal–Wallis test was used for continuous variables. All survival times were calculated from the date of diagnosis and were estimated by the Kaplan–Meier method with 95% confidence intervals (CI) using the following first-event definitions: locoregional relapse for locoregional control (LRC), metastatic relapse for freedom from metastases (FFM), locoregional relapse, metastatic relapse, other cancer or death from any cause for disease-free survival (DFS) and death from any cause for overall survival (OS). Univariate and multivariate analyses were performed using the logrank test and Cox proportional hazards model, respectively. All reported p-values were two sided. For all statistical tests, a statistical difference was considered significant at the 5% level. Statistical analyses were conducted using Stata®, version 13 (StataCorp LLC, College Station, TX, USA).

Results

A total of 183 patients were included in this study. Among them, 89 (49%) presented with p16 overexpression (p16+). When compared to p16-negative (p16–) patients, p16 overexpression correlated with better medical condition (International Prognostic Score [IPS] score 0: 84 vs. 36%; $p < 0.001$), smaller primary tumour (T1–2: 70 vs. 48%; $p = 0.003$) and a high rate of nodal extension (N2–N3: 64 vs. 54%; NS). There were no significant differences regarding final resection (margins involved or ≤2 mm: 37 vs. 34%) or extracapsular spreading (58 vs. 47%). The overall cohort repartition according to Ang's risk profile was equal to 38, 12 and 50% in low-, intermediate- and high-risk subgroups, respectively [9]. Patient and tumour characteristics according to p16 status are listed in Table 1.

Table 1 Initial demographic and disease characteristics according to p16 status

	Overall cohort ($n=183$)	p16– ($n=94$)	p16+ ($n=89$)	*P*-value
Median age at initial diagnosis (years; range; IQR)	58 (37–84) (52–65)	57 (42–84) (52–63)	60 (37–84) (53–65)	0.099
Male/female (%)	135 (74)/48 (26)	70 (74.5)/24 (25.5)	65 (73)/24 (27)	0.825
Initial IPS 0/1–3 (%)	109 (60)/74 (40)	34 (36)/60 (64)	75 (84)/14 (16)	<0.001*
Tobacco consumption >10 pack-years (%)	119 (69) Missing no. = 11	85 (98) Missing no. = 7	34 (40) Missing no. = 4	<0.001*
Alcohol abuse (%)	101 (55)	81 (86)	20 (22.5)	<0.001*
Primary stage T1–2/T3–4 (%)	107 (58)/76 (42)	45 (48)/49 (52)	62 (70)/27 (30)	0.003*
Nodal stage N0–1/N2–N3 (%)	75 (41)/108 (59)	43 (46)/51 (54)	32 (36)/57 (64)	0.178

IQR interquartile range, *IPS* International Prognostic Score
*Statistically significant *p*-value

Table 2 Treatment characteristics and pathological findings according to p16 status

	Overall cohort ($n=183$)	p16– ($n=94$)	p16+ ($n=89$)	*P*-value
Induction CT (%)	27 (15)	17 (18)	10 (11)	0.192
Primary tumour resection (%)	77 (42)	39 (42)	38 (43)	0.868
Type of surgery (n = 77)				
TORS	5 (7)	1 (3)	4 (11)	–
Transoral resection	27 (36)	13 (34)	14 (37)	–
Transmandibular resection	45 (58)	25 (64)	20 (53)	–
Flap reconstruction type (%)	50 (27)	25 (26)	25 (28)	0.821
Pediculised flap	13 (7)	6 (6)	7 (8)	–
Free flap	37 (20)	19 (20)	18 (20)	–
Margins ≤2 mm (%) (n = 77)	27 (36)	13 (34)	14 (37)	0.81
Cervical dissection (%)	102 (56)	45 (48)	57 (64)	0.028
Unilateral	75 (74)	29 (64)	46 (81)	–
Bilateral	27 (26)	16 (36)	11 (19)	–
Extracapsular spreading (%/n = 102)	54 (53)	21 (47)	33 (58)	0.317
Radiation therapy (%)	174 (95)	87 (93)	87 (98)	0.170
Postoperative RT (%)	68 (39)	32 (37)	36 (41)	–
Definitive RT (%)	106 (61)	55 (63)	51 (59)	–
Concurrent systemic therapy (%)	127 (73)	61 (70)	66 (76)	0.174
Cisplatin (%)	107 (84)	47 (77)	60 (91)	0.032
Cetuximab (%)	20 (16)	14 (23)	6 (9)	–

