Chapter 11
Where and when to Use Induction Chemotherapy in Head and Neck Squamous Cell Cancer

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Introduction

Worldwide cancer incidence and mortality are rapidly growing, and this is also true for head and neck squamous cell cancer (HNSCC). The 2018 estimates point at more than 750.000 new cases and more than 380.000 deaths [1]. The reasons are complex but reflect both aging and growth of the population, as well as changes in the prevalence and distribution of the main risk factors for cancer, several of which are associated with socioeconomic development [2, 3]. Sustained exposure to tobacco, tobacco-like products, and alcohol increase the risk of developing HNSCC [4]. Although HNSCC can arise within the oral cavity, oropharynx, hypopharynx, larynx, and nasopharynx, there has been a shift in primary site distribution, with a steady increase of oropharyngeal squamous cell carcinoma (OPSCC) and a decline in cancers of the larynx and hypopharynx, in particular in the Western world [5]. This change has been observed in parallel with a decrease in cigarette smoking and the identification of exposure to high-risk oncogenic human papillomavirus (HPV) as a risk factor for the development of OPSCC [6, 7]. This possible role for HPV in head and neck cancer was first reported in the 1990s, while the proof for a causal association between HPV and OPSCC was delivered in 2000 [8, 9]. A systematic review and meta-analysis showed that the overall HPV prevalence in OPSCC is increasing significantly over time: from 40.5% (95% CI,35.1–46.1) before 2000, to 64.3% (95% CI, 56.7–71.3) between 2000 and 2004, and 72.2% (95% CI, 52.9–85.7) between 2005 and 2009 ($p < .001$) [10]. Prevalence increased significantly initially in North America and subsequently in Europe, and the significant gap between them that existed before 2000 (50.7% vs 35.3%, respectively, $p = .008$) has now disappeared (69.7% vs 73.1%, respectively, $p = .8$).

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Many earlier studies have observed that patients with HPV-positive OPSCC had a distinct epidemiology when compared to patients with HPV-unrelated OPSCC, i.e. they were statistically younger, were more likely male, had fewer comorbidities, and reported less tobacco exposure but higher numbers of (oral) sex partners [11–13]. The prognosis for these younger patients with HPV-positive OPSCC was substantially better than that for patients with HPV-negative tobacco-related cancers treated similarly [5]. However, more recently, several studies portend that the population of elderly patients with HPV-positive OPSCC is expanding [14–16]. In fact, the age at OPSCC diagnosis is increasing for both HPV-positive and HPV-negative patients, and a rising proportion of older patients have HPV-positive tumors. In an analysis of the National Cancer Database (with 119,611 OPSCC patients) Rettig et al. [14] showed that although patients of ≥70 years of age with HPV-positive OPSCC had improved survival compared to those with HPV-negative OPSCC (adjusted hazard ration [aHR] = 0.65, 95%CI = 0.55–0.76), the survival benefit of HPV-positive tumor status was significantly attenuated compared to younger HPV-positive patients (50–59 years: aHR = 0.45, 95%CI = 0.39–0.51; $p_{interaction} < 0.001$). The outcome of these older patients with HPV-positive OPSCC was in fact essentially similar to survival for the young HPV-negative patients [14]. These data will have implications for the therapeutic approach that clinicians need to consider for these elderly patients, taking into account the higher comorbidity score, the distinct disease characteristics, the higher rates of treatment-related toxicities, and the increased risk of non-cancer-related deaths [14].

Milestones in Systemic Therapies for Locoregionally Advanced HNSCC

Before 1980, the initial treatment of patients with locoregionally advanced stage III or IV (M0) was surgery and/or radiation therapy (RT), a choice that depended on the site of the disease, the resectability of the cancer, the performance status of the patients, and his/her comorbidities. However, with these "traditional" therapies outcome was quite poor, in particular in those with stage IV or unresectable disease. The milestones in systemic therapies are summarized in Fig. 11.1**.**

Single agent chemotherapy, in particular methotrexate was used for palliation in patients with recurrent or metastatic disease already in the 1960s. Systemic therapy was introduced as part of combined modality therapy for LA-HNSCC in the mid 1970s, initially as single agent chemotherapy with methotrexate or cisplatin, usually with palliative intent to patients with stage IV disease, M1 cancers or recurrent disease beyond salvage local treatment [17]. The utilization of cisplatin as a single agent produced a range of responses from 14% to 41% [18]. The higher response rates were seen in previously untreated patients. Subsequently, experience was obtained with combination chemotherapy, initially with cisplatin/bleomycin combinations, to which then methotrexate or vinca-alkaloids were added and ultimately

