Prognostic factor analysis and long-term results of the TAX 323 (EORTC 24971) study in unresectable head and neck cancer patients

Prognostic factor analysis and long-term results of the TAX 323 (EORTC 24971) study in unresectable head and neck cancer patients

Petr Szturz[1], Marie Vinches[2*], Éva Remenár[3], Carla M. L. van Herpen[4], Cyril Abdeddaim[5], John S. Stewart[6], Catherine Fortpied[2] and Jan B. Vermorken[7,8]

[1]Medical Oncology, Department of Oncology, Lausanne University Hospital (CHUV), Lausanne, Switzerland

[2]The European Organisation for Research and Treatment of Cancer, Brussels, Belgium

[3]Hospitalier Order of Saint John of God Hospital Buda, Budapest, Hungary

[4]Department of Medical Oncology, Radboud university medical center, Nijmegen, the Netherlands

[5]Medical Oncology, Oscar Lambret Center, Lille, France

[6]Imperial College, London, United Kingdom

[7]Department of Medical Oncology, Antwerp University Hospital, Edegem, Belgium

[8]Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

*Former medical fellow at the EORTC

Correspondence:

Prof. Jan B. Vermorken, MD, PhD

Department of Medical Oncology,

Antwerp University Hospital,

Wilrijkstraat 10,

2650 Edegem, Belgium

Tel: +32.3.8214548

E-mail: JanB.Vermorken@uza.be

Abstract

Background: In the TAX 323 (EORTC 24971) phase III trial enrolling patients with unresectable locoregionally advanced squamous cell carcinoma of the head and neck (LA-SCCHN), the addition of docetaxel (T) to cisplatin and 5-fluorouracil (PF)-based induction chemotherapy prior to definite radiotherapy significantly improved progression-free survival (PFS) and overall survival (OS).

Methods: The data were updated for PFS, OS, and treatment-related long-term side effects. Baseline clinical and laboratory data of 17 variables were collected and subjected to univariate and multivariate prognostic factor analyses for OS.

Results: All 358 patients randomized between 1999 and 2002 were included in the long-term analysis with a median follow-up of 8.6 years. The primary endpoint of PFS remained significantly improved with TPF compared with PF (adjusted hazard ratio [HR], 0.70; 95% CI, 0.56—0.88, p=0.002), translating into a persisting benefit in OS (adjusted HR, 0.75; 95% CI, 0.60—0.95, p=0.015). Long-term side effects in the TPF/PF arms comprised tracheostomy (7%/5%), feeding tube dependency (3%/6%), and gastrostomy (11%/11%). Second malignancy occurred in 8%/3%, respectively. Out of 177 patients randomized to the TPF arm, 160 were included in the multivariate analysis. Grade 2 or more dysphagia (p=0.002) and grade 2 or more pain (p=0.004) at baseline were identified as independent negative prognostic factors. In addition, OS differed across primary tumour sites (p=0.027) and was worse in patients with a higher N-stage (p=0.025).

Conclusions: In LA-SCCHN patients treated with sequential chemoradiotherapy, TPF induction chemotherapy demonstrated long-lasting efficacy, superior to the PF regimen. Higher-grade dysphagia and pain are unfavourable prognosticators.

Key words: head and neck cancer; EORTC 24971/TAX 323 phase III clinical trial; induction chemotherapy; overall survival; late toxicity; prognostic factor

Introduction

In locoregionally advanced squamous cell carcinoma of the head and neck (LA-SCCHN), sequential therapy incorporates induction chemotherapy followed by definitive radiotherapy with or without concurrent systemic treatment. This curative non-surgical approach has been extensively studied across all phases of clinical research, but its role has remained controversial. Although certain benefits were suggested in patients with a high risk of distant failure presenting with multiple and large-volume cervical lymph nodes, the only application supported by level I evidence is organ preservation in laryngeal and hypopharyngeal carcinomas [1,2]. However, even in this setting, induction chemotherapy has not been uniformly accepted because of better larynx preservation and locoregional control rates attained with concurrent chemoradiotherapy [3]. Recently, the latter approach was questioned by long-term data with median follow-up of 10.8 years demonstrating a worrisome trend towards worse overall survival (OS) in the concurrent versus induction chemotherapy arm [4]. Nevertheless, this observation might be less relevant for current cancer patients receiving modern radiotherapy techniques which have been shown to be associated with a more favourable toxicity profile [5].

The TAX 323 (EORTC 24971) study was a phase III trial establishing the superiority of TPF (docetaxel, cisplatin, 5-fluorouracil) over PF induction chemotherapy prior to definitive radiotherapy in unresectable LA-SCCHN. As reported in the original publication, the triplet significantly improved median progression-free survival (PFS), OS, and overall response rate after a median follow-up of 32.5 months. Despite an increase in severe leukopenia and neutropenia, the TPF regimen was better tolerated with more patients completing the treatment, fewer toxic deaths, and lower rates of grade 3 to 4 thrombocytopenia, nausea, vomiting, stomatitis, and hearing loss [6]. Subsequent analyses of TAX 323 demonstrated that when compared with PF, the three-drug induction regimen can enhance patients' health-related quality of life in a more sustainable manner and is cost-effective [7,8]. Moreover, it was

scrutinized in three other phase III trials. The significant OS benefit conferred by the addition of docetaxel to PF induction chemotherapy was corroborated in TAX 324 conducted in both unresectable and resectable LA-SCCHN but not in the Spanish Head and Neck Cancer Cooperative Group (TTCC) 2002 trial in which radiotherapy was given concurrently to high-dose cisplatin [9-11]. In the Groupe d'Oncologie Radiothérapie Tête Et Cou (GORTEC) 2000-01 trial recruiting patients with laryngeal and hypopharyngeal cancers suitable for total laryngectomy TPF led to a significant improvement of laryngectomy-free survival [12].