TORS transoral robotic surgery, *RT* radiotherapy

Overall, 106 patients (58%) underwent definitive radio(chemo)therapy. Among them, 25 (24%) underwent initial neck dissection prior to definitive radio(chemo)therapy. In 77 patients (42%) surgical resection was performed, followed by adjuvant radio(chemo)therapy in 68 cases (88%). When compared to the definitive RCT group, surgical patients presented no significant difference in terms of median age (58 vs. 59 years; $p=0.74$), performance status ≥1 (42 vs. 38%; $p=0.51$), AJCC tumour stage ≥III (76 vs. 82%; $p=0.37$) or p16 overexpression (48 vs. 49%; $p=0.86$).

Treatment modalities and pathological findings according to p16 status are listed in Table 2.

Overall, 142 patients were assessable for delayed toxicities (follow-up ≥6 months without locoregional disease). Delayed severe toxicities, i.e. dysphagia, xerostomia and osteoradionecrosis according to treatment modality and p16 status are detailed in Table 3 and 4. In the p16+ group ($N=84$), surgical patients ($N=37$) presented with a significantly higher rate of delayed severe dysphagia as compared to definitive RCT patients ($N=47$): 35 vs. 4% respectively; $p=0.0002$.

After a median follow-up of 4.2 years (95%CI: 3.8–4.4 years), 3-year OS, DFS, FFM and locoregional control (LRC) were 76% (95%CI: 68–81), 64% (95%CI: 57–71),

Table 3 Delayed severe toxicity (≥grade 3) according to treatment modality among p16-negative patients ($n=58$)

	P16-negative patients $n=58$	Radio(chemo)therapy $n=27$	initial surgery $n=31$	*P*-value
Dysphagia (%)	19 (33)	8 (30)	11 (35)	0.635
Xerostomia (%)	3 (5)	3 (11)	0 (0)	–
Osteoradionecrosis (%)	1 (2)	0 (0)	1 (3)	–

Table 4 Delayed severe toxicity (≥grade 3) according to treatment modality among p16-positive patients ($n=84$)

	P16+ patients $n=84$	Radio(chemo)therapy $n=47$	(Radio)surgery $n=37$	*P*-value
Dysphagia (%)	15 (18)	2 (4)	13 (35)	0.0002
Xerostomia (%)	1 (1)	1 (2)	0 (0)	–
Osteoradionecrosis (%)	4 (5)	2 (4)	2 (5)	–

Table 5 Univariate and multivariate analyses of risk factors associated with DFS from the overall cohort

	Univariate analysis			Multivariate analysis	
	3-year DFS rate (%)	Hazard ratio (95%CI)	*P*-value		
p16– vs. p16+	47 vs. 82	0.25 (0.15–0.42)	<0.0001	0.4 (0.20; 0.79)	0.008
T1–2 vs. T3–4	74 vs. 50	2.10 (1.36–3.26)	0.0007	1.95 (1.22; 3.12)	0.005
Definitive radio(chemo)therapy vs. initial surgery	57 vs. 74	0.53 (0.33–0.85)	0.007	0.49 (0.30; 0.81)	0.005
IPS status 0 vs. 1–3	78 vs. 44	2.92 (1.87–4.56)	<0.0001	1.56 (0.91; 2.68)	0.104
Tobacco consumption ≤ vs. >10 pack-years	84 vs. 57	3.11 (1.68–5.79)	0.0002	1.11 (0.5; 2.45)	0.806
≤60 years vs. >60 years	60 vs. 70	0.69 (0.44–1.09)	0.109	–	–
Male vs. female	63 vs. 68	0.91 (0.55–1.51)	0.713	–	–

DFS disease-free survival, *IPS* International Prognostic Score

86% (95%CI: 79–90) and 78% (95%CI: 71–83), respectively. The factors significantly associated with DFS in univariate analysis were p16 status (p16+ versus p16–; 82 vs. 47%; $p<0.0001$), tumour stage (T1–2 vs. T3–4; 74 vs. 50%; 0.0007), treatment modality (initial surgery vs. definitive RCT; 74 vs. 57%; $p=0.007$), IPS status (0 vs. ≥1; 78 vs. 44%; $p<0.0001$) and tobacco consumption (<10 vs. ≥10 pack-years; 84 vs. 57%; $p=0.0002$). In multivariate analyses, p16 status, T stage and treatment modalities remained associated with DFS. Univariate and multivariate analyses of prognostic factors for DFS are outlined in Table 5. When considering p16 status, p16+ patients did not display any survival benefit from an initial surgical approach ($N=37$) compared to definitive RCT ($N=47$; 3-year DFS: 83 vs. 82%; $p=0.485$; Fig. 1).

