Diplomarbeit

Definitive radiochemotherapy with and without induction chemotherapy in patients with head and neck cancer – A retrospective comparative effectiveness study

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Graz, am 18.12.2018 *Stefanie Mollnar eh*

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Abbrevations

5-FU	5-Fluorouracil
95% CI	95% confidence interval
AJCC	American Joint Committee on Cancer
ATT	average treatment effect on the treated
BOTSCC	base of the tongue squamous cell carcinoma
CCI	Charleson Comorbidity Index
CR	complete remission
CRP	C-reactive protein
CRT	radiochemotherapy
CT	computer tomography
DCR	disease control rate
DSF	disease free survival
ECOG	Eastern Cooperative Oncology Group
EGFR	epithelial growth factor receptor
ENT	ear, nose, throat
FA	Fanconi Anaemia
Gy	Gray
HNC	head and neck cancer
HNSCC	head and neck squamous cell carcinoma
HPSCC	hypopharyngeal squamous cell carcinoma
HPV	Human Papilloma Virus
HR	Hazard Ratio
HSCT	hematopoietic stem cell transplantation
ICT	induction chemotherapy
IPTW	inverse probability of treatment weight
MRI	magnetic resonance imaging
OLP	oral lichen planus
OPSCC	oropharyngeal squamous cell carcinoma
ORR	objective response rate
OS	overall survival
OSCC	oral squamous cell carcinoma
OSF	oral submucous fibrosis
PD-L1	programmed cell death 1 ligand 1
PET	positron emission tomography
PMD	potentially malignant disorder
PFS	progression free survival
RS	relative survival
SCC	squamous cell carcinoma
SEER	Surveillance, Epidemiology and End Results
SMD	standardized mean difference
SPM	second primary malignancy

TNM	Tumor Node Metastasis classification
TRIM24	Tripartite Motif Containing 24
TSCC	tonsillar squamous cell carcinoma
TTF	time to treatment failure
UICC	Union internationale contre le cancer
VEGFR	vascular endothelial growth factor
VOM	volatile organic metabolite
WHO	World Health Organisation

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Zusammenfassung

Hintergrund

Die definitive Radiochemotherapie stellt nach wie vor die Standardtherapie bei PatientInnen mit lokal-fortgeschrittenen Kopf-Hals-Tumoren dar. Jedoch deuten Studien darauf hin, dass die Applikation einer vorangeschalteten Induktionschemotherapie womöglich zu einer Verbesserung des Rezidiv-freien Überlebens, sowie einer Senkung der Fernmetastasierungsrate beitragen könnte. Ob sich dies auch auf das Gesamtüberleben der PatientInnen überträgt ist unklar, beziehungsweise finden sich dazu unterschiedliche Ergebnisse. Aus diesem Grund haben wir eine Propensity-Score Analyse des Gesamtüberlebens bei PatientInnen mit fortgeschrittenen Kopf-Hals-Tumoren, die eine Radiochemotherapie mit oder ohne vorheriger Induktionschemotherapie erhalten haben, durchgeführt.

Material und Methoden

Es wurden retrospektiv 195 PatientInnen mit lokal-fortgeschrittenem/inoperablem, plattenepithelial differenzierten Kopf-Hals-Tumor in die Studie eingeschlossen. Das mediane Alter der Studienkohorte betrug 59 Jahre und 73% der PatientInnen hatte einen ECOG Performance Status von 0 Punkten. Von dieser Studienpopulation erhielten 76 PatientInnen (39%) eine der Radiochemotherapie (zumeist 35 x 2Gy + 3 Zyklen 100mg/m^2 Cisplatin in 3 wöchentlichen Abständen) vorangestellten Induktionschemotherapie, diese war für die meisten PatientInnen (82%) 3 Zyklen des TCF Schemas (Cisplatin, Docetaxel, 5-FU). Die beiden Co-primären Endpunkte der Studie waren das Rezidiv-freie Überleben und das Gesamtüberleben. Als Nebenzielgrößen wurden Toxizität, Response und die Risiken für Lokalprogression und Fernmetastasierung erfasst. Um mit retrospektiven Beobachtungsdaten ein quasi-experimentelles Setting zu generieren wurde eine inverse-Behandlungswahrscheinlichkeits-gewichtete Analyse (IPTW) durchgeführt.

Ergebnisse

Nach einem medianen follow-up von 3.6 Jahren für Rezidiv und 4.3 Jahren für Gesamtüberleben entwickelten 66 PatientInnen eine Krankheitsprogression, und 83 PatientInnen verstarben. Es zeigte sich eine 5-Jahres-Gesamtüberlebenswahrscheinlichkeit von 50%, ein 5-Jahres-Rezidiv-freies Überleben von 47%, eine Lokalprogressionsrate von

35% und eine Fernmetastasierungsrate von 19%. PatientInnen, die eine Induktionschemotherapie erhalten haben waren signifikant jünger (p=0.0001), hatten weniger Komorbiditäten (p=0.0001), seltener Zweitmalignome (p=0.03) und einen besseren ECOG Performance Status (p=0.0001). Um diese Ungleichheiten zwischen den beiden Gruppen auszugleichen wurde ein Propensity Score ermittelt und in einem zweiten Schritt die Daten mittels IPTW gewichtet. In der IPTW-gewichteten Kaplan-Meier Analyse zeigte sich keine statistisch signifikante Assoziation zwischen Induktionschemotherapie und Gesamtüberlebensvorteil (95%CI: 0.46-1.63, HR=0.86, p=0.65). In der Gruppe mit Induktionschemotherapie war jedoch eine signifikante Senkung des Risikos für Fernmetastasierungen ersichtlich (95%CI: 0.16-0.94, HR=0.38, p=0.04).

Conclusio

Die Daten dieser nicht-randomisierten Studie zeigen bezüglich einer Senkung des Fernmetastasierungsrisikos eine konsistente Übereinstimmung mit den Ergebnissen früherer randomisierter Studien, welches sich aber nicht in einem Gesamtüberlebensvorteil überträgt. Daher ist eine strenge Indikationsstellung zur Induktionschemotherapie notwendig, jedoch könnte sich diese Therapieform vor allem für all jene PatientInnen, mit hohem angenommenem systemischem Risiko und für PatientInnen mit Wunsch einer organerhaltenden Therapie, insbesondere beim Larynxkarzinom, eignen.

Abstract

Background

Definitive radiochemotherapy (CRT) is the current standard of care for patients with locally advanced head and neck cancer. However, recent studies indicate that prior induction chemotherapy (ICT) might improve progression free survival and reduce distant metastasis. Whether ICT improves outcomes in terms of overall survival in this patient population is still debated. To obtain further scientific evidence on these questions, we conducted a retrospective comparative effectiveness study in patients with head and neck cancer, who received CRT +/- ICT.

Methods

In this single-centre, observational, retrospective cohort study we included 195 head and neck squamous cell carcinoma patients, who received CRT at the department of ENT of the Medical University of Graz. The median age of the study population was 59 years and 73% had an ECOG Performance status grade 0. 76 patients (39%) received an ICT prior to concomitant CRT, the regimen for the induction treatment was TPF (consisting of Cisplatin, Docetaxel, 5-FU) for most of the patients (82%). Co-primary endpoints were progression-free survival (PFS) and overall survival (OS). An inverse-probability-of-treatment-weight (IPTW) analysis was conducted to generate a quasi-experimental setting with observational, retrospective data.

Results

During a median follow-up of 3.6 years for progression and 4.3 years for overall survival we observed 66 disease progressions and 83 patients died. 5-year OS and PFS estimates were 50% and 47%, respectively. Local progression rate after 5 years was 35%, and the corresponding rate for distant metastasis was 19%. Importantly, we observed significant differences in the distribution of baseline covariates between the two study groups. For example, patients who received ICT were significantly younger (p=0.0001), had fewer comorbidities (p=0.0001), were less likely to have a second primary malignancy (p=0.03) and had better ECOG Performance status (p=0.0001). After re-weighing of the data with the IPTW most imbalances between the two treatment groups were removed. IPTW-adjusted analysis of OS did not support the hypothesis that ICT is associated with improved survival

(Hazard Ratio (HR)=0.96, 95%CI: 0.46-1.63, p=0.65). However, after full IPTW adjustment, the rate of distant metastasis was significantly lower with ICT+CRT than with CRT alone (HR=0.38, 95%CI: 0.16-0.94, p=0.04).

Conclusion

The results of this non-randomised study fully corroborate previous randomised trials which showed that ICT improves systemic disease control by reducing the risk of distant metastasis. However, the data of this study suggest that this benefit does not translate into a meaningful improvement in OS. Therefore, each indication for ICT should be carefully assessed for every patient, weighing potential benefits and harms. For example, ICT+CRT may be considered an effective treatment strategy for patients presumed to have a very high systemic risk, or for patients who prefer an organ-preserving treatment strategy, especially in cases of laryngeal carcinoma.

Introduction

Classification and definition

Head and neck cancer (HNC) is a common malignancy originating from the mucosa of the upper aerodigestive tract. (1) HNC can arise in different anatomic locations, including the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, parapharyngeal space, salivary and thyroid glands as well as including different histopathologic entities, though most HNCs are squamous cell carcinomas (HNSCC) (2). In this diploma thesis, the primary focus is on HNSCCs deriving from the mucosal surfaces of the oral cavity, the two lower pharyngeal compartments; oropharynx and hypopharynx, and from the laryngeal mucosa. Pharyngeal tumors can be located between the skull base and the lower border of the cricoid cartilage. (3, 4) Tumors of the nasopharynx are located dorsally of the nasal cavity. As is the nasopharynx is not a part of the alimentary tract, there are different predisposing factors for the genesis of carcinomas at this location, such as EBV infection. (5)

HNCs classified as oropharyngeal squamous cell carcinomas (OPSCC) compromise tumors of the inferior soft palate, the posterior and lateral walls, the uvula, the pharyngeal tonsils and the glossotonsillar sulci. (4) The term hypopharyngeal squamous cell carcinoma (HPSCC) is used for tumors behind the larynx, the hypopharynx can be further subdivided into three compartments. Laryngeal carcinomas are located anywhere between the superior borders of the hyoid bone to the inferior border of the cricoid cartilage. (3) In addition to this, the term HNSCC comprises malignancies of the oral cavity, which is inferiorly bounded by the floor of the mouth and superiorly by the hard palate. Sagittal it extends from the lips to the papillae vallatae inferiorly and the junction of the hard and soft palate superiorly. (3, 4)

Furthermore, HNSCC can be classified in cancers arising from HPV (Human Papilloma Virus) related anatomical sites, including the tonsils, the base of the tongue, other oropharynx sites and Waldeyer's ring and cancers arising from sites unrelated to HPV infection such as the hypopharynx, the larynx and specific areas of the oral cavity. (6) Concerning the tumor extent HNSCCs are staged as localized, regional/locally advanced or distant disease. The term *localized* defines an invasive neoplasm limited entirely to the organ of origin, whereas *regional* indicates that the tumor has grown beyond the anatomic borders of the effected organ, into regional lymph nodes or both. (7) In this study, the main focus is on locally advanced HNSCC. Treatment options for HNSCC in general include surgery,

radiotherapy and radiotherapy combined with chemotherapy, whereby surgery is mainly the therapy of choice in patients with localized HNSCC. (8)

Epidemiology

Considering the risk factors and ethnicity there are large geographic differences in the incidence and primary site of HNCs. In Europe HNC accounts for an estimated 4 per cent of malignancies and is thought to be the seventh most common malignancy worldwide. The highest rates of HNSCC are in older males with an approximate incidence of 36/100000 a year. (8-10) It most commonly occurs between the fourth and sixth decade. Females are affected significantly less than males, with a ratio ranging from 2:1 to 4:1 and an incidence of 7/100000 per year. Exceptions of that are related to the relative distribution of risk factors such as smoking and alcohol consumption with the highest incidence rate in males, 63/100 000, reported in France, Bas Rhin. In females, the highest incident rate is found in India, Madras with 16/100000. (9) HNC accounts for about 25 percent of male and 10 percent of female cancers in India, which is related to the tobacco habits prevalent in the country. (11) The incidence of carcinomas in the oral cavity and the pharynx located at sites probably not related to HPV have slightly decreased in men since 1980, mainly associated to tobacco and alcohol reduction strategies. (2) HPV related- and potentially HPV related HNC, mainly located in the oropharynx, have significantly increased over the past years. (12) Due to public health efforts regarding tobacco control and education in Northern America, the prevalence of cigarette smoking has successfully been reduced, which seems to explain the lower incidence rates of HNC not related to HPV. Oropharyngeal cancers, on the other hand, have not been affected by this recent change in epidemiology, which likely reflects the increasing number of HPV-related OPSCC. (13)

Similar developments have been observed in Europe; a recent study from Italy shows decreasing incidence rates of cancers arising from sites unrelated to HPV infection and stable incidence rates for cancers from HPV related anatomical sites in males. Whereas significantly increasing incidence rates for HPV related cancers have been observed in females, with the highest number noted in those over 60. (6)

Prognosis

General

HNC has a poor prognosis and is traditionally considered to be difficult to cure beyond very early-stage disease. Due to local recurrence and distant progression about 60% of HNC patients die during the first 5 years after the initial diagnosis. (14, 15) According to the Clinical Practice Guidelines for HNC of the European Society for Medical Oncology (ESMO) the relative survival rate is 72% at one year and 42% at five years. There is a difference in the 5-year survival rate between the sexes, with 51% it is higher for women than for men (39%). Five-year relative survival (RS) is the highest for laryngeal cancer (59 %) and the poorest for carcinomas arising from the hypopharynx (25%). (8) The prognosis is mainly affected by tumor location, HPV status, age, sex, country and TNM (Tumor Node Metastasis classification) stage. (16) General prognosis is still poor for recurrent or metastatic disease with a median overall survival (OS) of 10 months. (10) In general, HNSCCs deriving from HPV positive locations respond better to treatment including radiotherapy and chemotherapy than HPV negative tumors. Thus, patients with HPV positive diseases have significantly better long-term survival rates. (17) Other histopathologic features affecting the clinical outcome are tumor grade, proximity of tumor mass to resection margins, invasion pattern and the presence of extranodal metastasis. Extranodal spread is an independent prognostic factor which leads to halved 5-year survival rates. (18) In addition, prognosis for HNC patients is significantly related to comorbidities, in these patients commonly caused by alcohol and/or tobacco abuse. Studies suggest that patients with high comorbidities seem to have a delay in prognosis, which results in advanced tumor stages at the time of diagnosis and subsequently in less aggressive therapy strategies. (19) In general, the conditions affecting the survival of HNSCC patients the most are congestive heart failure, cerebrovascular disease, ulcer disease, diabetes, chronic pulmonary disease and liver disease. (20)

Due to better access to medical treatment facilities RS is usually higher in Northern Europe and the United Kingdom than in Eastern countries. (16)

Oral cavity

About one quarter of all HNC cases affect parts of the oral cavity. According to data from the SEER (Surveillance, Epidemiology, and End Results) program of the National Cancer Institute the 5-year survival rate for patients diagnosed with locally advanced stage disease

is about 44% and 72% for localized stages, thus confirming that clinical stage is a significant prognostic factor. (7)

Oropharynx

OPSCC is the HNSCC sub-entity with the highest incidence rates in the group of pharyngeal HNCs. The majority of patients, about 70 %, are diagnosed with advanced stage disease, further subdivided into regional and distant stages. The 5-year survival rate for patients with regional stage tumors and local stage disease is about 51 % and 61 %, respectively. (2, 7) Especially for oropharyngeal cancer HPV p16 status is considered an independent favourable prognostic factor, showing significant higher rates of survival in HPV positive cases. For non-oropharyngeal HNSCC, HPV- and p16 status have not been shown to be of prognostic value in clinical practice so far. (21, 22) Another well-known factor associated with worse outcome is being underweight at the time of diagnosis. (22)

Nasopharynx

Similar to oropharyngeal cancer most patients already present with advanced stage disease. With 5-year survival rates of 59 % for patients with regional stage disease and 45 % in cases diagnosed with distant disease. Overall, nasopharyngeal cancer is associated with a better prognosis than oropharyngeal cancer. (7)

Hypopharynx

During the last decades significant increases in 5-year survival rate were observed for all stages. However, it still has the poorest prognosis from all HNSCC locations. 5-year survival rate in cases of regional and distant disease is about 35% and 13%, respectively. (2, 7, 14)

Larynx

The proportion of larynx cancers among all HNSCCs decreased over the past decades, and 5-year survival rates have been estimated at 55% for regional stage disease. (7) Survival rates vary for different tumor locations. They are usually higher for supraglottic- and lower for subglottic cancer. (23) About 40% of the patients present with stage III or IV disease at the time of initial diagnosis. (7) According to American Society of Clinical Oncology (ASCO) clinical practice guidelines, a larynx preservation approach with radiotherapy or chemo-radiotherapy is recommended for up to low volume advanced (T4) laryngeal cancer without tumor invasion through cartilage into soft tissues and does not lead to decreased OS rates. (24)

Risk factors

One of the links between the most common predisposing factors for HNSCC seems to be the chronic exposure to specific carcinogens, which leads to mutation and dysplastic lesions in the mucosa and ultimately results in HNC. Over the past years a change in aetiology of HNSCC has been observed, associated with the cancerous effects of HPV. (25)

Tobacco and alcohol

Smoking and the consumption of alcohol are two habits, which are strongly associated with each other, though the respective contributions of these predisposing factors are still discussed. At least three quarters of HNSCCs are attributable to the combination of these two factors and it is well known that the joint effect of tobacco and alcohol is greater than multiplicative on the risk of developing HNC. (26, 27)

Tobacco

A significant dose-response relationship was observed for duration and amount of tobacco consumption. Different patterns of smoking are associated with a higher risk of developing HNSCC at specific sites. The strongest risk factor for oral cancer seems to be chewing of tobacco, while tobacco smoking is considered as the main risk factor for pharyngeal cancers. (28) The risk for SCC in the pharynx or in the oral cavity only decreases to practically the same relative risk non-smokers have after 10 or more years since cessation. (29) A product that is of special interest to Scandinavian countries is oral snuff, which is placed under the upper lip containing nonfermented tobacco. It is known that oral snuff causes reversible white patches and ulcerations on the gum. Thus far, there is no evidence that HNSCC is associated with the use of Swedish oral snuff. Due to the contents of this product, including cancerous N-nitrosamines, the members of the European Union have urged the prohibition of oral snuff nevertheless. (30)