Prognosis of head and neck cancer patients is primarily determined by patient's age, performance status, and comorbid illnesses, the site of tumour origin and TNM (tumour, node, metastasis) stage, and is also more favourable in those with human papillomavirus (HPV) positive oropharyngeal cancer [13,14]. In patients undergoing induction chemotherapy, the positive prognostic value of tumour HPV/p16 status was demonstrated in retrospective analyses of the ECOG 2399 and TAX 324 studies but not in TAX 323, possibly due to a loss of statistical power or selection bias as only one third of the study patients could be assessed for HPV/p16 status [15-17]. In the present work, we evaluate clinical and laboratory prognostic factors in patients enrolled in the practice-changing TPF arm and report the long-term update of the TAX 323 study.

Methods

Study design

Detailed description of the TAX 323 phase III trial (ClinicalTrials.gov identifier NCT00003888) has been published previously [6]. The study objective was to compare PF (cisplatin 100 mg/m^2 on day 1 and 5-fluorouracil 1000 mg/m^2 by continuous infusion on days 1 to 5) with TPF (docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 on day 1 and 5-fluorouracil 750 mg/m^2 by continuous infusion on days 1 to 5) given

every 3 weeks for a maximum of four cycles as induction chemotherapy prior to definitive radiotherapy in patients with previously untreated, unresectable LA-SCCHN excluding tumours of the nasopharynx and the nasal and paranasal sinuses. Further eligibility criteria comprised age between 18 and 70 years, a World Health Organization (WHO) performance status of 1 or less, adequate hematologic, renal, and hepatic functions, and a signed informed consent. The primary end point was PFS. Secondary end points involved OS, best overall response rate after induction chemotherapy and after radiation therapy, duration of response, time to treatment failure, toxic effects, and health-related quality of life. At each participating centre, the protocol and, later on, the questionnaires to gather long-term clinical information were approved by the ethics committee or institutional review board.

Data collection

Long-term data were obtained retrospectively from follow-up forms sent to all participating centres. Subsequently, the clinical database was updated for PFS, OS, second primary tumours, and treatment-related long-term side effects consisting of tracheostomy, feeding tube dependency, and gastrostomy. The database was locked on January 10, 2011.

In the prognostic factor analysis, we assessed the prognostic value for OS of baseline characteristics in patients treated with TPF induction chemotherapy. The following baseline covariates were evaluated as candidate prognostic factors in the univariate analysis: age (<65 years vs. ≥65 years), sex (male vs. female), World Health Organization (WHO) performance status (0 vs. ≥1), primary tumour site (hypopharynx vs. larynx vs. oral cavity vs. oropharynx), T-stage (T1-2 vs. T3 vs. T4), N- stage (N0 vs. N1 vs. N2 vs. N3), histopathologic grade (well differentiated vs. moderately differentiated vs. poorly differentiated or undifferentiated vs. missing/unknown), number of organs involved (1 vs. ≥2), time from histology to randomization (≤21 days vs. >21 days), white blood cell count ($<10x10^9$ vs. $\geq 10x10^9$ cells/L),

platelet count (<400x10^9 vs. ≥400x10^9 cells/L), haemoglobin (≥120 vs. <120 g/L), albumin (≥35 vs. <35 g/L vs. missing), hoarseness (grade 0 vs. ≥1), weight loss (grade 0 vs. ≥1), dysphagia (grade <2 vs. ≥2), and pain (grade <2 vs. ≥2). Laboratory variables were dichotomised, and a conventional cut-off of 65 years was used to define elderly patients. In the multivariate analysis, laboratory variables and age were analysed as continuous covariates. To enable model fitting, some categories of categorical factors were pooled based on the number of patients and events (deaths) per factor level.

Clinical classification was determined according to the 4th edition of the TNM staging system of the American Joint Commission on Cancer. The expanded common toxicity criteria of the Clinical Trials Group of the National Cancer Institute of Canada, adopted in 1994 for evaluation of chemotherapy- and radiotherapy-related morbidity, were used to grade baseline hoarseness, weight loss, dysphagia, and pain.

Statistical analysis

The long-term analysis was based on the intention-to-treat population, whereas the population of interest in the prognostic factor analysis consisted of all patients eligible and randomized to the TPF arm and who received the TPF induction regimen, which is explained in the Discussion below. The Kaplan-Meier method was used to estimate PFS and OS, and the two treatment arms were compared with the Wald test at a two-sided significance level of 5%, based on a Cox proportional hazards regression model adjusted for disease location, T and N stage, and WHO performance score. Each prognostic factor was first evaluated in a univariate analysis using the unadjusted log-rank test. In the multivariate analysis, a Cox proportional hazards regression model was fitted. Model reduction was done in an attempt to identify factors with a higher prognostic value. Several procedures were applied including backward, forward, and stepwise selection. In addition, we performed a bootstrap procedure with backward selection according to the strategy B proposed by Sauerbrei and Schumacher [18]. Assumptions of linear effect of continuous factors

and of proportional hazards were checked, using the ASSESS statement in SAS® PROC PHREG and tested at 5% significance level. The goodness of fit was assessed by the Schempter-Henderson measure providing the proportion of variation explained by the Cox model [19]. The significance threshold was set at $p<0.05$ for a two-sided test. Statistical analyses were conducted using SAS®, version 9.4.