Discussion

This is a large series reporting on 183 OSCC patients treated in recent years (2009–2013) in the era of IMRT and modern surgical techniques (transoral robotic surgery, free flap reconstruction), including a review of p16 expression and a delayed toxicity evaluation. The optimal treatment for OSCC remains controversial; as such, our study focused on treatment-related outcomes according to p16 status, which represents a major prognostic factor in OSCC and is easily available in routine practice. Almost half of our cohort (49%) presented with p16 overexpression, which was associated with a significantly better medical condition (score IPS 0: 84 vs. 36%; $p<0.0001$), smaller primary tumours (T1–2: 70 vs. 48%; $p=0.003$) and a high rate of nodal extension at presentation (N2–N3: 64 vs. 54%; NS), and which correlated with a better prognosis (3-year DFS: 82 vs. 47%; $p<0.0001$) as compared to p16-negative patients. Our data are consistent with previously reported findings [10, 11]. After a median follow-up of 4.2 years, the 3-year DFS of initial surgery and definitive RCT patients was 74 vs. 57%, respectively ($p=0.007$). When considering p16 expression, p16+ patients did not display any survival benefit from an initial surgical approach as compared to definitive radio(chemo)therapy (3-year DFS: 83 vs. 82%; $p=0.485$). Although p16+ OSCC patients are likely to be eligible for initial surgery due to small primary tumours and better medical condition, pathological findings often require adjuvant treatment. In our series, among surgical p16+ patients

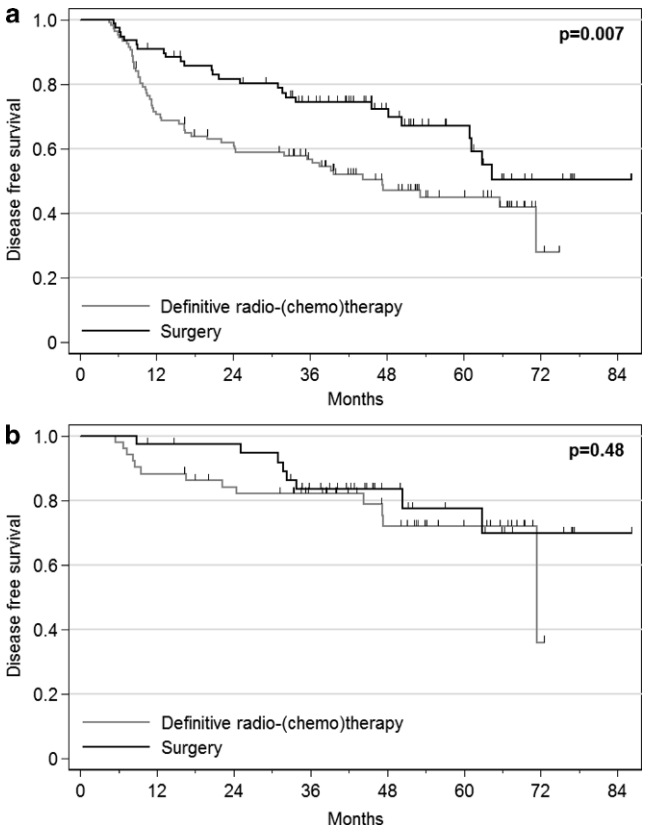

Fig. 1 Disease-free survival according to treatment strategies: overall cohort (**a**) and p16+ patients (**b**)