Alcohol

Alcohol abuse is most strongly associated with the risk of oro-/ and hypopharyngeal cancer, whereas it has less effects on the genesis of laryngeal cancers as the larynx having the least direct exposure. The amount of alcohol intake is an important factor determining the risk for HNC but after adapting for total intake there is a similar risk between the consumption of beer, wine and liquor. (31)

However, frequent consumption of tobacco and alcohol is not only considered as a major risk factor for the genesis of HNSCC, it also seems to be a significant prognostic factor. Patients who refuse or fail to change their current lifestyle are at higher risk of developing second primary malignancies (SPM) and poor survival rates. (32)

HPV

A significant increase in incident rates in OPSCC, mainly affecting white men younger than 50 years, who are less likely to have had a long history of alcohol and tobacco abuse, has been recorded over the past 30 years. (33) This tumor location is associated with human papilloma virus 16 (HPV16), a potentially carcinogenic sexually transmitted infection, characterised by P53 degradation, RB pathway inactivation and p16 upregulation. In contrast, oropharyngeal cancer associated with tobacco abuse is commonly characterised by TP53 mutation and downregulation of CDKN2A. (33, 34) HPV status can be tested by p16 immunohistochemical stain, with double positivity for HPV-DNA/$p16^{INK4a}$ as the strongest prognostic value and diagnostic accuracy. (35) In more than 90% of tonsillar and base of tongue squamous cell carcinoma (TSCC and BOTSCC) cases HPV16 infection is present, further HPV types contributing to OPSCC are HPV 33 and HPV 35. Due to a much better clinical outcome of patients with HPV positive tumors, it is important to identify HPV status and use additional predictive markers to provide better-tailored therapy strategies for those patients. 5-year disease free survival (DFS) in HPV positive TSCC and BOTSCC is 80% versus 40% for the corresponding HPV negative tumors, treated with primary radiotherapy alone or additional surgery if needed. Therefore, aggressive treatment regimens with intensified radiochemotherapy, associated with severe side effects, may not be beneficial for most of these patients. (36)

Risk factors for HPV positive OPSCC include a higher number of vaginal sex partners, more than 25 for a lifetime, and a higher number of lifetime oral sex partners (>5) and open-mouthed kissing partners. (37) Risk reduction can be achieved by HPV vaccination, mainly recommended for young girls to decrease the risk of cervical cancer. However, for the prevention of OPSCC, HPV vaccination needs be introduced for young boys, prior to their first sexual activity, as well. Especially since more than 70% of OPSCC cases affect men. (36, 38, 39)

Poor oral hygiene

Poor oral hygiene such as teeth loss or infrequent tooth brushing may result in an overgrowth of periodontopathogenic bacteria and changes to the oral microbiome, which is associated with a higher risk of oral cancer and acts synergistically with alcohol or tobacco abuse. Especially total tooth loss leads to lower microbial diversity, because the gum-tooth interface is a preferred site for bacterial colonization. Bacteria species associated with a higher OSCC risk are Fusobacterium nucleatum, Prevotella intermedia and Prevotella tannerae. (40, 41)
On the other hand, good oral hygiene with a minimal number of missing teeth, tooth brushing with toothpaste more than once daily, the use of dental floss and regular dental check-ups can reduce the risk for oral cancer significantly, particularly among alcohol and tobacco consumers. (42, 43)

Chronic inflammation

Chronic infection and inflammation are established risk factors in the pathogenesis of cancer. One of the key mechanisms of this process is the activation of pro-inflammatory pathways. Important transcription factors involved in the inflammatory response are nuclear factor-κB (NF-κB) and activators of transcription 3 (STAT3). NF-κB acts as regulator of various gene products promoting inflammation and similarly, most agents that lead to inflammation and proliferation activate NF-κB. (44) A study conducted in the United States shows that NF-κB is constitutively active in HNSCC and contributes to the proliferation of tumor cells due to the overweight of cytokines. (45)
As a consequence of chronic mucocutaneous inflammation, patients with immune-mediated inflammatory disorders such as oral lichen planus (OLP) are at higher risk of malignant transformation. The percentage of cases with malignant transformation varies from 0.4% to 3.7%. However, the malignant potential of OLP is still controversial, treating OLP, especially the erosive form, as a precancerous lesion at present. (46, 47)

Fanconi Anaemia

Fanconi Anaemia (FA) is an autosomal recessive chromosomal instability disorder characterized by congenital abnormalities, bone marrow failure and a higher incidence of malignancies compared to the general population. Although acute myeloid leukaemia is the most frequent malignant disease, FA patients have an increased risk of developing HNSCC, which is significantly higher after hematopoietic stem cell transplantation (HSCT). This is thought to result from FA patients' hypersensitivity to alkylating agents such as

cyclophosphamide and irradiation, which are part of HSCT conditioning treatment and known as independent transplant-related risk factors for SCC. (48) The risk for developing aggressive HNSCC at a young age is approximately 500 times higher in FA patients compared to the general population. (49)

Other hereditary factors

Besides Fanconi Anaemia other hereditary diseases including Li Fraumeni Syndrome, Bloom Syndrome, Lynch II Syndrome, xeroderma pigmentosum and ataxia telangiectasia are believed to be associated with an increased risk of developing HNC. (50) Bloom Syndrome is an inheritable disease with a predisposition towards hypopharyngeal and laryngeal SCC. (3) Patients with acquired immunodeficiency, due to, for instance, immunosuppressive therapy after organ transplantation, are at higher risk of developing malignancies of any kind, thus the risk for HNSCC is also increased. (51)

Precancerous lesions

It is established that especially OSCC is often preceded by precursor lesions, defined as potentially malignant disorders (PMDs). PMDs represent areas of genetically or environmentally altered tissue caused by accumulation of genetic abnormalities and are more likely to transform to cancer than normal tissue. The variety of PMDs include leucoplakia, erythroplakia, oral submucous fibrosis (OSF), actinic cheilitis, palatal keratosis, discoid lupus erythematosus, dyskeratosis congenita and epidermolysis bullosa. The most frequent are leucoplakia, erythroplakia, oral submucous fibrosis and OLP. (46, 52) Erythroplakia has the strongest malignant potential among the PMDs mentioned above and is used as clinical term for bright red velvety plaques. Transformation rates for erythroplakia vary from 14% to 51%. Areas frequently affected are the buccal mucosa, the soft palate and the floor of the mouth. (46, 53) Leucoplakia is defined as “a white patch or plaque that cannot be characterized clinically or pathologically as any other disease” by the World Health Organization (WHO) and is used as a clinical term, not connoting any specific histopathologic patterns. (54) The typical presentation of leucoplakia occurs in middle aged to older men and is mostly caused by alcohol consumption, smoking and betel quid. (46) Dysplastic or malignant transformation rates in leucoplakia are ranging from 16% to 39%, with the floor of the mouth identified as the highest risk site. (54) A PMD strongly associated with tobacco consumption is OSF, a chronic disease characterized by mucosal rigidity due

to fibrosis of the submucosa and juxta-epithelial inflammatory reaction. The risk of malignant transformation to OSCC is at least 19 times higher in OSF patients in comparison to the general population. (46) Clinical features of PMDs, which are at risk of progressing to cancer include red/red-white colour, irregularity and verrucous or granular surface texture. (55)

Molecular pathogenesis

Different alterations in the genetic profile affecting tumor suppressor genes as well as oncogenes have been associated with the genesis of HNSCC. As in many other malignant tumors p53 gene mutation is one of the most frequent genetic abnormalities in HNSCC with a prevalence of about 50-60% of the malignant cells. The importance of p53 gene mutational status in HNSCC as diagnostic and prognostic marker in the clinical management is still incompletely understood. (56) Though p53 is associated with poor patient survival and resistance to therapy. (57)

Furthermore, the oncogene TRIM24 (Tripartite Motif Containing 24) was found overexpressed in 43% of HNSCC cases and shows a correlation with TNM stage. TRIM24 modulates the cell cycle and leads to increased glucose uptake resulting in a switch in energy production from oxidative phosphorylation to glycolysis. Moreover, overexpression of TRIM24 activates GLUT3 production, which is associated with poor outcome rates for OSCC and laryngeal cancer if overexpressed. Silencing the expression of TRIM24 in HNSCC tumor cells results in induction of apoptosis and inhibition of proliferation. (58, 59)

Another molecular marker associated with HNSCC is PD-1/PD-L1 (programmed cell death 1 ligand 1), upregulated by STAT3. The PD-1/PD-L1 axis has now been confirmed as a therapeutic target for advanced HNSCC. (60) Additionally, the expression of a tumor suppressor gene called DKK3 has been observed in HNSCC, which is thought to be involved in cellular proliferation, invasion and tumor cell survival. (61) Compared to other cancer types, molecular changes in biology of this disease need further investigation, thus only few therapy strategies have targeted molecular markers so far. (62) Until now, only drugs targeting EGFR (epidermal growth factor receptor) or PD-1 are approved in advanced HNSCC and despite of a growing knowledge in precision medicine still none of the therapeutic decisions is biomarker driven. (63)

Pathology

Oral cavity and oropharyngeal carcinoma

SCC account for more than 90% of all malignancies originating in the oral cavity or the oropharynx. Upper and lower gingiva, buccal mucosal surface, floor of the mouth and the anterior two-thirds of the tongue are common locations for tumors of the oral cavity. (2) Low volume tumors are often found in the ventrolateral tongue and soft palate complex. The most frequent location for OPSCC is the base of the tongue. Macroscopically small SCCs may present as leuko- or erythroplakia, whereas in patients with advanced stage disease ulceroproliferative growths to orocutaneous fistula may be observed. (3, 64) Concerning the histopathologic appearance, grading is divided into well-, moderately- and poorly differentiated SCC. The ratio of keratinization decreases with lower grading, as the number of immature cells increases. Invasion may be expansive, infiltrative, or both, whereby infiltrative tumor growth is associated with worse prognosis. Tumors may spread directly to nearby structures or cause local and distant metastasis. SCCs located at the floor of the mouth are more likely to spread superficially, as neoplasms involving the tongue tend to extend in depth. Common problems include the spread into bone, usually into the mandible. In late stages distant metastases may occur, most commonly in the lung, followed by liver and bones. (3, 65)

Hypopharyngeal and laryngeal carcinoma

Similar to neoplasms located more cranially, SCC constitute more than 90% of all hypopharyngeal and laryngeal malignancies. Most LSCCs are located in the supraglottic and glottic regions, while the most common origins for HPSCCs are the pyriform sinus, followed by the posterior pharyngeal wall and the postcricoid area. The frequency of specific tumor locations varies according to geography and risk factors. Macroscopically the tumors present as flat plaques or with a polypoid exophytic appearance, sometimes with an ulcerated surface. Histopathologic patterns of LSCC and HPSCC do not differ from those of the oral cavity and oropharynx. Local spread of supraglottic SCC most commonly involves the base of the tongue or the piriform sinus, while HPSCC often extends to parts of the larynx. In cases of HPSCC, the invasion of the thyroid gland is associated with a poor prognosis. An uncommon complication after surgical therapy in form of total laryngectomy is stomal recurrence. SCCs frequently spread to regional lymph nodes, often resulting in neck

dissection as consequence in terms of treatment. (3) Patients with HPSCC more frequently present with distant metastases at initial diagnosis than patients with other HNSCCs. Compared to laryngeal cancer the incidence of distant tumor spread is three times greater. (65, 66) Most distant metastases occur as pulmonary metastasis, which may be difficult to distinguish from a second primary malignancy (SPM), particularly in cases of solitary nodules. (67)

Variants of the classic SCC appearance include verrucous SCC, which is non-metastasizing and well-differentiated, basaloid SCC, papillary SCC and acantholytic SCC. Spindle cell carcinomas are characterized by a squamous cell and a spindle cell component. Rare histopathologic diagnoses for this location are adenosquamous, lymphoepithelial and giant cell carcinomas. (3)

Immunohistochemistry

Usually the histopathologic diagnosis of SCC is based on morphology. Only in small biopsies, especially of high-grade tumors, confirmation of squamous origin is required. Squamous epithelial markers such as the cytokeratines 5 and 6 as well as the tumor supressor p53 are characteristically expressed by HNSCC. Differentiation from neuroendocrine tumors is performed by determining neuroendocrine markers such as chromogranin and synaptophysin, which would be negative in SCC. (68)

HPV status is usually tested indirectly by p16 immunohistochemical stain. However, the possibility that a tumor is HPV^- and $p16^+$ or HPV^+ and $p16^-$ exists. (69)

Staging

The TNM stage, describing tumor size and lymph node or distant metastasis status, provides an anatomically based classification, which affects treatment selection and prognosis (**Tables 1-4**). (70) Imaging methods for staging of HNSCC patients primarily include CT (computer tomography), PET-CT (positron emission tomography) and MRI (magnetic resonance imaging). This process is always combined with expert clinical examination by panendoscopy and an ultrasound scan of the neck. (71) MRI with contrast is optimal to assess soft tissue spread, while CT scanning may be helpful to assess the extent of nodal disease and possible bone invasion, moreover, it is recommended for the assessment of distant metastases. (72) Fluorine-18-fluorodeoxyglucose-PET offers complementary information and helps to identify invaded lymph nodes or distant metastasis and is an important tool for the delineation of radiotherapy target volume and posttreatment assessment. (73, 74) Due to different clinical behaviour and tumor biology new stage classifications of the AJCC include different staging for HPV positive and HPV negative OPSCC. (70)

Clinical stage

Concerning the clinical stages, stage I-II are defined as early stage disease and stage III-IV as advanced stage disease. About 58% of HNSCC patients present with advanced stage disease. (2) This proportion varies strongly for the different tumor sites, with the highest percentage for HPSCC, where 84% of the patients present with advanced stage disease at initial diagnosis. (75)

Patients with HPV positive tumors are more often diagnosed with small T-stage (T1, T2) together with higher N stage and have a lower incidence of distant metastases in comparison to HPV negative cases. (76)

Table 1. TNM classification OSCC, OPSCC, HPSCC

TNM classification according to the AJCC/UICC staging, 8th edition. (77, 78)

	OSCC	**OPSCC HPV+**	**OPSCC HPV-**	**HPSCC**
TIS	CIS		CIS	CIS
T1	Tumor ≤ 2 cm DOI ≤ 5 mm	Tumor ≤ 2 cm	Tumor ≤ 2 cm	Tumor limited to 1 subsite of the hypopharynx and/or ≤ 2 cm
T2	Tumor ≤ 2cm with DOI > 5mm or tumor > 2 cm and ≤ 4 cm with DOI ≤ 10 mm	Tumor ≥ 2 cm, but ≤ 4 cm	Tumor ≥ 2 cm, but ≤ 4 cm	Tumor invades more than 1 subsite of the hypopharynx or an adjacent site or measures > 2 cm but not more than 4 cm, without fixation of the hemilarynx
T3	Tumor > 2 cm and ≤ 4 cm with DOI > 10 mm or tumor > 4 cm with DOI ≤ 10mm	Tumor ≥ 4 cm or extension to lingual surface of epiglottis	Tumor ≥ 4 cm or extension to lingual surface of epiglottis	Tumor > 4 cm or with fixation of the hemilarynx or extension to the oesophagus
T4a	locally advanced: Tumor > 4 cm with DOI > 10 mm or tumor invades adjacent structure only, e.g. through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face	T4: Tumor invades any of the following: larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, mandible, lateral ptery-goid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases carotid artery	locally advanced: Tumor invades the larynx, deep/extrinsic muscle of the tongue, medial pterygoid, hard palate, or mandible	locally advanced: Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue
T4b	very advanced: Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery		very advanced: Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases the carotid artery	very advanced: Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures
NX	Regional nodes cannot be assessed			
N0	No regional lymph node metastasis			
N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE –			
N2a	Metastasis in a single ipsilateral lymph node, > 3 cm but ≤ 6 cm and ENE –			
N2b	Metastasis in multiple ipsilateral lymph nodes, ≤ 6 cm and ENE –			

N2c	Metastasis in bilateral or contralateral lymph nodes, ≤ 6 cm in greatest dimension and ENE –
N3a	Metastasis in a lymph node > 6 cm in greatest dimension and ENE –
N3b	Metastasis in any lymph node(s) with clinically overt ENE +
M0	No distant metastasis
M1	Distant metastasis
DOI: depth of invasion; ENE: extra nodal extension	

Table 2. TNM classification Larynx

TNM classification according to the AJCC/UICC staging, 8th edition. (78)

	Supraglottis	Glottis	Subglottis
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility	T1a: Tumor limited to one vocal cord T1b: Tumor involves both vocal cords	Tumor limited to the subglottis
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre- epiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space, and/or inner cortex of thyroid cartilage	Tumor limited to larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage
T4a	Locally advanced: Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid or oesophagus)		
T4b	Very advanced: Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures		
N	See table 1		
M	See table 1		

Table 3. Tumor stages

Tumor stages according to the AJCC/UICC staging, 8th edition. (78)

	T	**N**	**M**
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1, 2, 3	N1	M0
IVa	T4a	N0, 1	M0
	T1, 2, 3, 4a	N2	M0
IVb	T4b	Any N	M0
	Any T	N3	M0
IVc	Any T	Any N	M1

Table 4. Tumor stages for HPV/p16 positive OPSCC

New in 8th edition: Tumor Stages for HPV + OPSCC (77, 78)

	T	**N**	**M**
I	T1, 2	N0, 1	M0
II	T1, 2	N2	M0
	T3	N0, 1, 2	M0
III	T0, 1, 2, 3, 4	N3	M0
	T4	N0, 1, 2, 3	M0
IV	Any T	Any N	M1