Results

Between April 1999 and March 2002, a total of 358 patients were randomized in the TAX 323 study, with 181 assigned to the standard PF arm and 177 to the experimental TFP arm. The database was updated with long-term survival and safety information obtained from 308 patients (86%). At a median follow-up of the intention-to-treat population of 8.6 years (95% confidence interval [CI], 8.0-8.8), the significant survival benefit conferred by the experimental arm was maintained. The addition of docetaxel to the standard PF regimen resulted in improved PFS (adjusted hazard ratio [HR], 0.70; 95% CI, 0.56—0.88, $p=0.002$, medians of 12.7 vs. 8.6 months, and 5-years PFS 23% vs. 14%), because of less locoregional progression (Figure 1A). The distant recurrence rate before any locoregional progression was low and comparable between the two treatment arms (7%). The rates of death with no prior documented progression did not differ either. The tabulation of the PFS events is available in Table 1. Similarly, OS was better in the TPF arm (adjusted HR, 0.75; 95% CI, 0.60—0.95, $p=0.015$, medians of 18.8 vs. 14.5 months, 5-years OS 28% vs. 19%) as shown in Figure 1B. The main cause of death was disease progression in both arms. The tabulation of the causes of death is available in Table 2.

Long-term side effects in the TPF and PF arms comprised tracheostomy (7% and 5%, respectively), feeding tube dependency (3% and 6%, respectively), and gastrostomy (11% in both arms) as summarized in Table 3. Second primary tumours occurred at a higher frequency in the TPF arm (14 patients, 7.9%) than in the PF arm (6 patients, 3.3%). The following sites of second malignancies were involved in patients

treated in the TPF and PF arms: lungs (6 and 3 patients, respectively), head and neck (6 and 2 patients, respectively), and gastrointestinal track (2 and 1 patients, respectively). One of these patients had three different second primary cancers including the head and neck region, the lungs, and the bones.

Prognostic factor analysis

A total of 163 patients treated with TPF chemotherapy were included in the univariate comparison. Supplementary Figure 1 details the flow diagram of patient selection. The median OS was 1.5 years (95% CI: 1.3-2.0), and estimated 3- and 5-year survival rates were 36.0% and 27.2%, respectively (Supplementary Figure 2). Baseline demographic, clinical, pathological, and laboratory characteristics are summarized in Supplementary Tables 1 and 2 and baseline symptoms in Supplementary Table 3. At univariate analysis, the following variables were significantly associated with improved OS: age under 65 years (p=0.0016), WHO performance status of 0 (p=0.02), histology grade (p=0.0391), 21 days or less from histology to study entry (p=0.037), baseline platelets of less than $400x10^9$ cells/L (p=0.0308), dysphagia grade 0 or 1 (p<0.0001), and pain grade 0 or 1 (p=0.0009) (Table 4).

Multivariate analysis

Due to the presence of missing values for covariates, the full model was fitted with 160 patients and 127 events (deaths). During model reduction, the following five factors were kept in every model because of their generally accepted prognostic value: age, sex, site, T-stage, and N-stage. The backward, forward, and stepwise selection procedures, conducted at 5% significance level, led to the same reduced model with dysphagia and pain (grade <2 vs. ≥2) at baseline as significant prognostic factors when adjusted for the five predefined factors. Bootstrapping selected only pain as a significant prognostic factor in

addition to the predefined ones. However, owing to the rough rule of degrees of freedom (number of events divided by ten is approximately equal to 12), we finally opted to include baseline factors "dysphagia" and "pain" as prognostic factors for survival, so the final model involves age, sex, site, T-stage, N-stage, dysphagia, and pain (Table 5).

Consequently, our model demonstrates that after adjustment for age, sex, anatomical site, T- and N-stage, baseline dysphagia (p=0.002) and pain (p=0.004) of grade 2 or more are independent unfavourable prognostic factors for OS in patients with unresectable LA-SCCHN undergoing TPF induction chemotherapy. It also confirms that survival is different across different primary disease sites (p=0.027) and is worse in patients with a higher N-stage (p=0.025). However, the study data do not show a statistically significant effect of age, sex, and T-stage on OS.

Discussion

With a median follow-up of 8.6 years, the long-term efficacy outcomes of the TAX 323 study confirmed the initially reported significant survival advantage of patients with unresectable LA-SCCHN treated with TPF induction chemotherapy compared with the PF regimen. Although the evaluation of long-term toxicity remains purely descriptive, the sustained survival benefit observed in the experimental arm suggests a lack of excessive late mortality from chemotherapy. This is also in line with the better acute toxicity profile of the TPF regimen [6]. Moreover, the long-term efficacy results of the TPF arm did not seem to be substantially impacted by the higher incidence of second primary tumours. In patients with an index tumour in the head and neck area, second malignancies reflect the frequent tobacco and alcohol abuse and the ensuing field cancerisation, which may bias the treatment effect in cancer survivors and be challenging for conducting and interpretation of long-term follow-up studies [20,21]. Analogously, such lifestyle habits may lead to increased morbidity, but the present study suggests that the rates of non-

cancer related deaths were comparable between the two groups. Most first recurrences occurred at locoregional disease sites, preferentially in the PF arm, while distant relapses were uncommon and not influenced by the difference in study medication. This observation also supports the current notion of post-treatment surveillance focusing on early detection of locoregional relapses with some exceptions discussed elsewhere [22].