($N=37$), 37% presented a clear final margin ≤2 mm and 58% presented extracapsular spreading. The recent observation that p16+ OSCC patients have positive outcomes regardless of the considered treatment option has led many authors to consider that these patients are being overtreated and that a single-modality treatment should be preferred [12]. Lacau St Guily et al. recently suggested that the absence of upfront surgery worsened PFS in HPV-unrelated OSCC patients to a greater extent than in HPV-related patients [13]. Bossi et al. demonstrated distinct outcomes after definitive radio(chemo)therapy or initial surgical treatment followed by RT for HPV+ OSCC in favour of RCT for these patients [14]. In our study, initial surgery was associated with an overall higher rate of delayed severe dysphagia when compared to medical treatment: 35 vs. 4%, respectively ($p=0.0002$). Open radical surgery, even with state-of-the-art free flap reconstruction, yielded poor functional outcomes [15]. Nevertheless, alternative minimally invasive surgical techniques could be offered to p16+ OSCC patients, such as transoral robotic surgery, which results in improved functional outcomes; however, the final result is impaired in the case of adjuvant radio(chemo)therapy [16]. In a matched-pair study, Jackson et al. recently observed that adjuvant radio(chemo)therapy associated with transoral surgery in HPV-related OSCC was correlated with improved DFS when compared to surgery alone (hazard ratio: 0.067; 95% CI 0.01–0.62) [17]. The rate of late dysphagia after surgery ± adjuvant RT is similar irrespective of p16 status, i.e. 35% for each group. When focusing on the definitive RCT group, the rate of severe delayed dysphagia was 4 vs. 30% for p16+ and p16– patients, respectively. Interestingly, this is not explained by the initial tumour stage, nodal extension or adjuvant treatment, which were relatively similar between the two groups (p16+ vs. p16–) except for cisplatin use (Table 2). The most important characteristics distinguishing p16+ patients from p16– patients in our cohort are the proportion of tobacco consumption >10 pack-years: 40 vs 98% ($p<0.01$) and alcohol abuse 22.5 vs 86% ($p<0.01$), respectively. Tobacco consumption is a well-known predictive factor for late normal tissue complications following radiotherapy [18, 19]. In our study, given the important rate of high tobacco exposure in p16– patients, one might hypothesize that this may have contributed to enhancing radio-induced toxicity even without initial surgery. That HPV-related OSCC might respond more to RT is supported by a growing body of preclinical evidence underlining a higher intrinsic radiosensitivity of HPV+ OSCC cell lines as compared to HPV-unrelated cell lines, which could explain the lack of benefit of initial surgery among p16+ OSCC patients [20]. Indeed, these tumours have their own oncogenic process: cellular infection by viral DNA promotes overexpression of oncoproteins E6 and E7 that inhibit cell cycle regulators pRb and p53, favouring transcription of the tumour suppressor gene p16 that would in turn inhibit radiation-induced DNA damage repair [21]. Interestingly, HPV-related carcinomas from other sites (i.e. cervix and anal squamous cell carcinoma) are treated with definitive radio(chemo)therapy at first intent [22, 23]. Furthermore, tumour inflammation and PD-L1 expression are present at a higher degree in HPV+ OSCC when compared to HPV– OSCC, which may have a synergistic interaction with RT to elicit immune tumour recognition [24]. Optimum reduced-dose treatment regimens for these patients are being investigated by various groups [25]. Chera et al. reported a pathological response in 86% of patients after chemoradiotherapy with dose of 60 Gy and weekly cisplatin [26].

There are several limitations to our study in addition to its retrospective nature. Firstly, direct retrospective comparisons of surgical or medical approaches are hazardous given the numerous biases associated with selection of operated patients that favour surgery: resectable tumours and no contraindication for general anaesthesia. When considering definitive RCT or initial surgical treatment, even if the two groups appear well balanced with regard to tumour AJCC stage, performance status, median age and p16 overexpression, we cannot preclude that some patients treated with

definitive radio(chemo)therapy were not eligible for initial surgery due to tumoural extension or medical condition, which are commonly recognised as poor prognostic factors contributing to impair the results of patients treated with definitive RCT. However, when focusing on p16+ patients, the 3-year DFS did not vary depending on whether patients underwent definitive RCT or an initial surgical strategy. Secondly, although dysphagia and xerostomia were closely monitored by our dedicated speech and swallowing therapist and our dentist, some other delayed toxicities that contribute to quality of life impairment following neck dissection may have been under-evaluated during follow-up, such as cervical fibrosis or painful shoulder. There are still a number of unanswered issues regarding the role and the optimal timing of neck dissection. In our series, 22% of our p16+ patients ($N=20$) underwent initial neck dissection before definitive radio(chemo)therapy. Considering their high rate of nodal extension at diagnosis, we may not exclude the need for nodal resection in the definitive radio(chemo)therapy setting. Given their higher intrinsic radiosensitivity, we may hypothesise that not all p16+ locally advanced OSCC patients would require neck dissection after definitive RT. FDG PET performed within 3–4 months after RT completion is a reliable tool for shifting from initial planned dissection to surgery in the case of residual fixation [27, 28]. Likewise, Garden et al. reported equivalent neck recurrence rates among 401 locally advanced HPV+ OSCC patients treated with definitive RT, irrespective of whether they presented complete nodal response or underwent neck dissection because of residual FDG PET fixation (i.e. 8%; $p=0.4$) [29].