Signs and symptoms

Clinical signs and symptoms in early stage disease are often painless expansions which are difficult to detect for patients and physicians. The clinical features vary by different types of HNC. In OSCC symptoms may be unusual bleeding, a lump, a nonhealing ulcer or sore and dysphagia, often interpreted by patients as something of minor relevance, leading to diagnostic delay. Patients with later-stage symptoms may develop sudden tooth mobility, chronic earache, a neck mass, weight loss, difficulties with speaking and chewing, and mouth malodour. (3, 52, 54, 79) OPSCC patients may additionally complain about a change in voice quality, also called "hot potato voice". (72) Glottic carcinoma in early stages is commonly associated with raucousness, while supraglottic tumors and HPSCC lead to change in voice, dysphagia, foreign body sensation and haemoptysis. Subglottic tumor patients sometimes also suffer from dyspnoea and stridor. (3) Laryngeal cancer patients with advanced stage disease may develop respiratory compromise and need to undergo tracheotomy or tumor debulking for securing a safe airway. (80, 81)

Similar to many other cancer types, patients with advanced stage diseases often suffer from cancer cachexia, which is associated with worse survival. This syndrome has to be distinguished from starvation, a condition which may occur simultaneously in HNSCC patients as a result of pain and obstruction leading to dysphagia and loss of appetite resulting in limited food intake. (82-84)

Laboratory abnormalities and tumor markers

Widely accepted biochemical markers for detecting HNSCC have not been defined. HNSCC typically leads to elevated levels of CRP (C-reactive protein), ARG (arginase) and TNF-α (tumor necrosis factor-α). (85-87) Baseline CRP level seems to be a prognostic marker in primary and in recurrent HNSCC and usually increases with tumor progression during chemotherapy treatment. (88, 89)

Volatile organic metabolites (VOMs)

A recent study of Opitz et al. suggests that VOMs sampled in the urine may be potential tumor markers for HNSCC in the future. VOMs can be found on the skin, in exhaled air and in different body fluids. These metabolites are formed by cells in response to the disease and can be used to distinguish between different diseases. For example, exhaled VOMs can be

analysed for the diagnosis of allergic asthma or chronic obstructive pulmonary disease. It has been demonstrated that patients with HNSCC exhibit specific patterns of VOMs in comparison to control groups. A cancer related origin of certain VOMs has been observed in different kinds of cancer, which is why VOMs are being discussed as tumor markers for breast, lung, prostate and colorectal cancer. (90-92)

Therapy

The decision on a specific multidisciplinary treatment schedule depends on different tumor- and patient related factors such as primary tumor location, extension and comorbidities. In general, prior to therapy start it is important to achieve and maintain an adequate patient's nutritional status and dental rehabilitation should be scheduled before radiotherapy. (8)

Surgery

The surgical approach is influenced by primary site, location, size, proximity to bone in oral cancer and depth of infiltration. Local treatment is the therapy of choice for patients with early stage disease, as similar loco-regional control is achieved either with conservative surgery or radiotherapy. (8, 93) In the past, surgeries were performed through transfacial or transmandibular incisions, which often led to poor oral function and unfavourable cosmetic outcomes. At present, transoral endoscopic head and neck surgery is a new innovative surgical procedure for the treatment of HNC, especially for OPSCC. This minimally invasive procedure, which is performed without any external incision, minimizes long-term speech dysfunction and dysphagia. Transoral surgery can be performed with either robotic surgery or laser microsurgery. In transoral robotic surgery three-dimensional visualisation allows the surgeon to control the moves of the robotic system with a remote console by manipulating an endoscope and two additional instruments, which are placed in the mouth of the patient. (76, 94) Over the past years surgical therapy for advanced stage HNSCC has decreased. Particularly for laryngeal cancer, as organ preservation protocols were established.
Patients at high risk, with R1 resection or nodal extracapsular extension, should additionally receive postoperative radiochemotherapy (CRT) after surgery. (95, 96)

<u>Neck dissection</u>

Patients with advanced N stage (N2/N3) at diagnosis are at high risk for recurrent neck metastases after concomitant CRT. In these cases, neck dissection seems to contribute to an improved DFS and OS with a low complication rate. One of the major challenges is to correctly identify residual disease in the neck after CRT. If an assessment is performed and both physical examination andimaging (PET-CT) indicate a complete clinical response, neck dissection may not be beneficial for these patients. (97, 98) The negative predictive value of an insuspicious posttreatment PET-CT for being free of residual disease has been estimated at 94% in patients with N1 to N3 disease before treatment. (99) ESMO guidelines

recommend to accurately evaluate the response to CRT at the neck after finishing treatment and then decide individually whether performing a neck dissection is indicated. (8) In general, neck dissection is advisable for patients with partial response at the neck level after CRT to eradicate residual disease. In contrast, observation with regular check-ups is an option for patients with clinical negative necks. (100, 101)

Definitive radiochemotherapy

Definitive concomitant CRT is the standard treatment in resectable patients with poor anticipated surgical results and/or prognosis, as well as in patients with non-resectable tumors. (8) The Mach-NH meta-analysis showed a significant survival benefit of 8% at 5 years in favour of chemotherapy given concomitantly to radiotherapy versus radiotherapy alone. However, inclusion of studies using obsolete drugs (e.g. methotrexate or bleomycin containing chemotherapy as first line regimen) and radiotherapy schedules limits the generalizability of this meta-analysis. An OS benefit of 12.0 months for CRT compared to radiotherapy alone was seen in a meta-analysis with more strict eligibility criteria. (102, 103) Comparing different radiotherapy schedules, Bourhis et al. demonstrated that conventional CRT (with 70 Gray (Gy) in total and a daily dose of 2 Gy 5 days/week) is superior to accelerated CRT and very accelerated radiotherapy alone, suggesting that acceleration may not be beneficial in concomitant CRT regimen. (104)

Up to now, CRT with cisplatin 100 mg/m^2, administered once every 3 weeks, is the standard of care in locally advanced HNSCC. (105, 106) The issue of severe acute toxicity of this treatment schedule has been addressed in different studies. A randomized phase III trial showed superiority of once-every-3-weeks cisplatin compared to weekly cisplatin 30 mg/m^2 application in terms of locoregional control and a nonsignificant improvement of PFS and OS. Cumulative locoregional control rate was 73% versus 59% in the once-a-week cisplatin arm. However, significantly more patients suffered from severe acute toxicities after receiving cisplatin 100 every three weeks, whereas severe chronic side effects were similar in both arms. (105) Several retrospective studies came to similar conclusions in terms of survival suggesting cisplatin 100 every 3 weeks as the preferable CRT regimen. (107-109)

There seems to be a benefit for patients in completing systemic therapy, as this may decrease the risk of distant failure. A study assessing the impact of cumulative cisplatin dose on survival, showed higher three-year OS for the subgroup receiving more than 200mg/m^2

cisplatin compared to the <200mg/m^2 arm (72% vs. 52%). However, this result was only evident for patients with HPV negative tumors. Particularly T4 or N3 disease patients may develop a survival advantage from a higher cumulative cisplatin dose. (110, 111) Common dose limiting adverse events include ototoxicity, nephrotoxicity and peripheral neuropathy. Carboplatin is a platinum derivate with less oto- and nephrotoxicity, though it is more myelotoxic. (112) Generally, carboplatin is better tolerated but when compared to cisplatin, a higher relative carboplatin dose is required to achieve equivalent cytostatic effects. (106, 112)

Induction chemotherapy (ICT)

Routine use of ICT to improve OS is one of the most discussed topics in this field. The effects of ICT as neoadjuvant treatment for locally advanced stage disease include both benefit and harm. (113) Different studies suggest that ICT does not improve OS, DFS or locoregional control. However, induction therapy is associated with higher organ preservation rates and a decreased risk of distant tumor spread in patients without metastases at baseline. This might be explained by the effect of neoadjuvant treatment on potentially metastatic tumor cells in the periphery. (113-115) Several randomized trials aimed to establish superiority of neoadjuvant treatment in terms of OS, but found discrepant results. Two phase III trials, comparing ICT (cisplatin and 5-fluorouracil (5-FU)) with locoregional treatment, showed survival benefits for patients. However, there were some limitations to the studies. Zorat et al. observed a significant difference in survival at 5 and 10 years only among unresectable patients, and the study of Domenge et al. was limited to OPSCC. The data of Zorat et al. for inoperable patients showed an overall survival of 21% at 5 years in the induction arm vs. 8% for patients without induction treatment. Moreover, both studies compared ICT followed by locoregional treatment with locoregional treatment alone, which included radiotherapy alone and surgery with or without radiotherapy, but no direct comparison with definitive CRT. (116-118)

<u>TPF versus PF</u>

Comparing different types of induction regimen, the most effective induction regimen, according to the meta-analysis of Pignon et al., was the combination of 120 hour 5-FU infusion and cisplatin, applied in a study carried out between 1977 and 1991 at Wayne State University. (115, 119-121) The TAX 324 study subsequently compared TPF (=Docetaxel,

Cisplatin, 5-FU) with PF (=Cisplatin, 5-FU) as induction regimen and a significant OS benefit after TPF treatment was noted. This study compared three cycles of TPF ICT with three cycles of PF, followed by 7 weeks of CRT with carboplatin, including patients with resectable and unresectable disease. TPF ICT consisted of docetaxel (75 mg per square meter of body-surface area) and cisplatin (at a dose of 100 mg per square meter). After the cisplatin infusion patients received fluorouracil (1000 mg per square meter per day) as a continuous 24-hour infusion for 4 days. Patients in the PF arm received cisplatin (100 mg per square meter) and fluorouracil (1000 mg per square meter per day) for 5 days. Posner et al. observed a 30% risk reduction of death, with a median survival of 71 months in the TPF group and 30 months in the PF group. This study shows superiority of TPF treatment in median PFS (progression-free survival) as well. (36 vs. 13 months) Although patients in the TPF group had more myelotoxic side effects, significant fewer treatment delays were observed in this group compared to the patients receiving PF regimen (29% vs. 65%), reflecting a reduction in overall toxic effects. (122) A subgroup analysis of TAX 324 demonstrated that TPF increases laryngectomy-free survival in patients with laryngeal cancer with an absolute improvement of 20 % in 3 years compared to PF regimen. (123) One of the main determinants for treatment success is the adequate application of radiotherapy after induction treatment. A prolonged radiation treatment time is associated with lower survival rates and locoregional recurrence. (124) The TAX 323 study by Vermorken et al. compared a similar TPF regimen with PF followed by radiotherapy alone in patients with unresectable HNSCC. (122) In this study a relative reduction of 28% in the risk of disease progression or death was evident for treatment with TPF. Moreover, TPF showed superiority in median OS, median PFS and time to treatment failure (TTF). (119) Another randomized phase III trial examined the efficacy of a three-drug ICT regimen, used PF and PPF (a combination with paclitaxel instead of docetaxel), followed by CRT with cisplatin. Hitt et al. showed that PPF regimen is superior to PF in terms of overall response rate and complete remission rate (33% vs. 14%). (120)

ICT +/- CRT

Hitt et al. also compared ICT (TPF) plus CRT directly with definitive CRT and included non-metastatic, unresectable advanced stage HNSCC. This trial did not show a significant advantage for ICT, as PFS, TTF and OS were similar between the two treatment groups. Instead, the study highlighted the impact of ECOG performance status on treatment

adherence and prognosis, because an important proportion of patients dropped out of induction treatment due to toxicity. Most of these patients had ECOG 1 status and T4 tumors. Furthermore, patients with ECOG 0 showed higher PFS, TTF and OS compared to ECOG 1 patients. Regarding adverse events, grade 3-4 neutropenia, odynophagia, stomatitis and nephropathy were more frequent during CRT after induction treatment, than in patients who received only CRT. (125) Another directly comparing study was conducted in Italy. In this phase II trial a significantly higher complete remission (CR) rate was noted for the induction arm. (50% vs. 21.3%). However, there was no statistically significant benefit for median PFS and OS. (116) This result coincides with the findings of the PARADIGM study and a more recent meta-analysis of Budach et al. in terms of survival and PFS. (126, 127) Paccagnella et al. suggest in their study that induction treatment may improve short-term locoregional control and may reduce the need of surgery in patients with partial remission after CRT. (116) Another randomized phase III trial on larynx preservation of EORTC (European Organization for Research and Treatment of Cancer) compared the efficacy of PF induction followed by radiotherapy with PF CRT in patients with advanced HPSCC and laryngeal cancer. This study achieved similar results for both arms in terms of survival with a functional larynx, OS and PFS, but also for acute and late toxic effects. (128) In contrast to this, long term results of Intergroup RTOG 91-11 showed superiority of the concomitant CRT group in locoregional control and larynx preservation, with a 42% reduction in risk of laryngectomy compared to the induction arm. However, there was no association with improved OS. (129)

Feasibility of ICT

Driessen et al. studied the feasibility of cisplatin-containing CRT after ICT. Patients received TPF followed by Cisplatin 100 plus radiotherapy or Cisplatin 40 plus accelerated radiotherapy. Due to toxicity, the total planned dose of Cisplatin could be administered in only 32% of the patients. However, nearly all patients were able to receive more than 90% of the scheduled radiation dose. (130) Two other studies suggesting that there is no negative impact on CRT feasibility after induction had some limitations as they were using Cisplatin 80 plus 5-fluorouracil and Carboplatin AUC 1,5 as CRT regimen and in the study of Ghi et al. the number of planned chemotherapy cycles during CRT had to be reduced. (116, 131)

Targeted therapies

Anti-EGFR therapy

Multiple solid tumor types are associated with expression of EGFR, which correlates with resistance to therapy and poor prognosis in HNSCC. Cetuximab is an IgG1 monoclonal antibody that binds competitively to the EGFR and activates antibody-dependent cell-mediated cytotoxicity. (132, 133) A common side effect associated with cetuximab application is an acneiform rash. (132) It is approved for the treatment of patients with locally advanced HNSCC as monotherapy after platinum progression and concomitant with radiotherapy. (134) However, the direct comparison of cisplatin-based CRT with cetuximab plus radiation in a retrospective study showed superiority in OS and locoregional control for the chemotherapy arm. (135) The combination of cetuximab with a platinum derivate and 5-fluorouracil is a first line treatment option for metastatic or recurrent disease. (134) A randomized phase III trial has reported a 2.7 month increase in the median OS and a 20% reduction in the relative risk of death, as compared with the chemotherapy alone group. (133) Furthermore, cetuximab used to be administered in HPV positive OPSCC cases as a form of de-escalation treatment to avoid severe side effects associated with cisplatin and radiotherapy. However, Mehanna et al. recently observed in their study that cetuximab resulted in worse OS, a higher local recurrence rate and importantly did not cause less adverse events than cisplatin. (136)

Other EGFR tyrosine kinase inhibitors tested for the treatment of HNSCC include gefitinib and erlotinib, but both agents showed low response rates in clinical trials. Apart from that, a study of Khaznadar et al. found that EGFR activity is significantly lower in clinical samples than in cell lines and that the effects on cell proliferation and survival are much more associated with the activation of EGFR than with the expression level. Therefore, more studies are required to further investigate whether activating EGFR mutations or genomic amplifications can be detected in HNSCC patients. (137)

Checkpoint inhibition

Lyford-Pike et al. reported a PD-L1 (programmed cell death 1 ligand 1) expression (>5% was defined as positive) in about 70% of HPV positive HNSCC and in 29% of HPV negative tumors, suggesting PD-1/PD-L1 targeted therapy as a potent treatment option for patients with HNSCC. (138) Pembrolizumab, durvalumab and nivolumab have been tested as

treatment for metastatic or recurrent HNSCC so far. One of the first clinical trials with pembrolizumab in advanced HNSCC, KEYNOTE-012, showed overall response rates of 18% in all patients and 25% in HPV positive patients. (10, 139) Similar results were achieved in the KEYNOTE-055 study, including patients with metastatic or recurrent HNSCC who had disease progression on or after platinum chemotherapy. (10) Interim results of the phase III trial KEYNOTE-048 corroborate these findings, suggesting pembrolizumab and pembrolizumab combined with platinum and 5-FU as first-line standards of care for recurrent or metastatic HNSCC. (140) Ongoing trials are evaluating the efficacy of pembrolizumab in adjuvant and neoadjuvant setting. (10)

Nivolumab showed superiority in terms of OS (HR=0.55) and toxicity profile in platin-refractory recurrent HNSCC, compared to standard single-agent therapy (methotrexate, docetaxel or cetuximab). (141)

Other targeted agents assessed in clinical trials are VEGFR and mTOR inhibitors. For example, a non-randomized phase II trial of temsirolimus added to weekly low-dose carboplatin and paclitaxel in 36 patients with recurrent/metastatic HNSCC showed objective response rates of 42. However, further investigation and trials with larger patient cohorts are required to evaluate the benefit of these agents in HNSCC. (142, 143)

Rationale of this study

Optimal treatment indication of ICT+CRT vs. CRT for advanced HNSCC is challenging

As outlined above, optimal treatment indication for locally advanced HNSCC poses a clinical challenge for treating physicians since the relative efficacy of induction therapy followed by CRT versus CRT alone is still debated. Currently, various patient- and tumor-related factors have to be taken into consideration in order to determine whether a patient may benefit of additional induction therapy. Although several clinical trials tried to evaluate which induction regimen seems to be the most effective and tolerable, up to now it seems to be TPF. Nonetheless, the question whether TPF induction followed by CRT improves OS and PFS in comparison with CRT alone is still a matter of debate. (119, 126) Thus, even with all the available information and tumor characteristics, general guidelines which clearly advocate one approach over the other are currently lacking.

Conclusive randomized clinical trials are lacking

Several reasons can be identified why the question on ICT in advanced HNSCC is still debated. Firstly, a large proportion of the studies were conducted in a retrospective fashion, raising the question if a potential difference in OS was influenced by patients' physical condition, which may have played a decisive role in the process of setting up a treatment schedule with or without induction. Secondly, the conduct of large prospective, randomized trials in this setting is difficult, because enrolment and compliance can be limited in this challenging patient population. (127) Additionally, HNSCC are heterogenic with respect to their anatomic location, and location-specific trials are thus even harder to perform. As a consequence, the eligibility criteria of many studies include all different subtypes of HNSCC, which might be a possible confounder due to different pathophysiological mechanisms and carcinogens associated with specific tumor locations. Especially HPV status could be an important confounding factor. (125, 127) Furthermore, there are concerns about the feasibility of concomitant CRT after induction therapy, which has not yet been addressed in large prospective clinical trials.