The TAX 323 trial was paralleled by the TAX 324 trial randomizing 501 patients from North America, Argentina, and Europe with similar inclusion criteria but allowing enrolment of those with resectable disease as well (65% of the study population). Another notable difference was a shorter duration of induction chemotherapy in TAX 324 consisting of three cycles (versus four cycles in TAX 323). On the other hand, the doses of cisplatin (100 mg/m^2) and 5-fluorouracil (4000 mg/m^2 over 4 days) in the TPF arm were slightly higher and concurrent weekly carboplatin was delivered during the course of radiotherapy [9]. With a median follow-up of 6 years, the long-term results of TAX 324 demonstrated that the significant survival benefit conferred by the triplet was maintained with no apparent impact on the rates of gastric feeding tube dependency and tracheostomy, albeit late toxicity reporting was incomplete [23]. Also in our study the majority of patients did not suffer from late toxicity and this statement can be made with even more certainty considering the fact that only 20% of data on late toxicity were missing in TAX 323 versus 70% in TAX 324 (Table 3).

Notwithstanding a subset of HPV-positive oropharyngeal cancer cases with remarkably good prognosis, non-surgical management of LA-SCCHN (resectable and unresectable combined) leads to a 5-year OS of around 40% [24,25]. If the disease meets criteria for unresectability, the proportion of long-term survivors may decrease to only about 25% as confirmed in the present study [11,26,27]. In this particularly challenging population, we demonstrated that severity of dysphagia, severity of pain, primary tumour site, and nodal extension have independent prognostic significance in patients who started TPF

induction chemotherapy in the TAX 323 study. In fact, 5-year OS did not exceed 15% in case of baseline grade 2 or more dysphagia, grade 2 or more pain, N3 disease, and primary tumour in the oral cavity. Although these findings need to be validated in an independent study, they provide further insights into patient selection for intensification of both treatment schedules and post-treatment follow-up.

In oncology, presence of high-risk features for recurrence or metastases intuitively guides treatment choice towards more intensive and aggressive approaches aiming to eradicate microscopic disease. In patients with LA-SCCHN treated with sequential chemoradiotherapy, available literature based on phase III and large phase II trials or meta-analyses thereof supports the relevance of some well-known pre-treatment factors such as advanced age, male sex, poor performance status, clinical stage IV, high T- and N-classes, and in oropharyngeal carcinomas also negative HPV/p16 status [16,27-33]. Out of these studies, the only one showing significantly improved overall survival with TPF chemotherapy was TAX 324, in which a prognostic factor analysis focused solely on HPV-positivity in oropharyngeal cancers, confirming its favourable prognostic value [16]. Further, low haemoglobin level, tobacco smoking, and combined measures of quality of life and performance status were identified in large phase III trials incorporating one of the standard concurrent chemoradiotherapy schedules without induction chemotherapy [14,34-36]. In the presence of one of these risk factors, the hypothesis of a beneficial effect of treatment intensification has already been partially confirmed. The DeCIDE trial was a randomized phase III trial comparing sequential with concurrent chemoradiotherapy. In the experimental arm, TPF induction chemotherapy was added before definitive radiotherapy concurrent to a chemotherapy triplet with docetaxel, 5-fluorouracil, and hydroxyurea. The study did not meet its primary endpoint of OS except for a subset of patients with N2c or N3 node involvement who demonstrated a trend towards improved survival with the addition of the TPF regimen [1].

Our prognostic factor analysis confirms the negative impact of high-volume nodes. The difference in outcomes according to the primary tumour site (worse for hypopharynx and oral cavity, better for larynx and oropharynx) corresponds with the multivariate analysis of the TROG 02.02 trial [35]. In addition and most importantly, higher-grade dysphagia and pain were shown to exhibit independent prognostic value. To the best of our knowledge, this is the first published multivariate analysis of a phase III trial on sequential or concurrent chemoradiation in LA-SCCHN demonstrating prognostic value of disease-related symptoms at baseline. Symptomatic patients have always been in the forefront of oncologic care. In the palliative care setting, it is generally accepted that they need early treatment initiation. In the curative setting, according to our findings, they might also be candidates for treatment intensification. The strength of the present study is that the data are based on a large randomized practice-changing multicentric phase III trial with a median follow-up of 8.6 years which met its primary endpoint of PFS translating into a significant benefit in OS. On the other hand, the number of patients analysed for prognostic factors was limited to 163. Moreover, our findings suffer from potential biases common to retrospective studies, especially difficulties in gathering detailed information on all patients, cohort selection, and a lack of statistical power for small subgroups possibly reflected in the absence of statistically significant effects of age, sex, and T-stage on OS. A better model could have also been obtained if HPV/p16 status had been available in all patients or if supplementary information had been collected, such as information on tobacco exposure, alcohol consumption, and comorbid conditions.

A specific issue relates to the use of toxicity criteria to assess baseline symptoms because such grading scales were primarily developed to evaluate on-treatment or post-treatment adverse events. While this might still be acceptable, in our opinion, for most of the characteristics listed in Supplementary Tables 1—3, a correct collection of weight loss data at baseline would require precise retrospective information over a defined period of time in each patient, which was not available in TAX 323 and is inherently challenging to obtain from a general point of view, particularly due to recall bias.

Besides that, our model pooling did not comprise both treatment arms, which was due to several reasons concerning statistical properties of the model, its data interpretation, and clinical utility. First, the model fitted with data from both the PF and TPF arms was unstable, leading to different final models when even minor changes to the model specifications were carried out (e.g., handling of missing values, continuous versus categorical variables, dropping or adding variables). Furthermore, the resulting models consistently showed treatment interaction (PF versus TPF) for dysphagia, attesting thus a lack of a common model for both study arms. Finally, the clinical relevance of using an inferior treatment arm (PF) for prognostic factor analysis is questionable. Consequently, the final model was based only on the TPF arm. Fitted with seven factors (age, sex, site, T-stage, N-stage, dysphagia, pain), it shows an acceptable calibration but has a poor discriminant ability. Nevertheless, it brings important new clinical information for future modelling and can be used as a benchmark for future models with molecular data aiming at an improved prognostic value with the addition of these new molecular markers relative to standard clinical models.