Conclusion

In our cohort, p16+ patients did not benefit from an initial surgical approach as compared to definitive RCT (3-year DFS: 83 vs. 82%; $p=0.485$), whereas initial surgery did result in a significantly higher rate of delayed severe dysphagia, 35 vs. 4%; $p=0.0002$. Our findings—combined with those from previous studies—emphasise the distinct outcomes after initial surgery or definitive RCT according to p16 status, which should be taken into consideration during the decision process.

Conflict of interest A. Modesto, T. Galissier, A. Lusque, J.-P. Delord, E. Uro-Coste, J. Sarini, F. Mouchet, R. Lopez, A. Laprie, P. Graff, S. Vergez and M. Rives declare that they have no competing interests.

References

1. Braakhuis BJ, Visser O, Leemans CR (2009) Oral and oropharyngeal cancer in The Netherlands between 1989 and 2006: Increasing incidence, but not in young adults. Oral Oncol 45(9):e85–e89
2. Blomberg M, Nielsen A, Munk C, Kjaer SK (2011) Trends in head and neck cancer incidence in Denmark, 1978–2007: focus on human papillomavirus associated sites. Int J Cancer 129(3):733–741
3. Rischin D (2010) Oropharyngeal cancer, human papilloma virus, and clinical trials. J Clin Oncol 28(1):1–3
4. Mooren JJ, Gultekin SE, Straetmans JM, Haesevoets A, Peutz-Kootstra CJ, Huebbers CU, Dienes HP, Wieland U, Ramaekers FC, Kremer B et al (2014) P16(INK4A) immunostaining is a strong indicator for high-risk-HPV-associated oropharyngeal carcinomas and dysplasias, but is unreliable to predict low-risk-HPV-infection in head and neck papillomas and laryngeal dysplasias. Int J Cancer 134(9):2108–2117
5. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP (2017) The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 67(2):93–99
6. Licitra L, Felip E, Group EGW (2009) Squamous cell carcinoma of the head and neck: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 20(Suppl 4):121–122
7. Modesto A, Sarini J, Benlyazid A, Ouali M, Laprie A, Graff P, Vergez S, Uro-Coste E, Fauquet I, Delord JP et al (2016) Value of neck dissection before definitive radiation therapy for locoregionally advanced squamous cell carcinoma of the head and neck. Cancer Radiother 20(1):18–23
8. Modesto A, Laprie A, Vieillevigne L, Graff P, Sarini J, Vergez S, Delord JP, Farenc JC, Vigarios E, Filleron T et al (2015) Intensity-modulated radiotherapy for laryngeal and hypopharyngeal cancer: minimization of late dysphagia without jeopardizing tumor control. Strahlenther Onkol 191(3):225–233
9. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, Westra WH, Chung CH, Jordan RC, Lu C et al (2010) Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 363(1):24–35
10. Rischin D, Young RJ, Fisher R, Fox SB, Le QT, Peters LJ, Solomon B, Choi J, O'Sullivan B, Kenny LM et al (2010) Prognostic significance of p16INK4A and human papillomavirus in patients with oropharyngeal cancer treated on TROG 02.02 phase III trial. J Clin Oncol 28(27):4142–4148
11. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, Jiang B, Goodman MT, Sibug-Saber M, Cozen W et al (2011) Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol 29(32):4294–4301
12. O'Sullivan B, Huang SH, Siu LL, Waldron J, Zhao H, Perez-Ordonez B, Weinreb I, Kim J, Ringash J, Bayley A et al (2013) Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. J Clin Oncol 31(5):543–550
13. Lacau St Guily J, Rousseau A, Baujat B, Perie S, Schultz P, Barry B, Dufour X, Malard O, Pretet JL, Clavel C et al (2017) Oropharyngeal cancer prognosis by tumour HPV status in France: the multicentric papillophar study. Oral Oncol 67:29–36
14. Bossi P, Orlandi E, Miceli R, Perrone F, Guzzo M, Mariani L, Granata R, Locati L, Fallai C, Cortelazzi B et al (2014) Treatment-related outcome of oropharyngeal cancer patients differentiated by HPV dictated risk profile: a tertiary cancer centre series analysis. Ann Oncol 25(3):694–699
15. Denittis AS, Machtay M, Rosenthal DI, Sanfilippo NJ, Lee JH, Goldfeder S, Chalian AA, Weinstein GS, Weber RS (2001) Advanced oropharyngeal carcinoma treated with surgery and radiotherapy: oncologic outcome and functional assessment. Am J Otolaryngol 22(5):329–335
16. Leonhardt FD, Quon H, Abrahao M, O'Malley BW Jr., Weinstein GS (2012) Transoral robotic surgery for oropharyngeal carcinoma and its impact on patient-reported quality of life and function. Head Neck 34(2):146–154