Treatment effect estimation using observational rather than randomized data

In the absence of large randomized trials, analysis of observational data may help to guide treatment indication in this setting. However, naive comparison of outcomes in patients who received CRT or ICT+CRT will lead to highly biased results because in observational data

the assignment to these treatments is non-random. Specifically, it can be expected that patients who received ICT+CRT differ in terms of prognostically relevant variables, such as age, performance status and extent of disease. As physicians may tend to assign younger and fitter patients to ICT+CRT, this may lead to a bias in favour of this strategy. On the other hand, it is conceivable that physicians may assign patients with more extensive disease to ICT+CRT, which may lead to bias in favour of CRT only. To harness this non-random treatment assignment, specific statistical methods have been developed.

Propensity score analysis for treatment effect estimation in non-randomized data

Propensity score analysis has been developed to address the topic of treatment effect estimation in observational, non-randomized data, and has recently become a very popular tool in observational epidemiology and clinical research. In detail, propensity score analysis aims to create a "quasi-randomized" setting by first predicting treatment assignment conditional on baseline covariates. Then, various methods exist to weigh the observational data for this predicted treatment assignment, including propensity score matching, propensity score stratification, and inverse-probability-of-treatment weighting (IPTW). The aim of all these methods is to create an artificial population in which baseline covariates are independent of treatment status, which enables the comparison of outcome and toxicity profile between the two treatment groups using observational data. (144) In this thesis project, the IPTW method was used, which is believed to be statistically most efficient, or at least equivalent to propensity score matching. Simply stated, IPTW analysis assigns a higher weight to patients who are unlikely candidates for treatment based on their covariates but in fact did receive treatment, as well as to patients who are likely candidates for treatment based on their covariates but in fact did not receive treatment.

Aims of this study

Primary aim

The primary aim of this study is to perform a propensity score analysis of retrospectively obtained observational data on the outcome of patients with advanced HNSCC treated with CRT or ICT+CRT. Specifically, the focus is going to be on "hard" clinical endpoints including progression-free and overall survival. Results of this analysis should allow a better understanding of the value of ICT prior CRT in patients with advanced HNSCC.

Secondary aims

Moreover, this study aims to quantify and compare the acute and chronic toxicity profile of CRT and ICT+CRT. This is particularly important given that side effects are an important component for patients having to make a decision in favour or against a potentially quality of life-limiting treatment regimen such as ICT.

A further secondary aim will be to quantify treatment response according to the two treatment strategies. Data on treatment response may be of great interest for therapy indication in patients who have primary inoperable disease.

Finally, another aim of this study will be to perform exploratory subgroup analyses to generate hypotheses about which patients may benefit the most or the least from the two treatment concepts.

Methods

Study population and design

In this single-centre, observational cohort study we included all patients with histologically-confirmed locally advanced/unresectable HNSCC who received definitive CRT with or without prior induction treatment at the ENT (ear, nose and throat) Department of the Medical University of Graz (n=195). This study population was selected from the population of patients presented at the ENT head and neck tumor board of the Medical University of Graz Academic Hospital ("LKH Graz") between May 2010 and April 2018 (n=1,580, **Figure 1**). First, we excluded patients whose initial HNSCC diagnosis was before 2010 (n=73) and patients with tumors of a different histological entity than SCC (n=619).

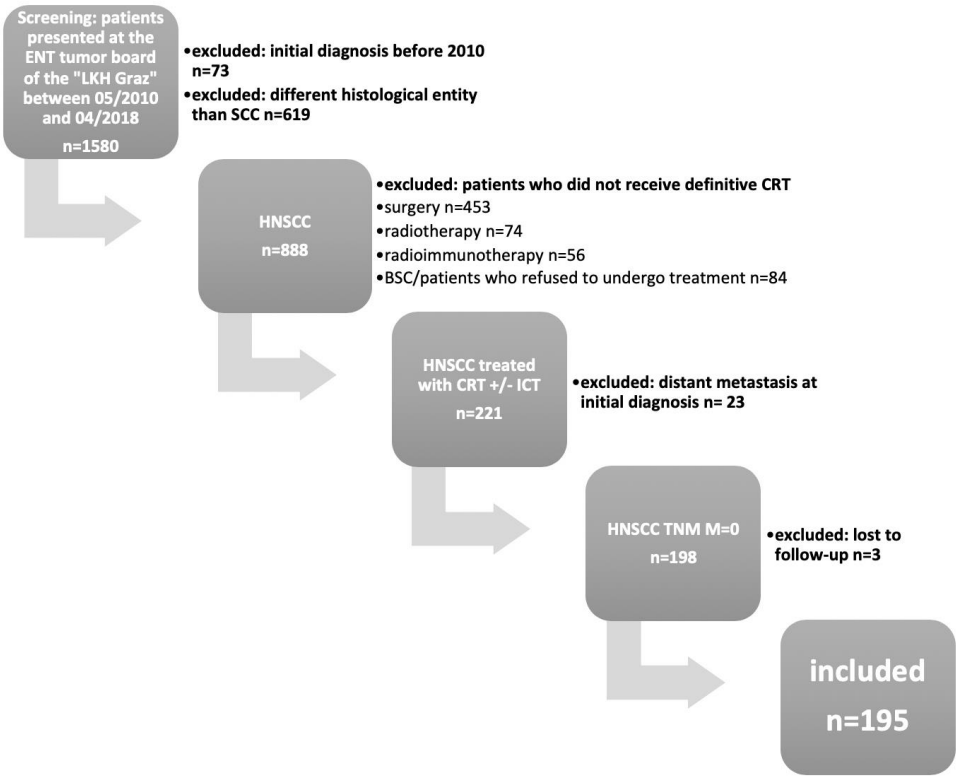

Figure 1. Patient flow - selection of the study population

Abbreviations: ENT – "ear, nose, throat", HNSCC – Head and neck squamous cell carcinoma, BSC – Best Supportive Care, TNM – Tumor Node Metastasis classification

Furthermore, we excluded patients who did not receive definitive CRT (n=667), patients who presented with distant metastasis at first diagnosis (n=23) and 3 patients who were lost to follow-up. The baseline date was defined as the date of the first day of treatment for both study groups. Baseline and short-/long-term outcome data were collected by using the local electronic health record system "medOCS" and data of the Medical University of Graz ENT head and neck tumorboard. The co-primary endpoints of this study were OS and PFS. In addition, secondary endpoints including toxicity, response, local progression and distant metastasis rates were analysed. Data collection and analysis was approved by the Ethics Committee of the Medical University of Graz (EK-Nr.: 31-091 ex 18/19).

Endpoints

Co-Primary Endpoint

Progression-free survival (PFS) and Overall Survival (OS) were defined as the co-primary endpoints of this study. The baseline date was defined as the date of start of ICT for patients who were treated with ICT before CRT, and as the date of start of CRT for patients who were treated with CRT only, respectively. PFS was defined as the time from the baseline date to disease progression, death, or censoring alive, whatever came first. For disease progression we considered local progression, local metastasis, and distant metastasis. OS was defined as the time from the baseline date to death-from-any-cause or censoring alive. Follow-up was truncated at 5 years for both PFS and OS.

Secondary endpoints

Secondary endpoints of the study were toxicity, treatment response, and the cumulative incidences of local progression and distant metastasis. Toxicity was defined as any event after the baseline date who could be retrospectively assigned a severity rating based on the Common Toxicity Criteria – Adverse Events (CTC-AE), Version 4.0. (145). Treatment response was defined as complete or partial remission during ICT and/or CRT according to Response Evaluation in Solid Tumors (RECIST) criteria, Version 1.1. (146). Local progression was defined as a composite of any local recurrence or any new local metastasis, whatever came first. Distant metastasis was defined as any metastasis that occurred beyond the primary tumor bed and local lymph node stations. For analysis of local progression and distant metastasis, follow-up was also truncated at 5 years.

Statistical methods

All statistical analyses were performed using Stata (Windows version 15.0, Stata Corp., Houston, TX, USA). OS and PFS functions between the two treatment groups were compared with log-rank tests and the hazard functions were modelled with Cox Models, or in case of a violation of the proportional hazard's assumption, with flexible parametric models. (147) Standardized mean differences (SMDs) were used to quantify differences in means and proportions between the two treatment groups. Potential between-group differences were further evaluated with Fisher's exact tests, $\chi 2$-tests and Wilcoxon's rank-sum tests, respectively. To generate the propensity score, we first constructed a multivariable model for predicting treatment assignment conditional on baseline covariates. This model was used to construct the propensity score, which was defined as the probability of receiving ICT + CRT treatment. (144) Then the propensity score was transformed into an inverse-probability-of-treatment-weight (IPTW) according to the "average treatment effect on the treated (ATT)" principle. (148) The IPTW was defined as the inverse of the probability of receiving the treatment that the patient received, where T is the treatment assignment (T=0 if CRT, T=1 if ICT+CRT) and PS is the propensity score:

$$IPTW = \frac{T}{PS} + \frac{1-T}{1-PS}$$

Afterwards, the data was re-weighted with the IPTW. To verify whether IPTW achieved sufficient balance, SMDs of baseline covariates between the two study groups were estimated before and after IPTW-weighting, following best-practice recommendations. (144) For the analysis of the co-primary endpoint, i.e. the "imbalance-adjusted" association between ICT and PFS and OS, IPTW-weighted Cox proportional hazards models and Kaplan-Meier estimators were fitted. The secondary endpoints "toxicity" and "treatment response" were analysed descriptively with charts and cross-tabulations, and inferentially with Fisher's exact tests, $\chi 2$-tests, Wilcoxon's rank-sum tests, as well as uni- and multivariable logistic regression models, respectively. The secondary endpoints "local progression" and "distant metastasis" were analysed with rude and IPTW-weighted competing risk cumulative incidence estimators, treating death-from-any-cause as the competing event of interest. Cumulative incidence functions between the two treatment groups were compared with Gray's test. Modelling of local progression and distant metastasis rates was performed with Cox proportional hazards as well as Fine & Gray

competing risk proportional subdistribution hazards regression models. In a sensitivity analysis, we fitted interactions between tumor site (oropharyngeal vs. non-oropharyngeal HNSCC) and treatment assignment within IPTW-weighted Cox and Fine & Gray models to gauge the potential modifying effect of tumor site on the relative association of treatment assignment on outcome. In these sensitivity analyses, due to the known lower statistical power of interaction tests, interaction p-values ≤ 0.1 were considered to be indicative of a statistically significant interaction ("relaxed" alpha). Missing data were reported in baseline tables and a complete-case analysis was performed.

Results

Baseline characteristics of the study population

One-hundred-ninety-five patients were included in the analysis (**Table 5**). At treatment initiation, the median age of the study cohort was 59 years [25th-75th percentile: 52-66], 44 (23%) patients were female and 53 (27%) of patients had an ECOG performance status of 1 point or more. Most of the patients presented with locally-advanced disease (clinical stage III-IV, n=187 (96%)) and loco-regional lymph node metastases at the neck (TNM N1-3, n=153 (78%)). A history of a second primary malignancy (SPM) and/or a currently active SPM was observed in 32 patients (16%). With 39 patients having a positive tumoral immunohistochemical staining for p16, the indirectly estimated prevalence of local HPV infection was 38%.

Treatment characteristics

Treatment regimens

Among the 195 patients included in the study, 119 patients received CRT only (61%) and 76 patients were treated with ICT prior CRT (39%, **Figure 2**).

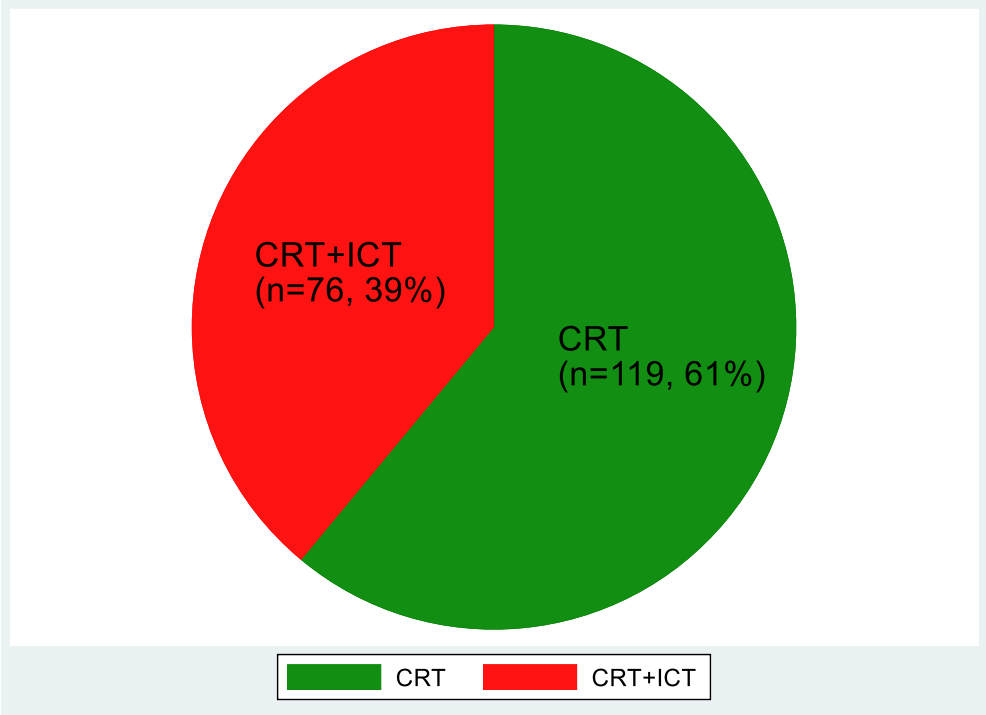

Figure 2. Distribution of CRT and CRT+ICT in the total study population (n=195).

Variable	n (% miss.)	Overall (n=195)	CRT (n=119)	CRT+ICT (n=76)	p	Δ_S	$\Delta_{S\text{-IPTW}}$
Demographics							
Age (years)	195 (0%)	59 [52-66]	63 [55-68]	55 [49-60]	<0.0001	0.89	0.22
Female Gender	195 (0%)	44 (23%)	30 (25%)	14 (18%)	0.269	0.16	0.04
BMI (kg/m²)	195 (0%)	24.5 [21.6-27.4]	24.5 [21.3-27.1]	24.4 [21.9-27.4]	0.536	0.11	0.18
Never smoked	191 (2%)	40 (21%)	27 (23%)	13 (18%)	0.402	0.13	0.26
History of alcohol abuse	195 (0%)	87 (45%)	57 (48%)	30 (39%)	0.248	0.17	0.27
Charleson Comorbidity Index	195 (0%)	4 [4-6]	5 [4-6]	4 [3-4]	<0.0001	1.12	0.25
ECOG 1+	195 (0%)	53 (27%)	46 (39%)	7 (9%)	<0.0001	0.73	0.01
History or current SPM	194 (1%)	32 (16%)	25 (21%)	7 (9%)	0.028	0.33	0.08
Caucasian ethnicity	195 (0%)	195 (100%)	119 (100%)	76 (100%)	N/A	N/A	N/A
Tumor characteristics							
Tumor location**	195 (0%)	/	/	/	0.010	/	/
---Oral cavity	/	22 (11%)	15 (13%)	7 (9%)	0.465	0.11	0.22
---Oropharynx	/	96 (49%)	62 (52%)	34 (45%)	0.316	0.15	0.22
---Hypopharnyx	/	39 (20%)	26 (22%)	13 (17%)	0.419	0.12	0.19
---Larynx	/	25 (13%)	7 (6%)	18 (24%)	<0.0001	0.51	0.16
---Two-level tumor/others	/	13 (7%)	9 (8%)	4 (5%)	0.530	0.09	0.14
TNM T4	195 (0%)	103 (53%)	62 (52%)	41 (54%)	0.801	0.04	0.05
TNM N2-N3	195 (0%)	120 (62%)	71 (60%)	49 (64%)	0.501	0.10	0.08
Clinical Stage IV	195 (0%)	154 (79%)	93 (78%)	61 (80%)	0.724	0.05	0.02
HPV/p16 positive***	104 (47%)	39 (38%)	33 (48%)	6 (17%)	0.002	0.69	0.26
Tumor grade G3-G4	195 (0%)	104 (53%)	67 (56%)	37 (49%)	0.298	0.15	0.23

Table 5. Distribution of baseline characteristics overall and by treatment group (n=195).

N (%miss.) reports the number of fully observed patients (% missing). Data are reported as medians [25th-75th percentile] or absolute counts (%). P-values are from rank-sum tests and χ^2-tests, Δ_S is the standardized mean difference (SMD), $\Delta_{S\text{-IPTW}}$ is the inverse-probability-of-treatment-weighted SMD, Abbreviations: CRT – Radiochemotherapy, ICT – Induction chemotherapy, BMI – Body mass index, ECOG – Eastern Cooperative Oncology Group, N/A – not applicable, SPM – Second primary malignancy, TNM – Tumor Node Metastasis classification, HPV – Human Papilloma Virus, p16 – HPV protein 16kDa.

ICT

For 76 patients (39%), the multidisciplinary HNC tumor board of the Medical University of Graz recommended the application of an ICT prior to concomitant CRT. Sixty-two (82%) of these 76 patients were treated with TPF induction, which is a 3-weekly chemotherapy protocol consisting of Docetaxel, Cisplatin and 5-fluorouracil with a planned administration of 3 cycles (**Figure 3**).