In conclusion, TPF induction chemotherapy can induce durable survival benefit, and currently, it represents the optimal strategy in sequential treatment protocols when used. The prognostic significance of baseline symptoms (dysphagia and pain) in LA-SCCHN patients treated with sequential chemoradiotherapy should be further explored in the context of treatment intensification trials, including novel approaches such as immune checkpoint inhibitors, and new follow-up protocols. The latter aspect of post-treatment oncologic care is still poorly understood, and a refinement of selection criteria is therefore imperative to identify patients who could possibly benefit from more frequent clinical and radiological surveillance.

Funding

This work was supported by the EORTC Academic Fund, the Swiss Cancer Research Foundation from Switzerland, and Kom op tegen Kanker (Stand up to Cancer), the Flemish cancer society from Belgium. Marie Vinches' work as Fellow at EORTC Headquarters was supported by a grant from Fonds Cancer (FOCA) from Belgium.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Prior presentations

The long-term results were previously presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2011.

Declaration of Interest statement

Petr Szturz: Has had in the last three years or has advisory relationships with: Merck-Serono, Servier, and BMS.

Marie Vinches has nothing to declare.

Éva Remenár has nothing to declare.

Carla M L van Herpen: Has had in the last three years or has advisory/consultant relationships with: Bayer, Bristol-Myers Squibb, Ipsen, MSD, and Regeneron and research grant/funding relationships with: Astra Zeneca, Bristol-Myers Squibb, MSD, Merck, Ipsen, Novartis, and Sanofi.

Cyril Abdeddaim: Has had in the last three years consulting/advisory relationships with GlaxoSmithKline.

John S Stewart has nothing to declare.

Catherine Fortpied has nothing to declare.

Jan B. Vermorken: Has had in the last three years or has consulting/advisory relationships with: Immunomedics, Innate Pharma, Merck-Serono, Merck Sharp & Dome Corp, PCI Biotech, Synthon Biopharmaceuticals, Debiopharm, Cue Biopharma, Nanobiotix, and WntResearch and received lecture fees from Merck-Serono, MSD, and BMS.

References

1. Cohen EE, Karrison TG, Kocherginsky M et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. J Clin Oncol 2014; 32: 2735–2743.
2. Haddad RI, Posner M, Hitt R et al. Induction chemotherapy in locally advanced squamous cell carcinoma of the head and neck: role, controversy, and future directions. Ann Oncol 2018; 29: 1130–1140.
3. Forastiere AA, Goepfert H, Maor M et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003; 349: 2091–2098.
4. Forastiere AA, Zhang Q, Weber RS et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. J Clin Oncol 2013; 31: 845–852.
5. Ward MC, Ross RB, Koyfman SA et al. Modern Image-Guided Intensity-Modulated Radiotherapy for Oropharynx Cancer and Severe Late Toxic Effects: Implications for Clinical Trial Design. JAMA Otolaryngol Head Neck Surg 2016; 142: 1164–1170.
6. Vermorken JB, Remenar E, van Herpen C et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007; 357: 1695–1704.
7. van Herpen CM, Mauer ME, Mesia R et al. Short-term health-related quality of life and symptom control with docetaxel, cisplatin, 5-fluorouracil and cisplatin (TPF), 5-fluorouracil (PF) for induction in unresectable locoregionally advanced head and neck cancer patients (EORTC 24971/TAX 323). Br J Cancer 2010; 103: 1173–1781.
8. Liberato NL, Rognoni C, Rubrichi S et al. Adding docetaxel to cisplatin and fluorouracil in patients with unresectable head and neck cancer: a cost-utility analysis. Ann Oncol 2012; 23: 1825–1832.
9. Posner MR, Hershock DM, Blajman CR et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007; 357: 1705–1715.

10. Posner MR, Norris CM, Wirth LJ et al. Sequential therapy for the locally advanced larynx and hypopharynx cancer subgroup in TAX 324: survival, surgery, and organ preservation. Ann Oncol 2009; 20: 921–927.
11. Hitt R, Grau JJ, López-Pousa A et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. Ann Oncol 2014; 25: 216–225.
12. Pointreau Y, Garaud P, Chapet S et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst 2009; 101: 498–506.
13. Mehanna H, West CM, Nutting C et al. Head and neck cancer--Part 2: Treatment and prognostic factors. BMJ 2010; 341: c4690.
14. Ang KK, Harris J, Wheeler R et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010; 363: 24–35.
15. Fakhry C, Westra WH, Li S et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 2008; 100: 261–269.
16. Posner MR, Lorch JH, Goloubeva O et al. Survival and human papillomavirus in oropharynx cancer in TAX 324: a subset analysis from an international phase III trial. Ann Oncol 2011; 22: 1071–1077.
17. Psyrri A, Fortpied C, Koutsodontis G et al. Evaluation of the impact of tumor HPV status on outcome in patients with locally advanced unresectable head and neck squamous cell carcinoma (HNSCC) receiving cisplatin, 5-fluorouracil with or without docetaxel: a subset analysis of EORTC 24971 study. Ann Oncol 2017; 28: 2213–2218.
18. Sauerbrei W, Schumacher M. A bootstrap resampling procedure for model building: application to the Cox regression model. Stat Med 1992; 11: 2093–2109.