17. Jackson RS, Sinha P, Zenga J, Kallogjeri D, Suko J, Martin E, Moore EJ, Haughey BH (2017) Transoral resection of human papillomavirus (HPV)-positive squamous cell carcinoma of the oropharynx: outcomes with and without adjuvant therapy. Ann Surg Oncol. https://doi.org/10.1245/s10434-017-6041-x
18. Lilla C, Ambrosone CB, Kropp S, Helmbold I, Schmezer P, von Fournier D, Haase W, Sautter-Bihl ML, Wenz F, Chang-Claude J (2007) Predictive factors for late normal tissue complications following radiotherapy for breast cancer. Breast Cancer Res Treat 106(1):143–150
19. Solanki AA, Liauw SL (2013) Tobacco use and external beam radiation therapy for prostate cancer: influence on biochemical control and late toxicity. Cancer 119(15):2807–2814
20. Arenz A, Ziemann F, Mayer C, Wittig A, Dreffke K, Preising S, Wagner S, Klussmann JP, Engenhart-Cabillic R, Wittekindt C (2014) Increased radiosensitivity of HPV-positive head and neck cancer cell lines due to cell cycle dysregulation and induction of apoptosis. Strahlenther Onkol 190(9):839–846
21. Rieckmann T, Tribius S, Grob TJ, Meyer F, Busch CJ, Petersen C, Dikomey E, Kriegs M (2013) HNSCC cell lines positive for HPV and p16 possess higher cellular radiosensitivity due to an impaired DSB repair capacity. Radiother Oncol 107(2):242–246
22. Peters WA 3rd, Liu PY, Barrett RJ 2nd, Stock RJ, Monk BJ, Berek JS, Souhami L, Grigsby P, Gordon W Jr., Alberts DS (2000) Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 18(8):1606–1613
23. Glynne-Jones R, Nilsson PJ, Aschele C, Goh V, Peiffert D, Cervantes A, Arnold D (2014) Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Radiother Oncol 111(3):330–339
24. Balermpas P, Rodel F, Krause M, Linge A, Lohaus F, Baumann M, Tinhofer I, Budach V, Sak A, Stuschke M et al (2017) The PD-1/PD-L1 axis and human papilloma virus in patients with head and neck cancer after adjuvant chemoradiotherapy: a multicentre study of the German cancer consortium radiation oncology group (DKTK-ROG). Int J Cancer 141(3):594–603
25. Mesia R, Taberna M (2017) HPV-related oropharyngeal carcinoma de-escalation protocols. Lancet Oncol 18(6):704–705
26. Chera BS, Amdur RJ, Tepper J, Qaqish B, Green R, Aumer SL, Hayes N, Weiss J, Grilley-Olson J, Zanation A et al (2015) Phase 2 trial of de-intensified chemoradiation therapy for favorable-risk human papillomavirus-associated oropharyngeal squamous cell carcinoma. Int J Radiat Oncol Biol Phys 93(5):976–985
27. Gupta T, Jain S, Agarwal JP, Rangarajan V, Purandare N, Ghosh-Laskar S, Dinshaw KA (2010) Diagnostic performance of response assessment FDG-PET/CT in patients with head and neck squamous cell carcinoma treated with high-precision definitive (chemo)radiation. Radiother Oncol 97(2):194–199
28. Mehanna H, Wong WL, McConkey CC, Rahman JK, Robinson M, Hartley AG, Nutting C, Powell N, Al-Booz H, Robinson M et al (2016) PET-CT surveillance versus neck dissection in advanced head and neck cancer. N Engl J Med 374(15):1444–1454
29. Garden AS, Gunn GB, Hessel A, Beadle BM, Ahmed S, El-Naggar AK, Fuller CD, Byers LA, Phan J, Frank SJ et al (2014) Management of the lymph node-positive neck in the patient with human papillomavirus-associated oropharyngeal cancer. Cancer 120(19):3082–3088