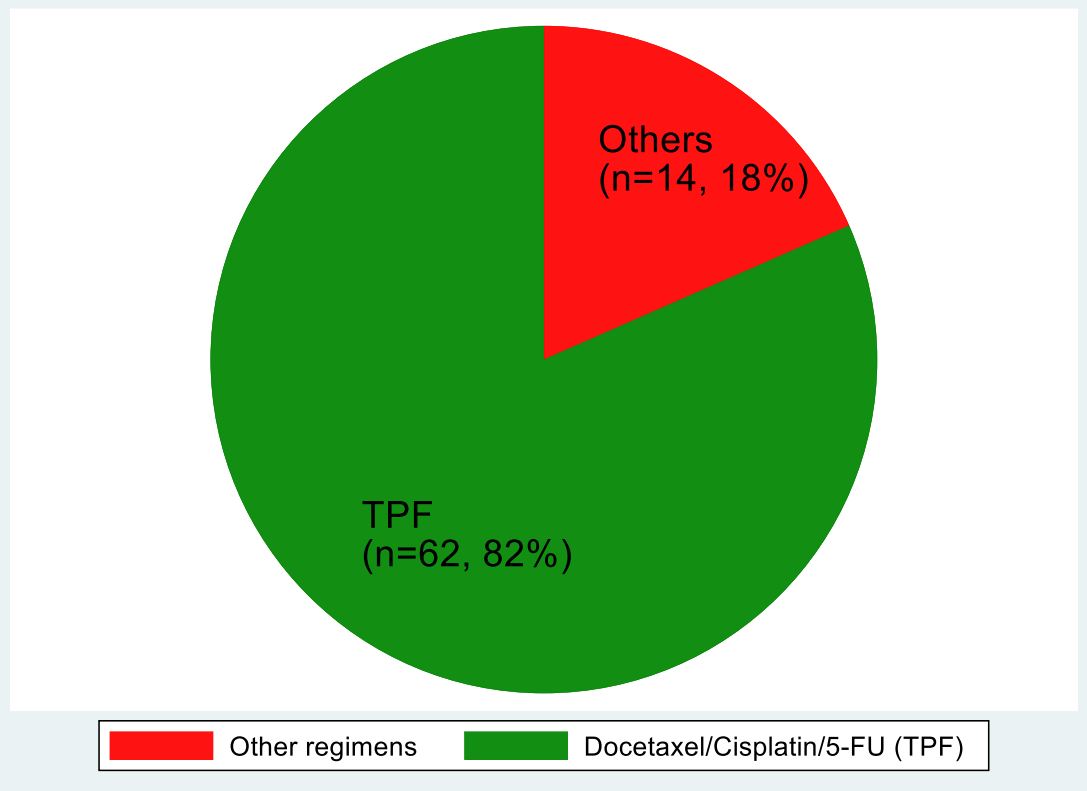

Figure 3. Pie chart of induction chemotherapy regimens.

Only 18% of patients who underwent ICT received a treatment regimen other than TPF. The most common other treatment regimen was Docetaxel + Cisplatin (**Table 6**). In terms of treatment intensity, 51 patients (67%) were able to receive all 3 cycles of ICT at the planned schedule and planned dose. The other patients either had to discontinue ICT permanently due to acute side effects, or disease progression (n=8, 11%), or needed treatment interruptions, dose reductions, or a change to a different treatment regimen (n=17, 23%).

No patient died during ICT, and therefore the G5 toxicity rate was 0 %. Only one patient developed a G4 toxicity, which was gastric perforation. The G3 toxicity rate was very low. In detail, only 16 of the 72 patients (21%) developed at least one G3 toxicity. The most common G3 toxicities during ICT were cytopenia (n=5), infection (n=5), and diarrhoea (n=5).

Table 6. Characteristics of induction chemotherapy (ICT, n=76 patients)	
Variable	Absolute count (%)
Initiated treatment regimen	
---Docetaxel/Cisplatin/5-FU (TPF)	62 (82%)
---Docetaxel/Cisplatin	6 (8%)
---Docetaxel/Carboplatin/5-FU	4 (5%)
---Docetaxel/Carboplatin	2 (3%)
---Docetaxel/Cisplatin/Cetuximab ("Delos-II-regimen")	2 (3%)
Treatment intensity	
---Received all 3 planned cycles in expected time frame	51 (67%)
---Permanent discontinuation	8 (11%)
---Treatment interruption / Dose reduction / Change to other treatment regimen	17 (23%)
Treatment response	
---Complete remission (CR)	7 (9%)
---Partial remission (PR)	27 (36%)
---Stable disease (SD)	12 (16%)
---Progressive disease (PD)	1 (1%)
---Response not evaluated (NE)	29 (38%)
---Overall response rate (ORR=CR+PR)	34 (45%)
---Disease control rate (DCR=CR+PR+SD)	46 (61%)
Treatment toxicity*	
---≥1 G5 toxicity	0 (0%)
---≥1 G4 toxicity (Gastric perforation)	1 (1%)
---≥1 G3 toxicity	16 (21%)
Did not receive CRT anymore	6 (8%)

Table 6. Characteristics of induction chemotherapy (n=76 patients).
*Treatment toxicities were retrospectively graded into grade (G) G1 to G5 according to Common Toxicity Criteria for Adverse Events (CTCAE, version 4.0). Abbreviations: 5-FU – 5-Fluorouracil, CRT – Radiochemotherapy, ICT – Induction chemotherapy.

CRT

Importantly, in 6 of the 76 patients (8%) the subsequent administration of CRT was not feasible anymore. Thus, a total of 189 out of the 195 patients finally started CRT, and 119 of the 195 patients were treated with CRT only ("CRT group", 61%). In all cases, the HNC tumor board at the LKH Graz indicated a radiotherapy schedule consisting of standard fractioned radiotherapy of 2 Gray (Gy) per day, for 5 days per week, for 7 consecutive weeks,

cumulating to a planned dose of 70 Gy. Adherence to this schedule was very high, with only 11 patients (6%) not reaching the projected dose within the projected time frame (**Table 7**). The most frequently applied concomitant chemotherapy regimen (79% of patients) were 3 cycles of a 3-weekly schedule of intravenous cisplatin at a dose of 100 mg/m^2 of body surface-area (**Figure 4**).

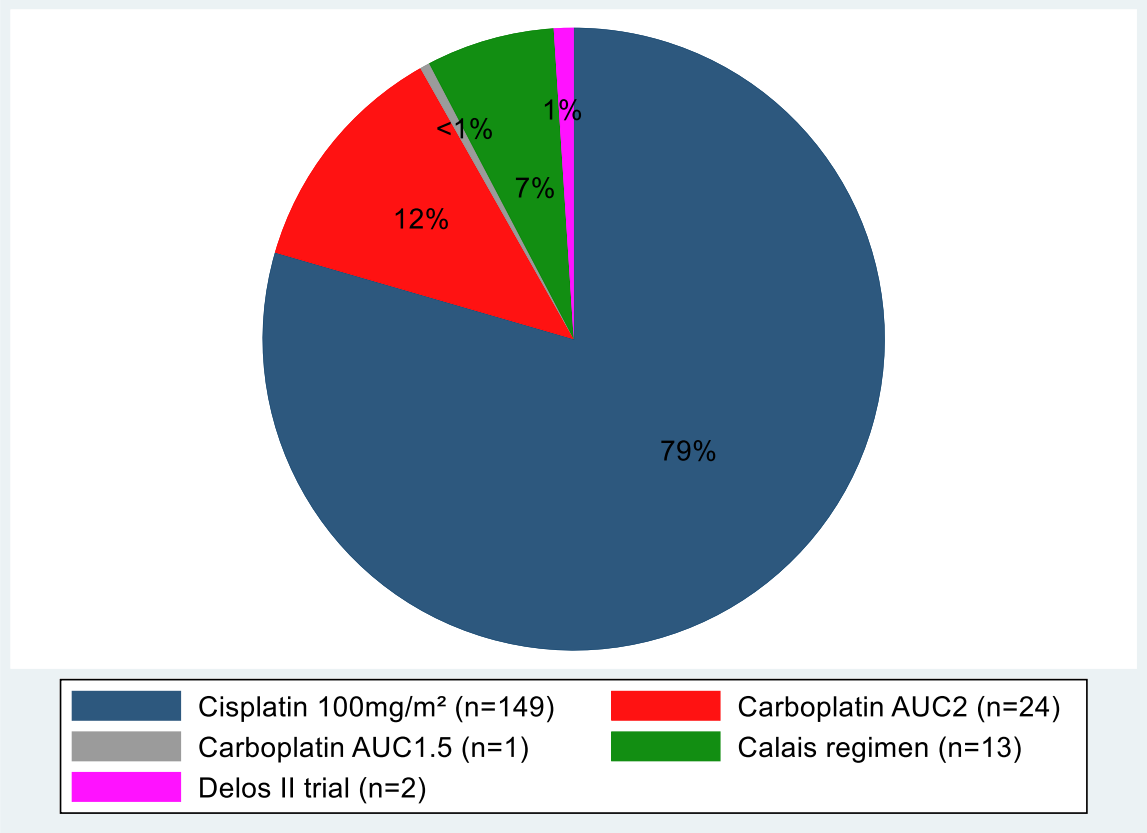

Figure 4. Pie chart of chemotherapy backbones for chemoradiation (n=189).

Abbreviations: AUC – Area under the curve.

Other concomitant chemotherapy regimens included for example carboplatin AUC2 and the so-called Calais regimen (**Table 7**). About one third of the patients (35%) received all three cycles of chemotherapy, while 51 patients (27%) had an interruption of chemotherapy or a dose modification and in 69 (37%) patients chemotherapy had to be stopped.

Table 7. Characteristics of chemoradiation (CRT, n=189 patients)	
Variable	Median [25th-75th percentile], or absolute count (%)
Radiotherapy modality and intensity	
---Projected total radiotherapy dose (Gy)	70 [70-70]
---Did not reach projected total radiotherapy dose	11 (6%)
Chemotherapy modality	
---Cisplatin 100mg/m² BSA for 3 cycles	141 (75%)
---Cisplatin <100mg/m² BSA for 3 cycles	8 (4%)
---Carboplatin AUC 2	24 (13%)
---Carboplatin AUC 1.5	1 (<1%)
---CALAIS regimen	13 (7%)
---Delos II trial regimen	2 (1%)
Treatment intensity	
---Received all 3 planned cycles in expected time frame	67 (35%)
---Permanent discontinuation	69 (37%)
---Treatment interruption / Dose reduction / Change to other treatment regimen	51 (27%)
Treatment response	
---Complete remission (CR)	133 (70%)
---Partial remission (PR)	29 (15%)
---Stable disease (SD)	7 (4%)
---Progressive disease (PD)	4 (2%)
---Response not evaluated (NE)	16 (8%)
---Overall response rate (ORR=CR+PR)	162 (86%)
---Disease control rate (DCR=CR+PR+SD)	169 (89%)
Treatment toxicity*	
---≥1 G5 toxicity	3 (2%)
---≥1 G4 toxicity	6 (3%)
---≥1 G3 toxicity	71 (38%)
---Leukopenia (any grade)	75 (40%)
---Mucodermatitis (any grade)	180 (95%)
---Nephrotoxicity (any grade)	30 (16%)
---Hearing impairment (any grade)	20 (11%)

Table 7. Characteristics of chemoradiation (n=189 patients).

*Treatment toxicities were retrospectively graded into grade (G) G1 to G5 according to Common Toxicity Criteria for Adverse Events (CTCAE, version 4.0). Abbreviations: AUC – Area under the curve, BSA – Body Surface Area, CRT – Radiochemotherapy, Gy – Gray.

Response rates

In the 76 patients who were treated with ICT, the objective response rate (ORR) of ICT was 45% (95% binomial exact CI: 33%-57%), including 7 (9%) complete responses and 27 (36%) partial remissions. Only 1 patient (1%) experienced progressive disease during ICT (**Table 6**).

In the overall cohort of 189 patients who were treated with CRT, 162 patients had an objective response, corresponding to an ORR of 86% (95%CI: 80%-90%, **Table 7**). The disease control rate (DCR) defined as the proportion of patients who either experienced a complete or partial remission or stable disease (n=169) was 89% (95%CI: 84%-93%).

Crude outcome rates

The patients were followed up for a median interval of 3.6 years for PFS and 4.3 years for OS. During this interval 83 (42.6%) patients died, and 66 (33.8%) patients developed progressive disease, including 40 local recurrences, 15 local metastasis and 28 distant metastasis formations. The 5-year OS and PFS estimates were 50% and 47%, and the corresponding 5-year local progression and distant metastasis rates were 35% and 19%, respectively (**Table 8**, **Figure 5**).

Endpoint	**1-year estimate (95%CI)**	**3-year estimate (95%CI)**	**5-year estimate (95%CI)**
Overall survival (OS)	86% (80-90)	64% (56-71)	50% (41-58)
Progression-free survival (PFS)	77% (70-82)	57% (49-65)	47% (37-55)
Local Progression	15% (10-20)	26% (19-33)	35% (26-43)
Distant Metastasis	6% (3-11)	17% (12-25)	19% (13-26)

Table 8. Crude outcome risks of the overall study cohort (n=195).

OS and PFS were estimated with Kaplan-Meier estimators, and risk of local progression and distant metastasis with competing risk cumulative incidence estimators according to Marubini & Valsecchi treating death-from-any-cause as the competing event of interest. Abbreviations: 95%CI – 95% confidence interval.

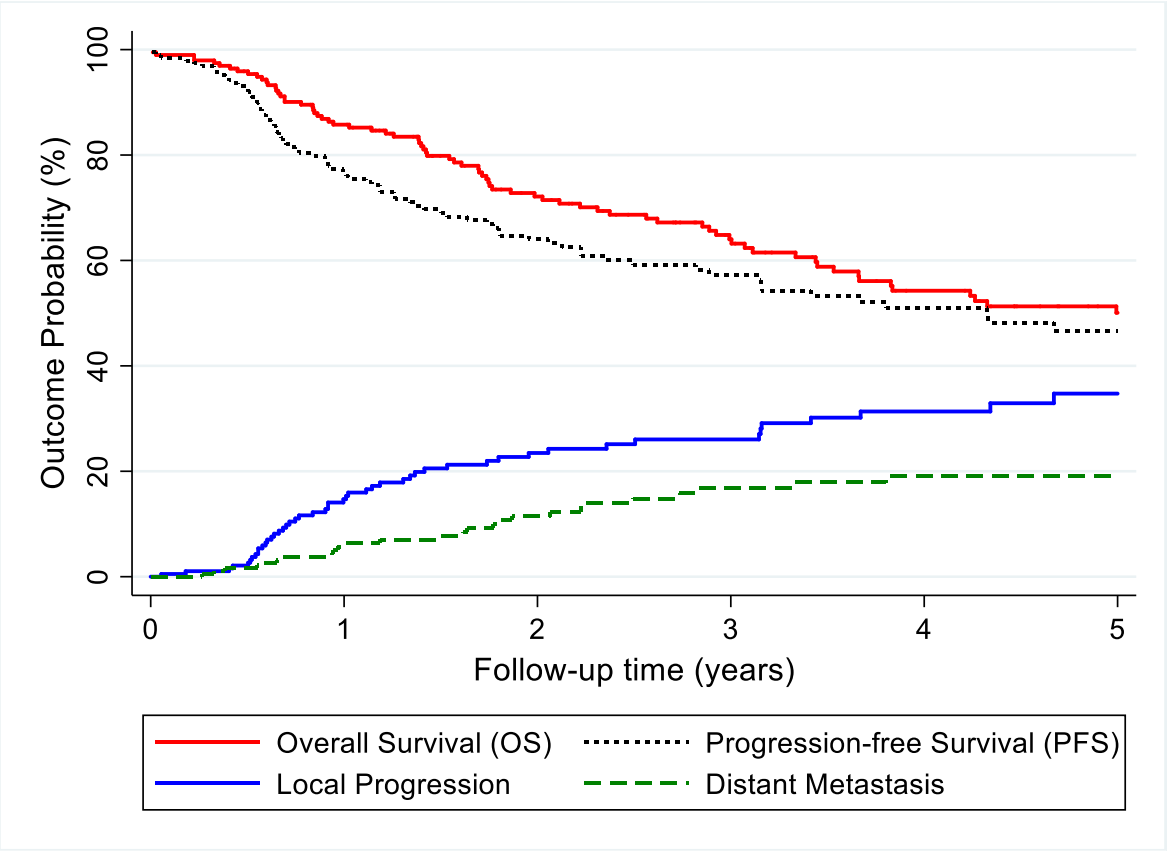

Figure 5. Five-year outcomes of the overall study population (n=195).
OS and PFS were estimated with Kaplan-Meier estimators, whereas risks of local progression and distant metastasis were computed with competing risk cumulative incidence estimators treating death-from-any-cause as the competing event of interest.

Comparison of CRT with CRT+ICT - Derivation of the IPTW

Concerning the baseline covariates, significant differences between the ICT+CRT and the CRT group were observed (**Table 5**). For example, patients who received ICT+CRT were significantly younger (median age of 55 vs. 63 years, rank-sum p=0.0001, standardized mean difference (SMD)=0.89) and had better ECOG performance status (SMD=0.73). On the other hand, patients who were only treated with CRT were more likely to have a SPM (SMD=0.33), had a higher Charleson comorbidity index (CCI, SMD=1.12) and were more likely to have HPV/p16 negative tumors (SMD=0.69) and less likely to have laryngeal primaries (SMD=0.51). SMD's >0.30 were considered as potentially relevant imbalances between the two study groups, leading to a major source of selection bias for the comparison of ICT+CRT vs. CRT alone. (144) Therefore, we constructed a propensity score with the use of a multivariable logistic regression model, in which the treatment decision is regressed

on observed baseline covariates. Using a combination of statistical results of the SMD analysis and clinical subject matter knowledge, we included the following variables in the model: age, ECOG performance status, Charleson comorbidity index, a history or current SPM, laryngeal primary, TNM T4 classification, and HPV / p16 positivity (**Table 9**). The model achieved a pseudo-R^2-statistic of 0.376. Thus, the model explains roughly 38% of the variation in treatment decision towards ICT+CRT and CRT by the local HNC tumor board. The distribution of the propensity score is depicted in **Figure 6A**.

Variable		**Odds ratio (OR)**	**95%CI**	**p**
Age (per 5 years increase)		0.86	0.65-1.14	0.299
ECOG (per point increase)		0.14	0.05-0.40	<0.0001
CCI (per point increase)		0.44	0.29-0.66	<0.0001
HPV / p16 positivity*		0.35	0.11-1.13	0.078
SPM		0.18	0.06-0.58	0.004
Laryngeal primary		9.29	2.58-33.54	0.001
TNM T4 tumor		2.11	0.93-4.77	0.073

Table 9. Propensity score model for treatment assignment to ICT+CRT vs. CRT alone (n=195).

*Patients with missing HPV status were treated as being HPV / p16 negative in this analysis in order to reduce the number of patients who are excluded from analysis due to missing data. The propensity score model represent a multivariable logistic regression model. Abbreviations: 95%CI – 95% confidence interval, p – Wald test p-value, ECOG – Eastern Cooperative Oncology Group performance status, CCI – Charleson Comorbidity Index, HPV – Human Papilloma Virus, p16 – HPV protein 16kDa, SPM – History or current second primary malignancy, TNM – Tumor Node Metastasis classification.