19. Schemper M, Henderson R. Predictive accuracy and explained variation in Cox regression. Biometrics 2000; 56: 249–255.
20. Cooper JS, Pajak TF, Rubin P et al. Second malignancies in patients who have head and neck cancer: incidence, effect on survival and implications based on the RTOG experience. Int J Radiat Oncol Biol Phys 1989; 17: 449–456.
21. Ng SP, Pollard C 3rd, Kamal M et al. Risk of second primary malignancies in head and neck cancer patients treated with definitive radiotherapy. NPJ Precis Oncol 2019; 3: 22.
22. Szturz P, Van Laer C, Simon C et al. Follow-Up of Head and Neck Cancer Survivors: Tipping the Balance of Intensity. Front Oncol 2020; 10: 688.
23. Lorch JH, Goloubeva O, Haddad RI et al. Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX 324 randomised phase 3 trial. Lancet Oncol 2011; 12: 153–159.
24. Blanchard P, Bourhis J, Lacas B et al. Taxane-cisplatin-fluorouracil as induction chemotherapy in locally advanced head and neck cancers: an individual patient data meta-analysis of the meta-analysis of chemotherapy in head and neck cancer group. J Clin Oncol 2013; 31: 2854–2860.
25. Szturz P, Wouters K, Kiyota N et al. Weekly Low-Dose Versus Three-Weekly High-Dose Cisplatin for Concurrent Chemoradiation in Locoregionally Advanced Non-Nasopharyngeal Head and Neck Cancer: A Systematic Review and Meta-Analysis of Aggregate Data. Oncologist 2017; 22: 1056–1066.
26. Adelstein DJ, Li Y, Adams GL et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003; 21: 92–98.
27. Hitt R, López-Pousa A, Martínez-Trufero J et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. J Clin Oncol 2005; 23: 8636–8645.

28. Cognetti F, Pinnarö P, Ruggeri EM et al. Prognostic factors for chemotherapy response and survival using combination chemotherapy as initial treatment of advanced head and neck squamous cell cancer. J Clin Oncol 1989; 7: 829–837.
29. Fountzilas G, Kosmidis P, Avramidis V et al. Long-term survival data and prognostic factors of a complete response to chemotherapy in patients with head and neck cancer treated with platinum-based induction chemotherapy: a Hellenic Co-operative oncology Group study. Med Pediatr Oncol 1997; 28: 401–410.
30. Pignon JP, Syz N, Posner M et al. Adjusting for patient selection suggests the addition of docetaxel to 5-fluorouracil-cisplatin induction therapy may offer survival benefit in squamous cell cancer of the head and neck. Anticancer Drugs 2004; 15: 331–340.
31. Salama JK, Stenson KM, Kistner EO et al. Induction chemotherapy and concurrent chemoradiotherapy for locoregionally advanced head and neck cancer: a multi-institutional phase II trial investigating three radiotherapy dose levels. Ann Oncol 2008; 19: 1787–1794.
32. Lefebvre JL, Rolland F, Tesselaar M et al. Phase 3 randomized trial on larynx preservation comparing sequential vs alternating chemotherapy and radiotherapy. J Natl Cancer Inst 2009; 101: 142–152.
33. Seiwert TY, Melotek JM, Blair EA et al. Final Results of a Randomized Phase 2 Trial Investigating the Addition of Cetuximab to Induction Chemotherapy and Accelerated or Hyperfractionated Chemoradiation for Locoregionally Advanced Head and Neck Cancer. Int J Radiat Oncol Biol Phys 2016; 96: 21–29.
34. Denis F, Garaud P, Bardet E et al. Late toxicity results of the GORTEC 94-01 randomized trial comparing radiotherapy with concomitant radiochemotherapy for advanced-stage oropharynx carcinoma: comparison of LENT/SOMA, RTOG/EORTC, and NCI-CTC scoring systems. Int J Radiat Oncol Biol Phys 2003; 55: 93–98.

35. Rischin D, Peters LJ, O'Sullivan B et al. Tirapazamine, cisplatin, and radiation versus cisplatin and radiation for advanced squamous cell carcinoma of the head and neck (TROG 02.02, HeadSTART): a phase III trial of the Trans-Tasman Radiation Oncology Group. J Clin Oncol 2010; 28: 2989–2995.
36. Ang KK, Zhang Q, Rosenthal DI et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. J Clin Oncol 2014; 32: 2940–2950.

Figure 1. Progression-free survival (A) and overall survival (B) estimates with an 8.6-year median follow-up in the intention-to-treat population.