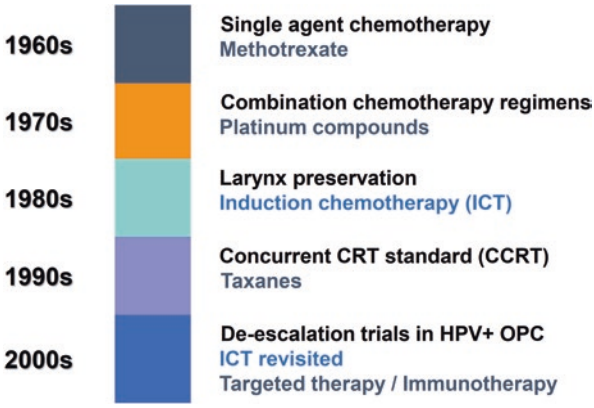

Fig. 11.1 Milestones in systemic therapy (± TRT) in head and neck squamous cell cancer

Table 11.1 Induction chemotherapy in locoregionally advanced HNSCC*

Type of induction Chemotherapy	No. of patients	CR No. (%)	PR No. (%)	OR No. (%)
Single MTX, BLM or P	188	4 (2)	81 (43)	85 [45]
Combo PB	467	34 (7)	193 (41)	227 (48)
Combo PBM	323	51 (16)	187 (58)	238 (74)
Combo PB-Vinca	474	96 (20)	231 (49)	327 (69)
Combo PF	461	162 (35)	236 (51)	398 (86)
Combo P-other	445	89 (20)	236 (53)	325 (73)

MTX metrotrexate, *BLM* bleomycin, *P* cisplatin, *PB* cisplatin/bleomycin, *PBM* PB + MTX, *Vinca* vinca alkaloid, *PF* cisplatin/infusional 5-FU, *CR* complete response, *PR* partial response, *OR* overall response. *modified from Choski et al. [19]

the cisplatin/infusional 5-fluorouracil (5-FU) regimen [19; Table 11.1). At Wayne State University in 1977, they initiated a pilot study for advanced previously untreated patients with head and neck cancer utilizing cisplatin, vincristine, and bleomycin. An overall response rate of 80% was achieved, with a 29% complete response (CR) rate [18]. With the known pulmonary toxicity of bleomycin and the in vitro synergism of 5-FU and cisplatin, they started a second pilot study with cisplatin (100 mg/m^2 IV, day 1) and 5-FU (1000 mg/m^2/day by continuous IV infusion over 96 hours), the so-called PF regimen. The response rate with that regimen was 88% overall, with a 19% CR rate [20]. Increasing the infusion time of 5-FU to 120 hrs and the number of courses from 2 to 3, increased the overall response rate to 93% and the CR rate to 54% [21]. The feasibility of the latter scheme was established and the efficacy confirmed in a multi-institutional study within the Radiation Therapy Oncology Group (RTOG). An overall response rate of 86% was obtained, with a 38% CR rate [22]. An attempt to further improve the regimen by using higher dosages of cisplatin (40 → 30 mg/m^2/day x5 for 3 cycles), given in hypertonic saline, failed to show any further improvement over the 120 hrs PF regimen [23]. Although non-randomized trials were very promising with respect to response rate and sometimes also suggesting an improvement of survival, the impact on survival could only be assessed in randomized trials. Five randomized trials executed

between 1979 and 1987 using methotrexate as a single agent for induction before local treatment were, apart from one study, all negative with respect to survival benefit [24]. In the single positive study the methotrexate had been administered intra-arterially. Looking in more detail at that study, a difference in survival was present only in patients with oral cavity cancer. Further analysis of the oral cavity cases showed that the 5-year survival difference had significance only in stage II patients. The very high response rates, and in particular the very high CR rates stimulated investigators to do randomized trials with the hope to improve survival. However, the disappointment came rather fast when early randomized trials were all negative with respect to survival benefit, apart from one in patients with oral cavity cancer, in which again chemotherapy was administered by the intra-arterial route [24]. However, apart from a high response rate in untreated patients with locoregionally advanced HNSCC, it became clear that those patients that responded well to chemotherapy subsequently also responded more favorably to radiotherapy (RT) [25]. This observation formed the rationale for the first-generation larynx preservation trials (see below).