Next, we transformed the propensity score into the IPTW according to the so-called ATT principle whose formula is reported in the statistical methods section. The distribution of the IPTW is depicted in **Figure 6B**.

IPTW weighing using the propensity score aims to create a setting in which the treatment assignment (in this case to ICT+CRT vs. CRT) is independent of baseline covariates, thus generating a so-called pseudo-randomized scenario. Every patient's weight is equal to the inverse of the probability of receiving the treatment that the patient actually received. (148)

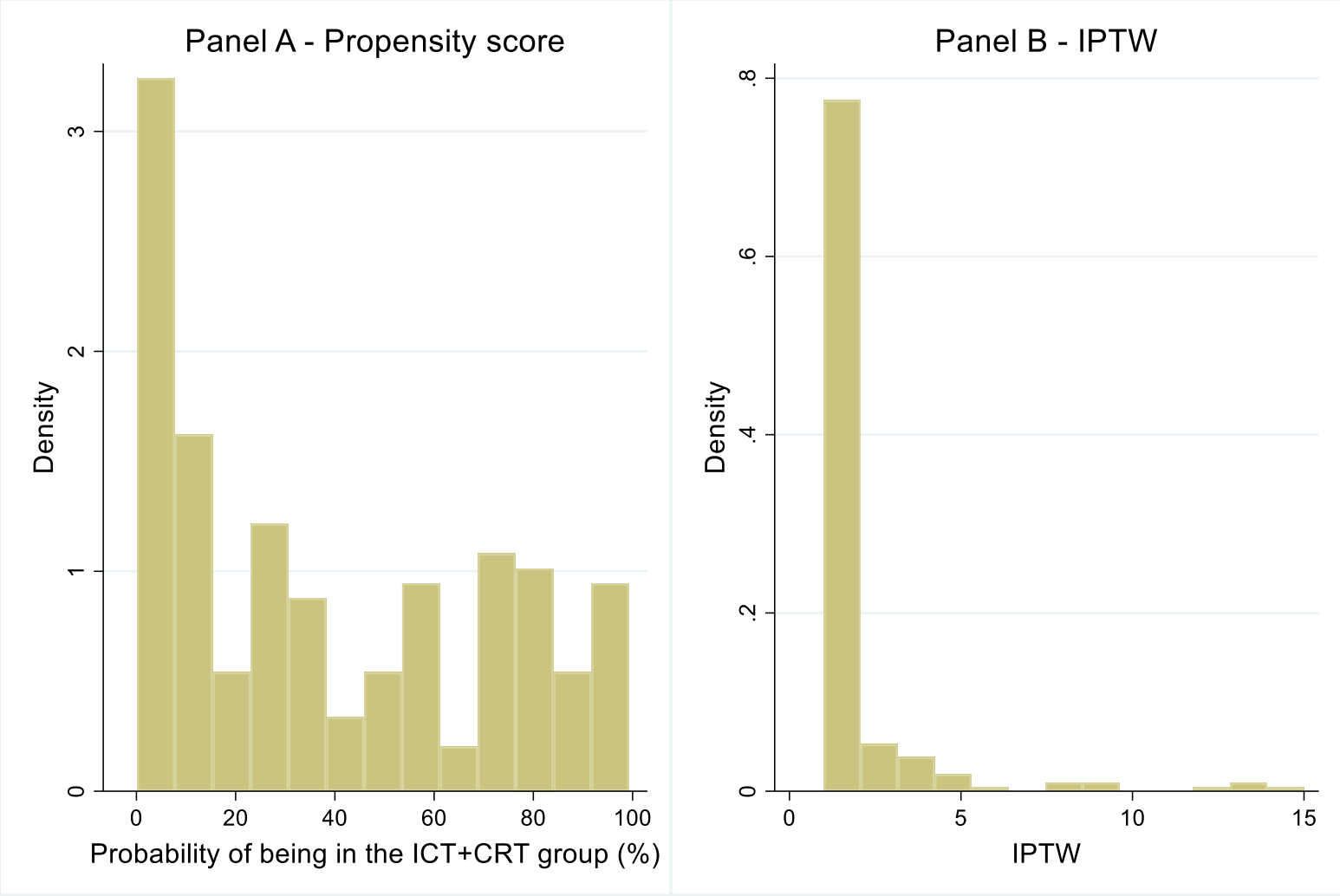

Figure 6AB. Histograms of the propensity score (Panel A) and the inverse-probability-of-treatment-weights (IPTW, Panel B).

To gauge whether the propensity score achieved sufficient balance between the two treatment groups, we performed balance diagnostics by computing updated SMDs that were re-weighted by the IPTW. In this analysis, the propensity score strongly reduced between-group imbalances in baseline covariates, consistent with sufficient balance for a further potentially unbiased comparison of outcomes between the ICT+CRT and CRT group, respectively (**Table 5**). For example, SMD for age was reduced from 0.89 to 0.22, for CCI from 1.12 to 0.25, for ECOG from 0.73 to 0.01, and for laryngeal primary from 0.51 to 0.16.

Crude and IPTW-weighted analysis of OS according to treatment group

In crude analysis, the OS experience of patients in the ICT+CRT and the CRT treatment group were highly similar. In detail, 5-year OS was 53% in the ICT+CRT group, and 47% in the CRT group, respectively (log-rank p=0.630, **Figure 7 (Left Panel), Table 10**). In univariable time-to-death regression, induction chemotherapy was not associated with a lower risk of death-from-any-cause (Hazard Ratio (HR)=0.89, 95%CI: 0.56-1.42, p=0.630).

IPTW-weighting of the data did not materially change these results. Five-year OS estimates were 54% and 45% in the ICT+CRT and the CRT group (log-rank p=0.673, **Figure 7 (Right Panel), Table 10**), and induction chemotherapy was also not associated with improved overall survival in univariable Cox regression (IPTW-weighted HR=0.87, 95%CI: 0.46-1.65, p=0.673).

Crude and IPTW-weighted analysis of PFS according to treatment group

In crude analysis, the 5-year PFS of patients in the ICT+CRT and the CRT treatment group were comparable. Briefly, 5-year PFS was 53% in the ICT+CRT group, and 42% in the CRT group, respectively (log-rank p=0.636, **Figure 8 (Left Panel), Table 10**). In univariable time-to-PFS regression, induction chemotherapy was not associated with a lower risk of progression or death (Hazard Ratio (HR)=0.90, 95%CI: 0.57-1.41, p=0.637).

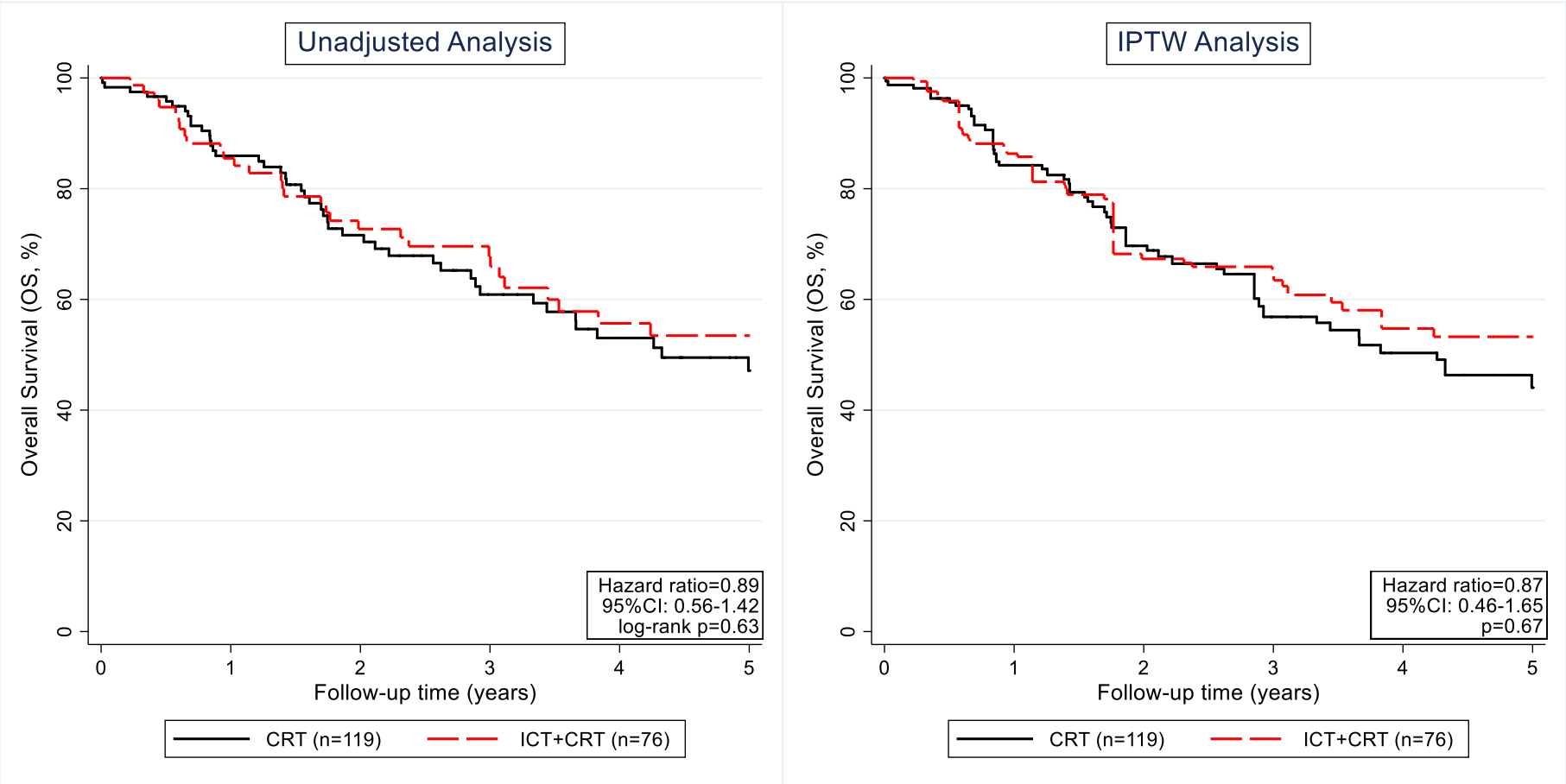

Figure 7. Crude and IPTW-weighted Kaplan-Meier curves of overall survival according to treatment groups (n=195).
Left panel: Unadjusted analysis, Right panel: Analysis after weighing the Kaplan-Meier estimator for the IPTW. Abbreviations: IPTW – Inverse Probability of Treatment Weight, CRT – Radiochemotherapy, ICT – Induction Chemotherapy, 95%CI: 95% confidence interval.

After IPTW-weighting, PFS was numerically but not statistically significantly higher in patients receiving ICT+CRT. In detail, 5-year IPTW-weighted PFS estimates were 62% and 40% in the ICT+CRT and the CRT group (log-rank p=0.212, **Figure 8 (Right Panel), Table 10**). This result was confirmed in univariable Cox regression, where the regression coefficient was in favour of the ICT+CRT group, but this did not reach statistical significance at the 5% level (IPTW-weighted HR=0.67, 95%CI: 0.35-1.26, p=0.212).

Crude and IPTW-weighted analysis of local progression risk according to treatment group

The 5-year risks of local progression, as estimated with a 1-Kaplan-Meier estimator not accounting for competing mortality, were 35% in the ICT+CRT and 40% in the CRT treatment group, respectively (log-rank p=0.942, **Figure 9 (Left Panel), Table 10**). In univariable Cox regression, we did not observe evidence for a prognostic relationship between induction chemotherapy and a lower risk of local progression (Hazard Ratio (HR)=1.02, 95%CI: 0.58-1.80, p=0.942).

In IPTW-weighted analysis, 5-year risks of local progression were 27% in the ICT+CRT group, and 43% in the CRT group (log-rank p=0.256, **Figure 9 (Right Panel), Table 10**). The relative risk of developing local progression was 0.7-fold lower in the ICT-CRT group, with the confidence interval of this estimate including unity (IPTW-weighted HR=0.65, 95%CI: 0.32-1.37, p=0.256).

Crude and IPTW-weighted analysis of distant metastasis risk according to treatment group

In unadjusted 1-Kaplan-Meier analysis of distant metastasis risk, 5-year risks for this endpoint were 20% in the ICT+CRT and 23% in the CRT treatment group, respectively (log-rank p=0.566, **Figure 10 (Left Panel), Table 10**). In univariable Cox regression, induction chemotherapy was associated with an 0.8-fold lower risk of distant metastasis (HR)=0.79, 95%CI: 0.36-1.75, p=0.566).

Endpoint	Analysis	Treatment Group		1-year estimate (95%CI)	3-year estimate (95%CI)	5-year estimate (95%CI)	p
Overall Survival (OS)	Crude	CRT		86% (78-91)	61% (50-70)	47% (35-58)	0.630
		ICT+CRT		85% (75-92)	68% (55-77)	53% (40-65)	
	IPTW	CRT		84%	57%	45%	0.673
		ICT+CRT		86%	65%	54%	
Progression-free Survival (PFS)	Crude	CRT		77% (68-84)	58% (47-68)	42% (29-54)	0.636
		ICT+CRT		77% (65-85)	56% (43-67)	53% (40-65)	
	IPTW	CRT		75%	55%	40%	0.212
		ICT+CRT		82%	65%	62%	
Local Progression	Crude	CRT		15% (9-23)	24% (17-35)	40% (27-55)	0.942
		ICT+CRT		16% (9-27)	32% (22-45)	35% (24-50)	
	IPTW	CRT		17%	29%	43%	0.256
		ICT+CRT		9%	24%	27%	
Distant Metastasis	Crude	CRT		8% (4-16)	20% (12-32)	23% (14-36)	0.566
		ICT+CRT		5% (2-14)	17% (9-31)	20% (11-34)	
	IPTW	CRT		12%	22%	24%	0.039
		ICT+CRT		2%	10%	12%	

Table 10. Crude and IPTW-weighted outcome rates of the study cohort.

OS and PFS were estimated with a Kaplan-Meier estimator, whereas risks of local progression and distant metastasis were computed with a 1-Kaplan-Meier estimator. The 1-Kaplan-Meier estimators did not account for competing mortality. Because weights are not implemented in standard errors of Kaplan-Meier estimators, the outcome risks for the IPTW-weighted analyses do not report 95% confidence intervals. Abbreviations: p – log-rank p-value, 95%CI – 95% confidence interval, IPTW – Inverse Probability of Treatment Weight, CRT – Radiochemotherapy, ICT – Induction Chemotherapy.

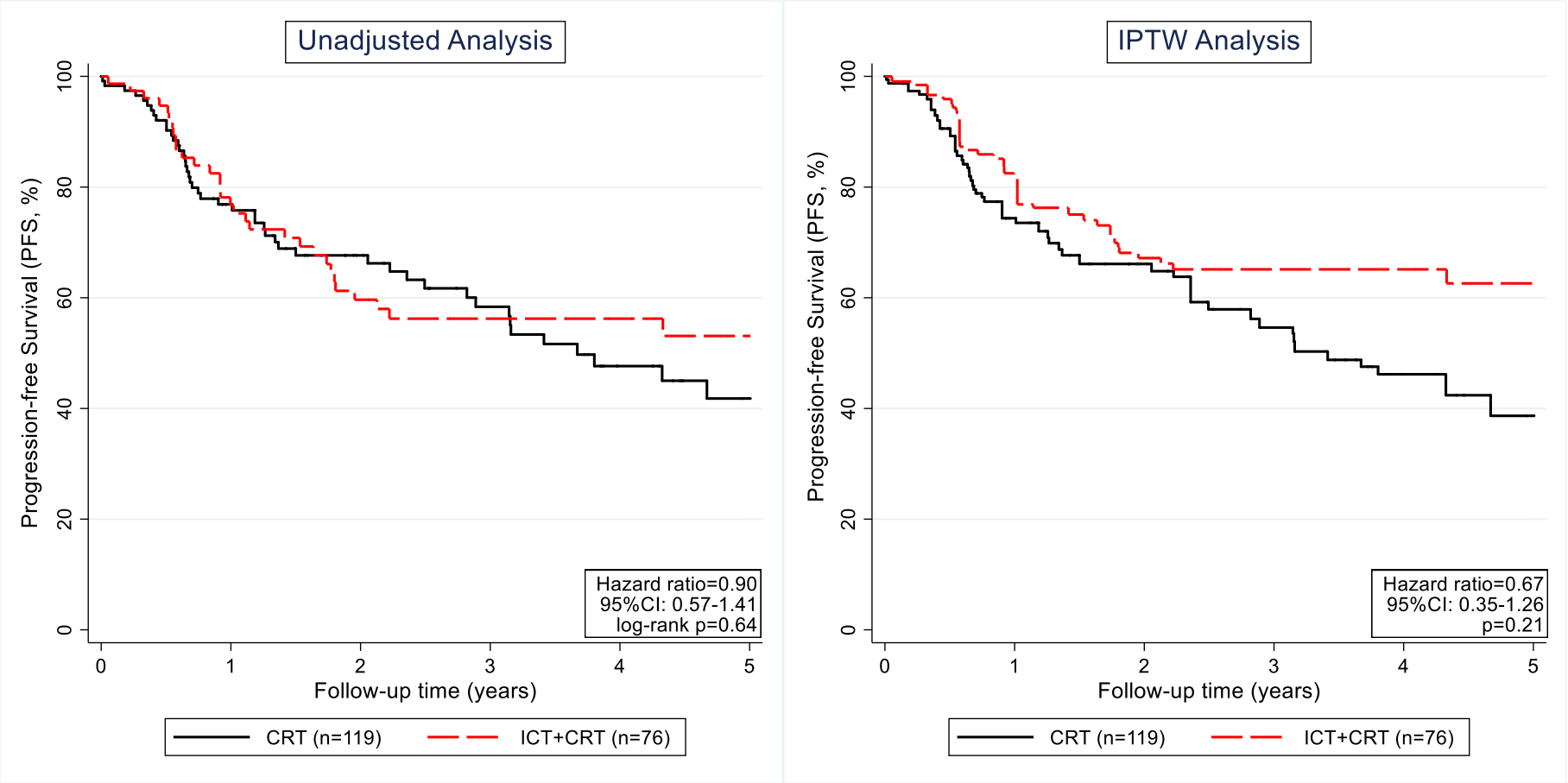

Figure 8. Crude and IPTW-weighted Kaplan-Meier curves of progression-free survival according to treatment groups (n=195).
Left panel: Unadjusted analysis, Right panel: Analysis after weighing the Kaplan-Meier estimator for the IPTW. Abbreviations: IPTW – Inverse Probability of Treatment Weight, CRT – Radiochemotherapy, ICT – Induction Chemotherapy, 95%CI: 95% confidence interval.