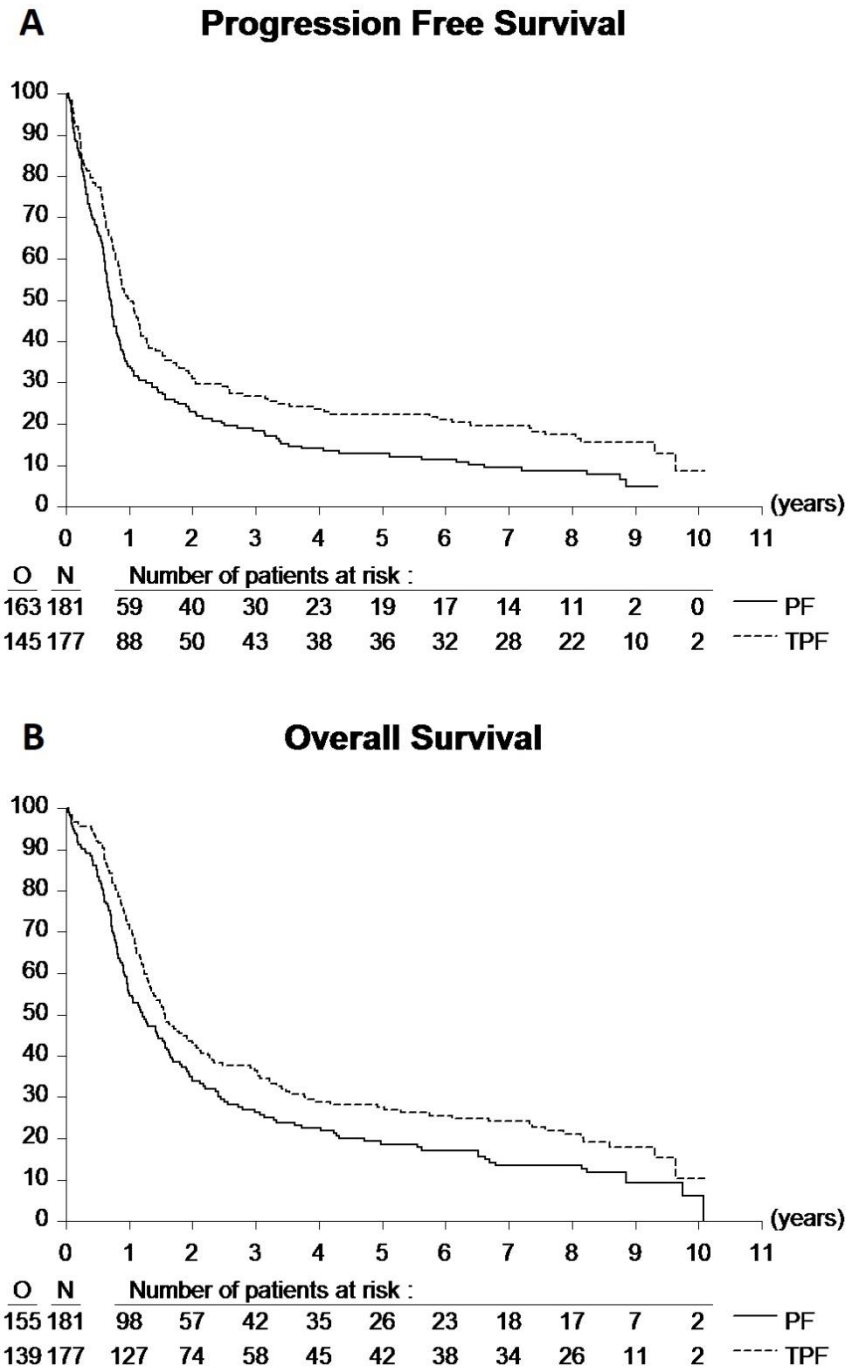

Table 1. Progression-free survival events.

Event	N (%) PF (N=181)	TPF (N=177)	Total (N=358)
No events	18 (9.9)	32 (18.1)	50 (14.0)
Progression or death	163 (90.1)	145 (81.9)	308 (86.0)
Death	23 (12.7)	29 (16.4)	52 (14.5)
Locoregional progression only	101 (55.8)	87 (49.2)	188 (52.5)
Distant metastasis only	12 (6.6)	12 (6.8)	24 (6.7)
Both locoregional and distant progression	4 (2.2)	5 (2.8)	9 (2.5)
Unknown type of progression	23 (12.7)	12 (6.8)	35 (9.8)

Abbreviations: N, number; PF, induction chemotherapy with cisplatin and 5-fluorouracil; TPF, induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil

Table 2. Cause of death.

Events	N (%) PF (N=181)	TPF (N=177)	Total (N=358)
Death			
No	26 (14.4)	38 (21.5)	64 (17.9)
Yes*	155 (85.6)	139 (78.5)	294 (82.1)
Progressive disease	118 (76.1)	100 (71.9)	218 (74.1)
Toxicity	11 (7.1)	4 (2.9)	15 (5.1)
Infection	5 (3.2)	3 (2.2)	8 (2.7)
Cardiovascular disease	2 (1.3)	2 (1.4)	4 (1.4)
Other chronic disease	1 (0.6)	3 (2.2)	4 (1.4)
Pulmonary embolism	1 (0.6)	3 (2.2)	4 (1.4)
Intercurrent non-malignant disease	3 (1.9)	6 (4.3)	9 (3.1)
Second primary tumours	1 (0.6)	3 (2.2)	4 (1.4)
Other	11 (7.1)	12 (8.6)	23 (7.8)
Unknown	2 (1.3)	3 (2.2)	5 (1.7)

Abbreviations: N, number; PF, induction chemotherapy with cisplatin and 5-fluorouracil; TPF, induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil

*The respective figures serve as baseline for percentage calculations of causes of death.

Table 3. Late treatment-related toxicity.

	N (%)	
	PF (N=181)	**TPF (N=177)**
Did the patient undergo tracheostomy?		
no	131 (72.4)	137 (77.4)
yes	9 (5.0)	13 (7.3)
unknown	41 (22.7)	27 (15.3)
Did the patient experience feeding tube dependence?		
no	132 (72.9)	144 (81.4)
yes	10 (5.5)	6 (3.4)
unknown	39 (21.5)	27 (15.3)
Did the patient undergo gastrostomy?		
no	121 (66.9)	132 (74.6)
yes	19 (10.5)	19 (10.7)
unknown	41 (22.6)	26 (14.7)

Abbreviations: N, number; PF, induction chemotherapy with cisplatin and 5-fluorouracil; TPF, induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil

Table 4. Univariate analysis of prognostic factors.