In the 1990s, with the disappointing results with respect to survival gain in many randomized trials utilizing induction chemotherapy (ICT), the concept of concurrent chemotherapy with radiation therapy was revisited with the introduction of cisplatin given concurrently with radiation as the primary treatment for patients with inoperable and/or unresectable head and neck cancers [26]. The large individual patient-based meta-analysis, reported in 2000, demonstrated that cisplatin given concurrently with radiation (100 mg/m^2 on days 1, 22, and 43 of the RT) achieved substantially more survival benefit versus RT alone when cisplatin was given sequentially (before or after the radiation) [27, 28; Table 11.2]. That is also true for the comparison versus the at that moment considered to be the best type of ICT, i.e. the PF regimen. Since that time enthusiasm to use ICT diminished strongly and colleagues on both sides of the Atlantic started to accept concurrent cisplatin-based chemoradiotherapy (CCRT) as the preferred treatment for both patients with resectable disease and those with inoperable or unresectable disease. For the first category of patients, i.e. those with resectable disease, it was used as an adjuvant CCRT in case there were unfavorable features in the pathology specimen (positive margins and/or extracapsular extension), in the second category it was used as a definitive nonsurgical treatment (definitive CCRT). Determinative in this change of attitude

Table 11.2 Summary of the meta-analysis of the MACH-NC collaborative Group [27, 28]

Trial category	No. of trials	No. of patients	Absolute benefit at 5 years	Risk reduction	P value
All trials	65	10,850	4%	10%	<0.0001
Adjuvant	8	1854	1%	2%	0.74
Induction	31	5269	2%	5%	0.10
Induction with PF	15	2487	5%	12%	0.01
Concomitant	26	3727	8%	19%	<0.0001

PF cisplatin +5-fluorouracil combination

were four large randomized controlled trials which irrefutably showed benefit of this combined modality approach [29–32].

The first two decades in 2000 are fascinating in that new treatment approaches, initially targeted therapies, but later also immunotherapies came forward [33–40]. Both targeted therapies (in particular cetuximab) and immunotherapies (especially immune checkpoint inhibitors [CPIs]) have been practice changing. Not only were they extensively studied in the recurrent/metastatic (R/M) disease setting [34, 38–40], they also found their way in patients with LA-HNSCC [35, 36], although for CPIs that has not been fully developed yet. There arose a renewed interest in ICT since the introduction of the taxanes, which proved to be active compounds for this disease [41, 42]. Two randomized controlled trials (RCTs), one in the US and one in Europe, showed that adding docetaxel to the PF combination made this regimen more efficacious, better tolerable for the patients, did not lead to a negative effect on quality of life (QoL), and was cost-effective [43–46]. This so-called TPF regimen is now considered standard for those situations in which ICT is indicated.

Comparison of the Practice Changing TPF Protocols (TAX 323/EORTC 24971 and TAX 324)

The results of the European TPF regimen (protocol TAX 323/EORTC 24971) and the American TPF regimen (TAX 324) were published back to back in the New England Journal of Medicine in 2007 [43, 44]. In both phase III trials, LA-HNSCC patients were randomized to receive three (TAX 324) or four (TAX 323/EORTC 24971) cycles of TPF or PF as induction before local treatments. Details on the respective regimens can be found in Table 11.3. The studies were executed in different patient populations. TAX 323/EORTC 24971 included only patients with previously untreated, unresectable LA-HNSCC, while in TAX 324 there was a mixture of patients involved, i.e. those with either unresectable disease or disease of low surgical curability, as well as patients with LA-HNSCC who were candidates for organ preservation. Both studies also differed in the local treatment part of the protocol following the induction phase. In TAX 323/EORTC 24971, patients who did not have progressive disease underwent conventionally fractionated RT within 4 to 7 weeks after the completion of chemotherapy (total dose, 66 to 70 Gy) or accelerated or hyperfractionated regimens (total maximum dose 70 Gy for the accelerated