In IPTW-weighted analysis, the risk of developing distant metastasis was significantly lower in patients treated with ICT+CRT than in patients treated with CRT only. Briefly, IPTW-weighted distant metastasis risks were estimated at 12% in the ICT+CRT group, and 24% in the CRT group, respectively (log-rank p=0.039, **Figure 10 (Right Panel), Table 10**). This result was confirmed in univariable IPTW-weighted Cox regression of time-to-distant metastasis, were the rate of distant metastasis was 0.4-fold lower in ICT+CRT group than in the CRT group (IPTW-weighted HR=0.39, 95%CI: 0.16-0.95, p=0.039).

Sensitivity analysis: Crude and IPTW-weighted analysis of outcomes in patients with oropharyngeal tumors

Due to the known higher prevalence of HPV infection in oropharyngeal HNSCC and the potential favourable effect of HPV infection on overall prognosis as well as the potential for a treatment-modifying effect of HPV infection on ICT and CRT, we conducted an exploratory, hypothesis-generating sensitivity analysis comparing the ICT+CRT and CRT group within an IPTW framework in oropharyngeal and non-oropharyngeal tumors.

Notably, also in our study cohort the prevalence of HPV infection as assessed by indirect immunohistochemical diagnosis (p16) was significantly higher in the 99 patients with oropharyngeal cancer than in patients with other HNSCC tumor sites (χ^2 p<0.0001, **Table 11**). In contrast, the prevalence of patients with unknown/undetermined HPV status was significantly higher in patients with non-oropharyngeal HNSCC, likely reflecting the propensity of treating physicians to determine HPV status predominantly in oropharyngeal tumors.

Tumor site		**p16 IHC positive**	**p16 IHC negative**	**p16 IHC unknown**
Other sites (n=99)		6 (6%)	37 (37%)	56 (57%)
Oropharynx (n=96)		33 (34%)	28 (29%)	35 (36%)

Table 11. HPV infection status and oropharyngeal versus non-oropharyngeal tumor site (n=195).

HPV infection was indirectly assessed by p16 immunohistochemistry. Data represent absolute counts with row percentages in round brackets. Abbreviation: p16 – HPV protein 16kDa, IHC – Immunohistochemistry.

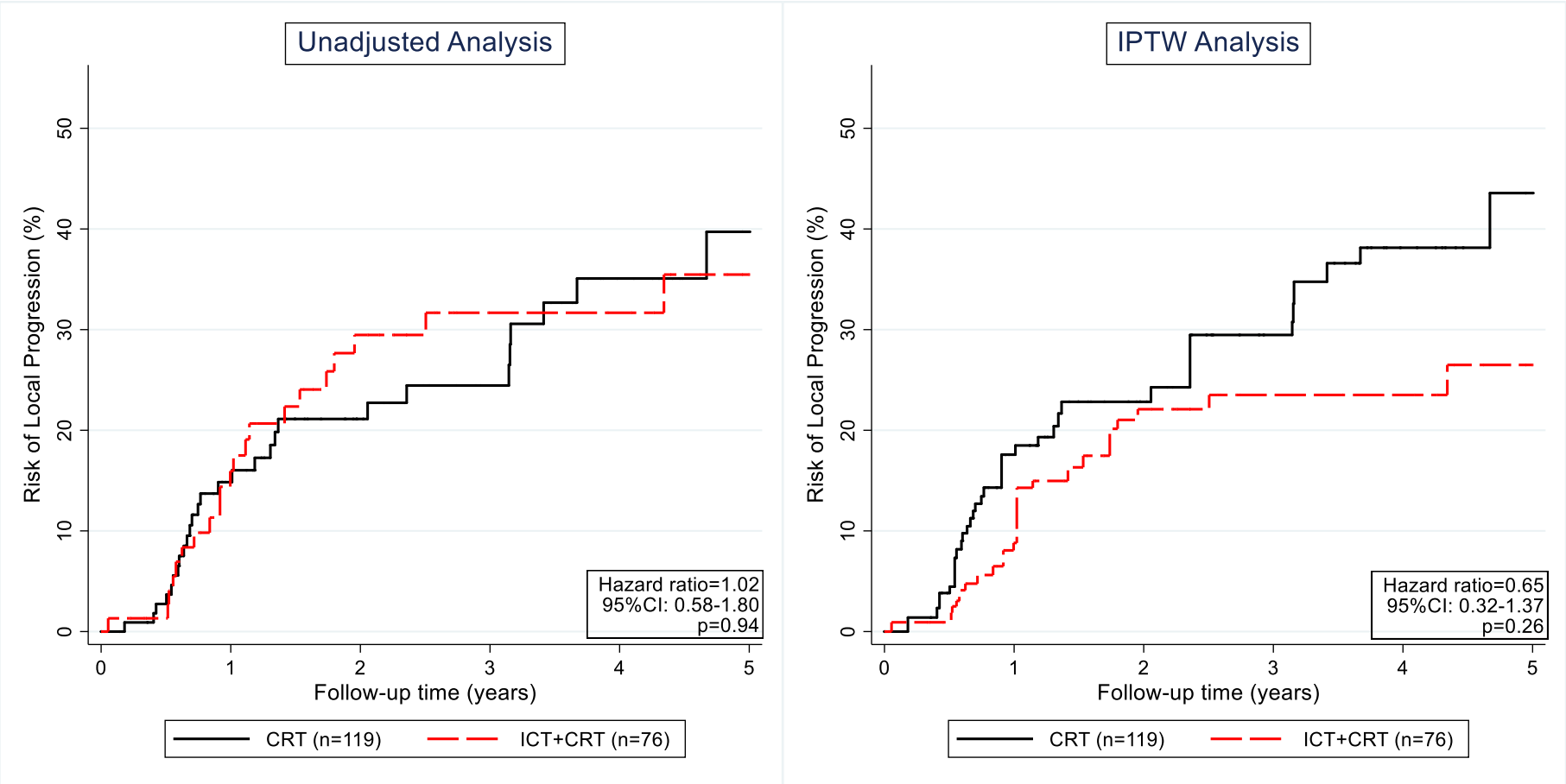

Figure 9. Crude and IPTW-weighted Kaplan-Meier curves of local progression according to treatment groups (n=195).
Left panel: Unadjusted analysis, Right panel: Analysis after weighing the Kaplan-Meier estimator for the IPTW. Abbreviations: IPTW – Inverse Probability of Treatment Weight, CRT – Radiochemotherapy, ICT – Induction Chemotherapy, 95%CI: 95% confidence interval.

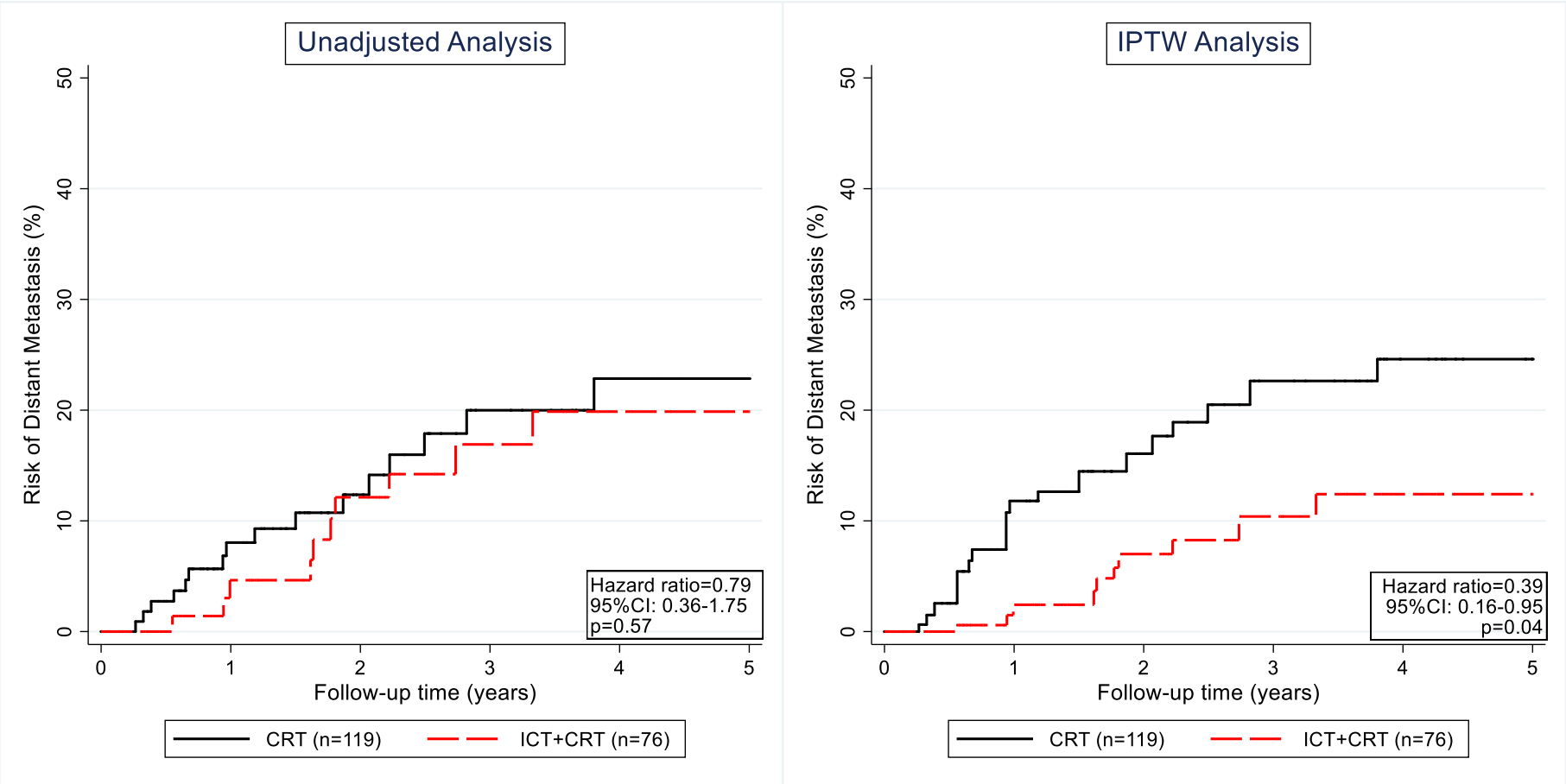

Figure 10. Crude and IPTW-weighted Kaplan-Meier curves of distant metastasis according to treatment groups (n=195).
Left panel: Unadjusted analysis, Right panel: Analysis after weighing the Kaplan-Meier estimator for the IPTW. Abbreviations: IPTW – Inverse Probability of Treatment Weight, CRT – Radiochemotherapy, ICT – Induction Chemotherapy, 95%CI: 95% confidence interval.

For the sensitivity analysis, we performed IPTW-weighted univariable Cox proportional hazards regressions (OS and PFS) or univariable Fine & Gray proportional subdistribution hazards regressions (local progression, distant metastasis) each including three predictor variables:

- Treatment assignment (ICT+CRT versus CRT)
- HNSCC tumor site (Oropharynx vs. Other tumor sites)
- Interaction term of treatment assignment and HNSCC tumor site

Overall, we observed that patients with oropharyngeal tumors appeared to have a more favourable prognosis with respect to higher OS (**Figure 11**), higher PFS (**Figure 12**), and lower local progression risk (**Figure 13**) than patients with non-oropharyngeal tumors, respectively, whereas the overall prognosis with respect to distant metastasis was comparable between oropharyngeal and non-oropharyngeal tumors (**Figure 14**).

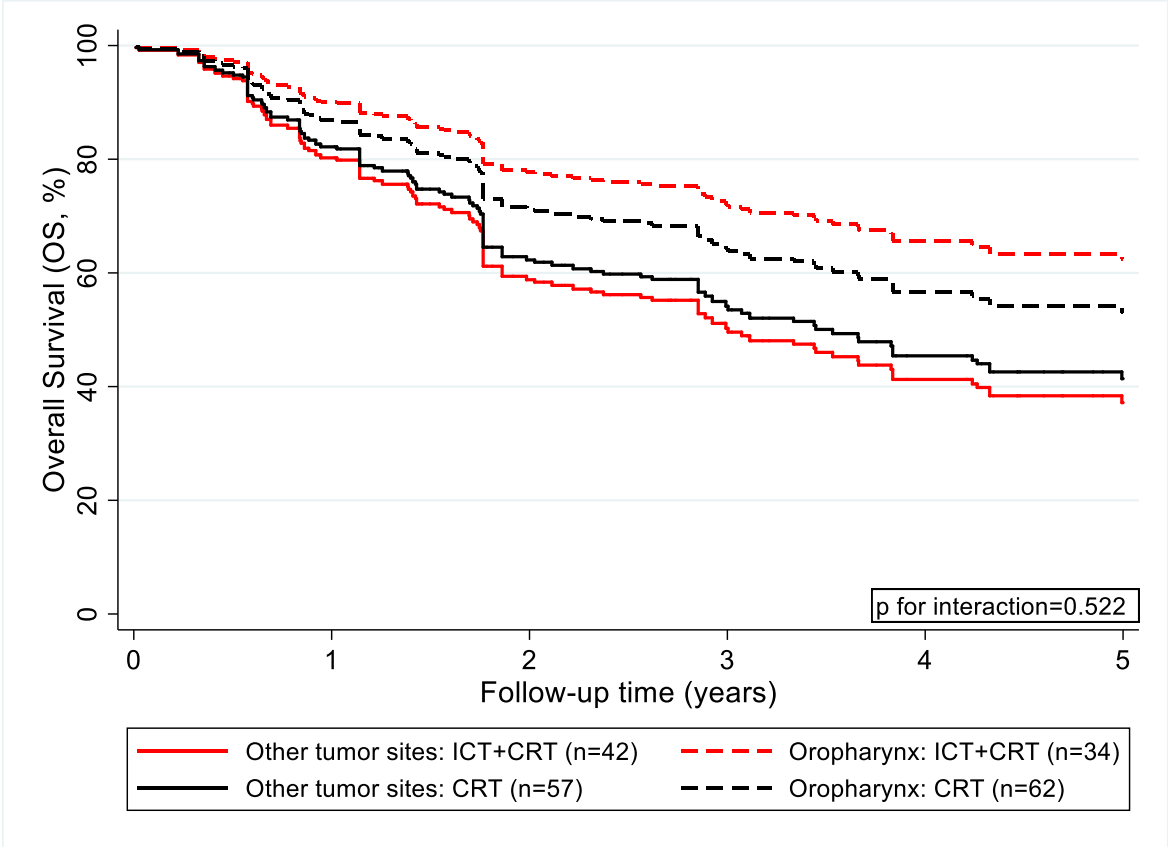

Figure 11. Predicted Overall Survival over 5 years after treatment initiation according to tumor site and treatment group.
Curves were predicted from an IPTW-weighted multivariable Cox proportional hazards model including tumor site (oropharyngeal vs. other sites), treatment assignment, and the interaction of these two terms. Abbreviations: ICT – induction chemotherapy, CRT – radiochemotherapy.

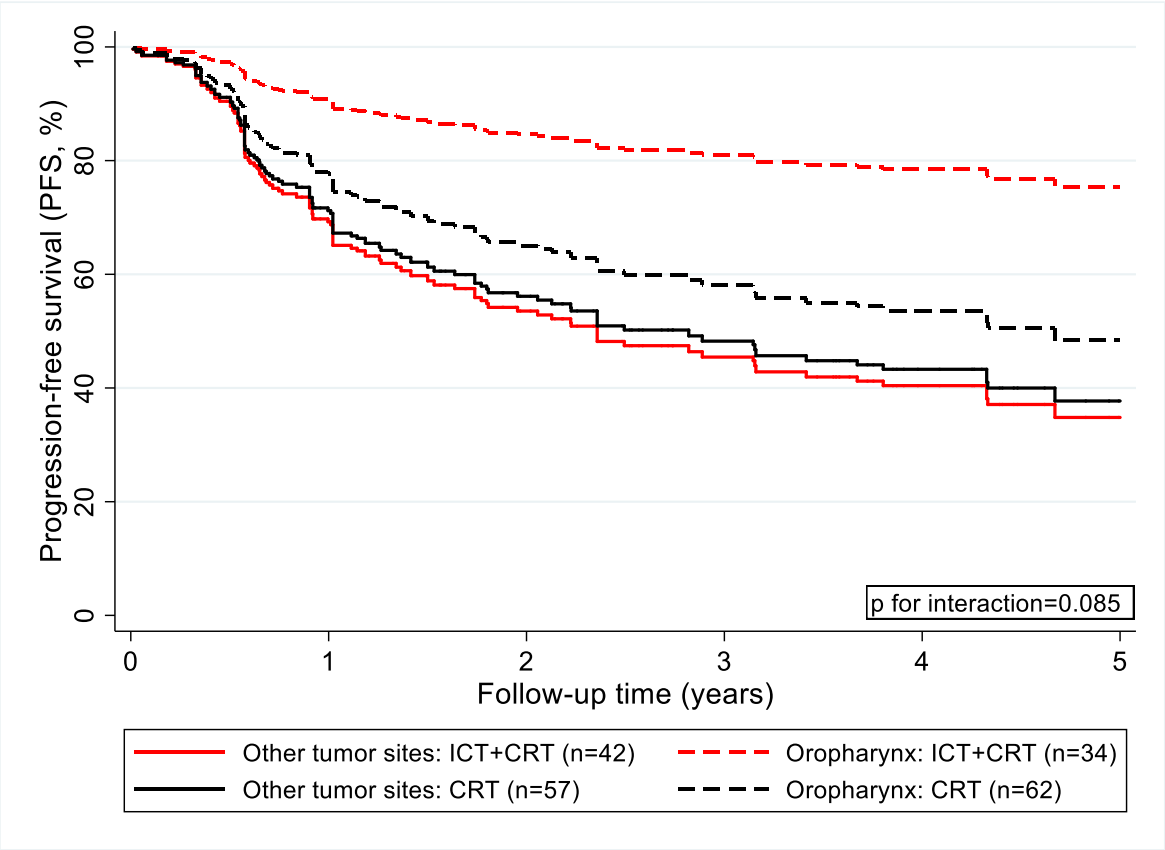

Figure 12. Predicted Progression-free Survival over 5 years after treatment initiation according to tumor site and treatment group.
Curves were predicted from an IPTW-weighted multivariable Cox proportional hazards model including tumor site (oropharyngeal vs. other sites), treatment assignment, and the interaction of these two terms. Abbreviations: ICT – induction chemotherapy, CRT – radiochemotherapy.