Parameter	N	OS probability at 3 years (95% CI)	OS probability at 5 years (95% CI)	p-value*
Age				
<65 years	147	37.9 (30.0-45.7%)	29.5 (22.2-37.2%)	0.0016
≥65 years	16	18.8 (4.6-40.2%)	6.3 (0.4-24.7%)	
Sex				
Male	146	34.8 (27.1-42.6%)	25.2 (18.3-32.6%)	0.0573
Female	17	45.8 (21.5-67.2%)	45.8 (21.5-67.2%)	
Performance status				
0	82	45.1 (33.9-55.6%)	36.6 (26.0-47.3%)	0.02
≥1	81	26.9 (17.8-36.9%)	17.9 (10.4-27.1%)	
Primary tumour site				
Hypopharynx	44	34.1 (20.7-48.0%)	21.0 (10.2-34.4%)	0.0846
Larynx	8	50.0 (15.2-77.5%)	50.0 (15.2-77.5%)	
Oral cavity	31	22.2 (9.1-38.9%)	13.3 (3.6-29.4%)	
Oropharynx	80	40.5 (29.7-51.1%)	32.7 (22.6-43.1%)	
T-stage				
T1 or T2	12	41.7 (15.2-66.5%)	25.0 (6.0-50.5%)	0.6204
T3	34	48.6 (30.8-64.2%)	34.4 (18.4-51.0%)	
T4	117	31.9 (23.6-40.5%)	25.3 (17.7-33.6%)	
N-stage				
N0	14	51.1 (21.6-74.5%)	42.6 (15.8-67.4%)	0.1110
N1	25	44.0 (24.5-61.9%)	30.8 (14.1-49.3%)	
N2	95	37.5 (27.8-47.2%)	28.1 (19.3-37.6%)	
N3	29	17.2 (6.3-32.7%)	13.8 (4.3-28.6%)	
Histology grade				
Well differentiated	26	52.1 (31.1-69.4%)	39.0 (20.2-57.6%)	0.0391
Moderately differentiated	76	27.4 (17.9-37.8%)	18.3 (10.3-28.0%)	
Poorly or undifferentiated	37	44.5 (28.0-59.8%)	41.5 (25.4-57.0%)	
Missing/Unknown	24	33.3 (15.9-51.9%)	20.8 (7.6-38.5%)	
Number of organs				
1	17	34.6 (12.8-57.7%)	34.6 (12.8-57.7%)	0.5958
≥2	146	36.1 (28.3-43.8%)	26.3 (19.3-33.8%)	
Time from histology to entry				
Within limits (≤21 days)	74	46.5 (34.7-57.4%)	31.5 (21.0-42.5%)	0.037
>21 days	88	27.6 (18.7-37.3%)	23.8 (15.4-33.3%)	
Baseline white blood cells				
<10 x10^9 cells/L	97	43.8 (33.7-53.4%)	32.5 (23.3-42.1%)	0.1412
≥10 x10^9 cells/L	66	24.4 (14.7-35.4%)	19.2 (10.5-29.8%)	
Baseline platelets				

<400 x10^9 cells/L	131	39.1 (30.6-47.4%)	30.5 (22.7-38.7%)	0.0308
≥400 x10^9 cells/L	32	23.2 (10.3-39.0%)	13.2 (4.2-27.5%)	
Baseline haemoglobin				
≥120 g/L	141	37.5 (29.4-45.5%)	28.1 (20.8-35.8%)	0.0645
<120 g/L	22	27.3 (11.1-46.4%)	21.8 (7.5-40.9%)	
Albumin				
<35 g/L	17	32.4 (12.0-54.9%)	25.9 (8.1-48.3%)	0.7327
≥35 g/L	122	34.6 (26.2-43.1%)	25.5 (18.0-33.7%)	
Missing	24	45.8 (25.6-64.0%)	36.7 (18.1-55.5%)	
Hoarseness				
Grade 0	141	35.9 (28.0-43.9%)	26.3 (19.2-34.0%)	0.8309
Grade ≥1	21	38.1 (18.3-57.8%)	33.3 (14.9-53.1%)	
Weight loss				
Grade 0	132	38.3 (30.0-46.6%)	28.5 (21.0-36.5%)	0.3573
Grade ≥1	31	25.4 (11.4-42.1%)	21.1 (8.4-37.7%)	
Dysphagia				
Grade <2	130	40.9 (32.3-49.2%)	30.6 (22.7-38.8%)	<0.0001
Grade ≥2	31	14.7 (4.9-29.8%)	11.1 (2.9-25.4%)	
Pain				
Grade <2	107	43.2 (33.6-52.4%)	35.0 (25.9-44.2%)	0.0009
Grade ≥2	56	22.1 (12.3-33.8%)	12.1 (5.0-22.4%)	

Abbreviations: N, number of patients; OS, overall survival; CI, confidence interval

* Log-rank test

Table 5. Final Cox proportional hazards regression model resulting from the multivariate prognostic factor analysis for overall survival

Parameter	Hazard Ratio (95% CI)	p-value
Age	1.00 (0.97, 1.02)	0.813
Sex		
Male	1.00	0.235
Female	0.66 (0.33, 1.32)	
Primary tumour site		
Oral cavity	1.00	0.027
Hypopharynx	1.52 (0.83, 2.80)	
Larynx	0.70 (0.26, 1.87)	
Oropharynx	0.78 (0.47, 1,31)	
T-stage		
T1 or T2	1.00	0.844
T3	0.81 (0.37, 1.77)	
T4	0.90 (0.44, 1.83)	
N-stage		
N0	1.00	0.025
N1	1.01 (0.46, 2.21)	
N2	0.98 (0.49, 1.95)	
N3	2.10 (0.96, 4.58)	
Dysphagia		
Grade <2	1.00	0.002
Grade ≥2	2.09 (1.30, 3.37)	
Pain		
Grade <2	1.00	0.004
Grade ≥2	1.91 (1.23, 2.95)	

Abbreviations: CI, confidence interval