Moreover, some of these analyses suggested that the magnitude of association between ICT and favourable outcome was modified by tumor site. In detail, considering interaction p-values ≤ 0.1 as indicative of a statistically significant interaction between tumor site and treatment assignment ("relaxed" alpha for interaction tests), we observed that assignment to ICT+CRT was strongly associated with favourable PFS in patients with oropharyngeal tumors, whereas this was not the case in patients with tumors at other sites (p for interaction=0.085, **Figure 8**). Results were similar (albeit not statistically significant) for the endpoints OS and local progression (**Figure 7**, **Figure 9**). In terms of distant metastasis risk, the sensitivity analysis was consistent with a similar relative association of ICT with distant metastasis risk in both oropharyngeal and non-oropharyngeal HNSCCs (**Figure 10**).

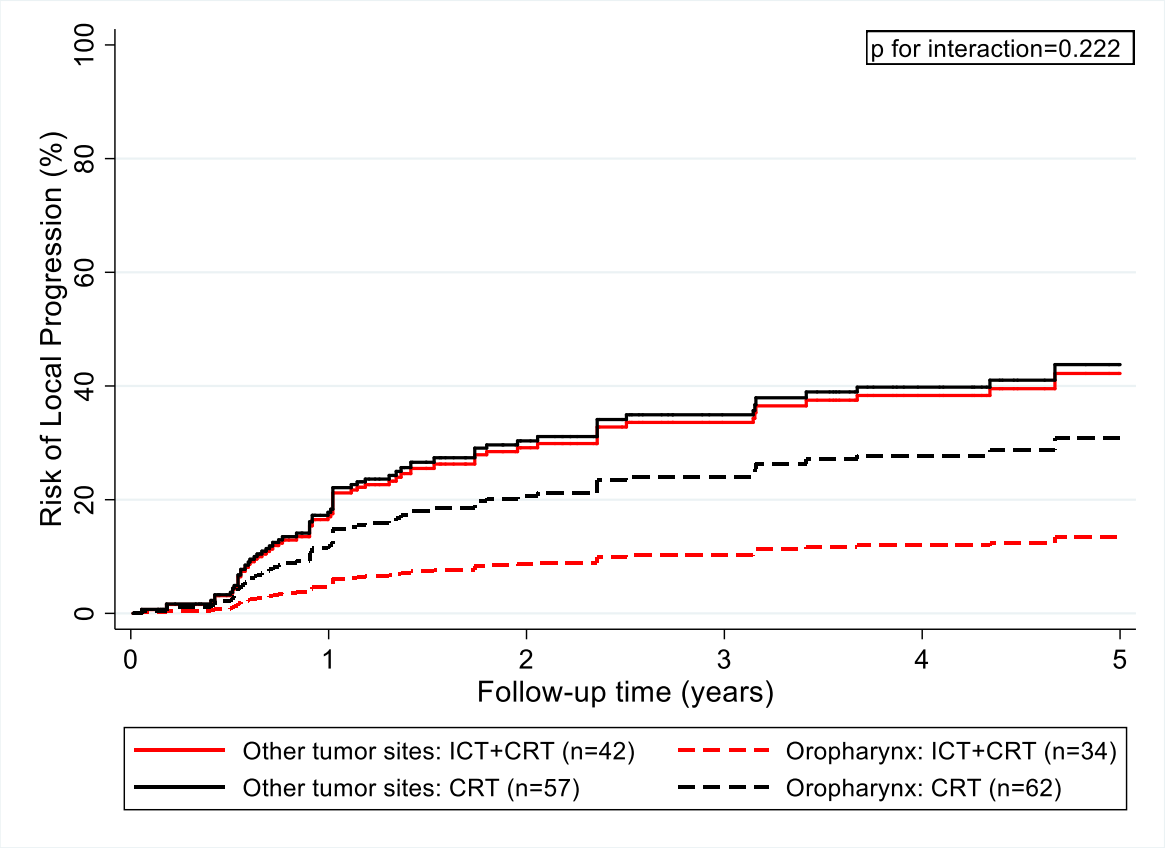

Figure 13. Predicted Cumulative Incidence of Local Progression over 5 years after treatment initiation according to tumor site and treatment group.

Curves were predicted from an IPTW-weighted multivariable Fine & Gray proportional subdistribution hazards model including tumor site (oropharyngeal vs. other sites), treatment assignment, and the interaction of these two terms. This model accounted for competing mortality. Abbreviations: ICT – induction chemotherapy, CRT – Radiochemotherapy.

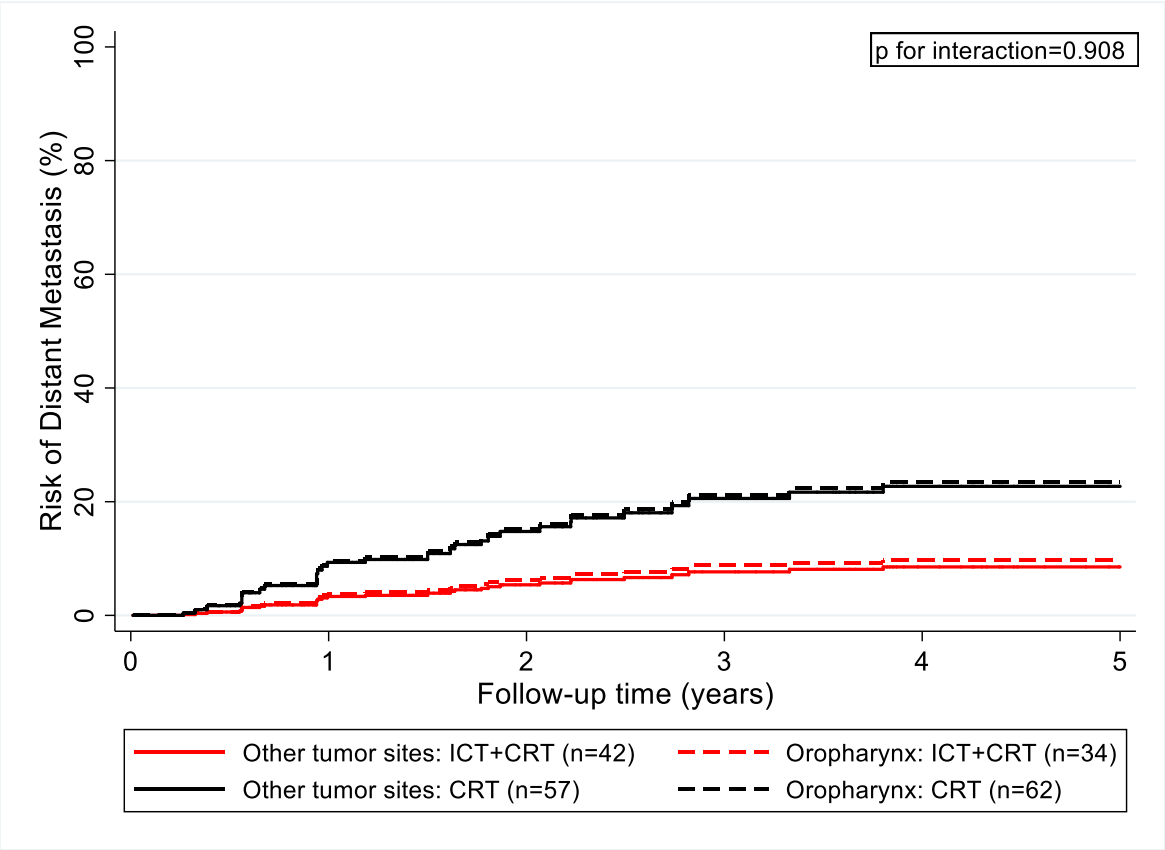

Figure 14. Predicted Cumulative Incidence of Distant Metastasis over 5 years after treatment initiation according to tumor site and treatment group.

Curves were predicted from an IPTW-weighted multivariable Fine & Gray proportional subdistribution hazards model including tumor site (oropharyngeal vs. other sites), treatment assignment, and the interaction of these two terms. This model accounted for competing mortality. Abbreviations: ICT – induction chemotherapy, CRT – Radiochemotherapy

Discussion

The standard treatment approach for patients with locally-advanced HNSCC, which are either unresectable, or resectable with poor functional outcome and/or prognosis is so poor that mutilating surgery is not justified, is combined concomitant CRT. Whether an ICT prior to definitive CRT improves outcomes in this patient group is still a matter of debate. In this project we conducted a propensity score weighted analysis of PFS and OS from retrospective data of 195 patients to assess the association between ICT and survival outcomes. Re-weighing the data with the IPTW enabled the direct comparison of endpoints between the two groups using observational data, despite statistically significant differences in terms of prognostically relevant variables between the CRT alone and the ICT+CRT group. This approach helped us to generate a pseudo-population, in which treatment status was independent of baseline covariates.

Overall, we found that OS was comparable between the two treatment groups, regardless of receiving ICT prior CRT. This finding did not materially change after IPTW-weighting and compares well with previous randomised clinical trials and a recent meta-analysis of Budach et al., supporting the current situation that ICT is not routinely recommended for the treatment of locally-advanced HNSCC. (125, 126) Although IPTW-weighted analysis of PFS and local progression risk showed numerically higher PFS and lower risk of local progression in patients who received ICT+CRT, no statistically significance was reached with the number of patients we had. Previous randomised clinical trials and a meta-analysis by Kim et al. observed a trend towards improved PFS and a lower incidence of local progression in the ICT+CRT group, similar to what was observed in our study. (149)

Another secondary endpoint focused on the risk of developing distant metastasis. We found that patients receiving ICT prior to CRT had significant lower risk of distant metastasis upon IPTW-adjustment for baseline confounders. In detail, the rate of distant metastasis in the ICT+CRT group was 0.4-fold lower than in the CRT alone group. One may assume that a lower incidence of distant metastasis may lead to an improved overall survival, however, the discrepancy between the efficacy of ICT on OS and distant metastasis rate may suggest that patients with locally advanced HNSCC usually do not only die from distant tumour

complications, but from locoregional progression or other diseases such as pulmonary diseases or second primary malignancies, which are often present in this very challenging patient population with a high prevalence of alcohol and/or tobacco abuse.

In this study we constructed a multivariable logistic regression model to predict the treatment decision of the local ENT tumor board. Using SMD analysis and clinical subject matter knowledge, the following baseline covariates were included in this model: age, ECOG performance status, CCI, a history or current SPM, TNM T4 classification, laryngeal primary and HPV/p16 status, suggesting that these baseline covariates affect physicians clinical decision-making process to assign a patient to a specific treatment, either CRT alone or ICT+CRT. Additional adjustments of this multivariable logistic regression model including other presumed prognostic variables such as a high TNM N status or advanced clinical stage showed that these baseline covariates did not materially affect the physicians' treatment decision.

A very important aspect of research in this field of medicine is to identify patient subgroups who may have a high likelihood of benefiting from a specific treatment. We found that patients with locally advanced laryngeal carcinomas may benefit from ICT prior to concomitant CRT in terms of larynx preservation, albeit not changing overall survival outcomes. Since the larynx is involved in many important physical functions, such as speaking and swallowing, preserving the function of this organ may significantly affect quality of life of these patients. However, the benefit of this finding is limited by the extent of the disease, results of randomised phase III trials suggest that patients with very advanced T4 tumors have an improved overall survival after surgical approach compared to a larynx preservation approach with induction treatment. (150)

Furthermore, we performed a sensitivity analysis of outcomes in patients with oropharyngeal tumors to compare the ICT+CRT and CRT group depending on tumor site and HPV status, as the prevalence of HPV infection is notably higher in oropharyngeal HNSCCs. In our study cohort HPV status was determined by indirect immunohistochemical diagnosis of p16. We observed that patients with primaries located in the oropharynx have a higher OS, higher PFS, as well as a lower incidence of local progression, suggesting that HPV infection is a strong prognostic factor, which compares well to previous reports about the difference of HPV positive and negative tumors at molecular level leading to a more favourable prognosis.

(151) The results of the sensitivity analysis of distant metastasis risk were independent of tumor site and showed a similar relative association of distant metastasis risk and ICT in oropharyngeal and non-oropharyngeal tumors, explained by the observed efficacy of ICT on distant metastasis rate in both groups. However, caution must be exercised in interpreting the findings of this subgroup analysis, considering the relatively low number of patients included in this analysis.

Additionally, it has to be mentioned that standard determination of HPV infection using immunohistochemistry might lead to misinterpretation and incorrect patient stratification. Nowadays, routine clinical diagnostic procedures to determine the HPV status of a tumor include PCR (polymerase chain reaction) and immunohistochemistry, with varying cost expenditures but comparable results. In fact, detecting mRNA and protein of HPV oncogenes to evaluate the activity of HPV would be a better way to avoid undertreatment in case of HPV bystander infection, which results in an $HPV^{+}/p16^{+}$ phenotype in a non-HPV driven tumor, or in case of $HPV^{-}/p16^{+}$ phenotype. (69)

Another important question for physicians treating HNC patients is whether concomitant CRT is still feasible after induction treatment with TPF. This question has been addressed in several studies yielding heterogeneous results. For example, Ghi et al. found that three cycles of TPF are feasible without compromising subsequent CRT. However, in this study the number of planned chemotherapy cycles during CRT had to be reduced on average from three to two because adverse events led to an interruption of planned radiotherapy. (131)

In our study only 35% of the 189 patients received all three planned cycles of chemotherapy during CRT within the expected time frame. Moreover, in more than one third of patients chemotherapy had to be stopped permanently. Interestingly, there was no correlation between ICT and permanent discontinuation of chemotherapy or dose modification. Only in six cases of the 76 patients from the ICT+CRT group the administration of subsequent CRT was not feasible anymore after ICT. Considering the high number of complete remissions and an overall response rate of 86% despite the small proportion of patients receiving all 3 cycles of CRT, this allows us to carefully speculate that achieving the projected total radiotherapy dose of 70 Gy seems to be an important prognostic factor for treatment response. This is corroborated by the fact that 94% of the patients in our study cohort reached the full projected radiotherapy dose of 70 Gy.

Some adverse event rates during ICT were contrary to our expectations. For example, only 21% of the patients developed at least one treatment-related G3 toxicity, with cytopenia, diarrhoea and infection as the most common adverse events. No toxicity-related death was reported during ICT and only one patient had a G4 toxicity. Overall, ICT was well tolerated, considering that 67% of the patients received all 3 planned cycles in expected time frame and only 11 % were forced to permanently discontinue ICT due to toxicities. These findings indicate that ICT-related toxicities are manageable upon an adequate patient selection and optimal supportive therapy.

Interestingly, a relatively high number of cisplatin-related toxicities during chemoradiation could be observed. In detail, the proportion of patients developing any grade nephrotoxicity, or any grade hearing impairment were 16% and 11%, respectively. Ototoxic impact of cisplatin on inner ear functions is difficult to control, but nephrotoxicity might be reduced by even more careful patient selection, accurate assessment of renal function at time of treatment start and by switching to a different chemotherapy regimen, like carboplatin, if indicated.

Finally, several limitations to this study have to be discussed. Although IPTW weighting removed most differences in baseline covariates between the two treatment groups, the retrospective fashion of this study may not remove all potential confounding factors, including residual confounding not accounted for by the IPTW, differences in outcome assessment or recordkeeping of adverse events. Moreover, different treatment regimens and dosages were included in the ICT as well as in the CRT group in order to increase the number of patients of this study cohort, however, these regimens may differ in their efficacy. Another limitation of this study is the relatively high number of patients with unknown HPV status, especially concerning patient records set up before 2012, as HPV status has not been routinely assessed until then. Due to these missing data, the findings on HPV subgroup analysis should be considered as preliminary data and need to be interpreted with caution. In order to increase the significance of these findings, the missing HPV status of these 91 patients is going to be determined and a second analysis will be conducted in the future. Besides that, various tumor locations were included in this study.. Although many prospective clinical trials included different tumor sites in their study cohort because of slow patient enrolment in order to increase the study population, it is well known, that prognosis and outcome rates are significantly affected by tumor location. For example, five-year

overall survival for laryngeal cancer and hypopharyngeal cancer is about 59% and 25%, respectively. (8) This means that our results may not be fully generalizable to each individual HNSCC tumor location. In addition, more than a third of the patients who received ICT did not have radiographic staging examination after ICT, and we thus include more patients with unkown ICT response than what would for example be expected in a well-conducted prospective clinical trial. Finally, our dataset does not include surgical approaches after ICT, as ICT can also be applied as a form of neoadjuvant treatment to achieve a downsizing of locally advanced primary tumors, which may modify results on overall survival and locoregional control of this patient population.

Conclusion

The results of this non-randomised study fully corroborate previous randomised trials which showed that ICT improves systemic disease control by reducing the risk of distant metastasis. However, the data of this study suggest that this benefit does not translate into a meaningful improvement in OS. Considering potentially quality of life-limiting toxicities associated with induction treatment, each indication for ICT should be carefully assessed for every patient, weighing potential benefits and harms. For example, ICT+CRT may be considered an effective treatment strategy for patients presumed to have a very high systemic risk, or for patients who prefer an organ-preserving treatment strategy, especially in cases of laryngeal carcinoma. Future studies should further evaluate the benefit of ICT in locally advanced HNSCC in terms of overall survival within a randomised setting and with a particular focus on patients with HPV/p16 positive tumors.

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