Table 11.3 TPF regimens in accordance with TAX 323/E ORTC 24971 and TAX 324

Study	TPF regimen
TAX 323/EORTC 24971 [44] – four cycles of TPF	Docetaxel (75 mg/m^2) as a 1-hour infusion on day 1 Cisplatin (75 mg/m^2) as a 1-hour infusion on day 1 5-FU (750 mg/m^2/day) by continuous IV infusion, day 1–5
TAX 324 [43] – three cycles TPF	Docetaxel (75 mg/m^2) as a 1-hour infusion on day 1- Cisplatin (100 mg/m^2) over a period of 0.5–3 hours 5-FU (1000 mg/m^2/day) by continuous IV infusion, day 1–4

regimen and 74 Gy for the hyperfractionated regimen), decided before the start of the protocol for each institution. Neck dissections could be performed, if indicated, before or after the RT. In TAX 324, all patients were assigned to receive CCRT beginning 3 to 8 weeks after the start of the third cycle of ICT (day 22 to day 56 of cycle 3). Weekly carboplatin at an area under the curve of 1.5 was given as an intravenous infusion during a 1-hour period for a maximum of seven weekly doses during the course of RT. The definitive curative radiation dose administered to the primary tumor was between 70 and 74 Gy, administered as fractions of 2 Gy per day 5 days per week. The dose administered to uninvolved lymph nodes was at least 50 Gy. Involved lymph nodes were to receive 60 to 74 Gy, depending on whether an elective neck dissection was indicated after completion of treatment. Surgery was performed 6 to 12 weeks after completion of chemoradiotherapy in patients who had an initial nodal stage of N2 and a partial response to ICT or N3 disease, or residual disease after chemoradiotherapy. Surgery was also allowed for patients who did not complete chemoradiotherapy and had resectable residual disease at the primary site or in the neck.

Both trials concluded that the overall response rate with TPF was significantly (TAX 323/EORTC 24971) or numerically (TAX 324) higher than with PF. Both TPF regimens also clearly demonstrated survival benefit over PF ICT (Fig. 11.2). About three-quarters of the patients completed both TPF and RT per protocol and 24% to 29% had treatment delays during ICT. As mentioned above, the TAX 323/EORTC 24971 regimen was associated with a more favorable safety profile than the previously standard PF regimen, likely owing to the lower overall doses of the cisplatin (75 mg/m^2 instead of 100 mg/m^2 on day 1) and 5-FU (750 mg/m^2/day x5 instead of 1000 mg/m^2/day x5). This resulted in a lower frequency of grade 3/4 stomatitis, nausea/vomiting, dysphagia, and thrombocytopenia [44]. Patients in the

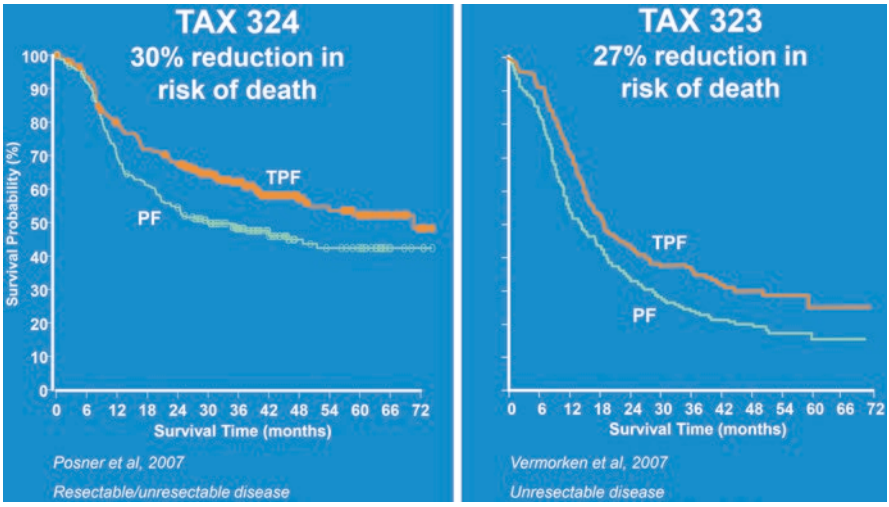

Fig. 11.2 Landmark trials of TPF versus PF in locoregionally advanced HNSCC

TPF arm had fewer treatment delays then did those in the PF group despite differences in peak neutropenia during ICT in the TPF group [43, 44]. The superiority of TPF over PF has been confirmed in a meta-analysis of pooled data from five phase III studies, including the two mentioned above [47]. This analysis concluded that the TPF regimen, compared to the PF regimen, led to benefits in progression-free survival (PFS), overall survival (OS), locoregional failure rate (LFR) and distant failure rate (DFR). Nevertheless, despite the fact that this meta-analysis confirmed that TPF was a better ICT than PF, some critical remarks were made with respect to the pooling methodology used on the five rather heterogeneous studies, the missing treatment failure data in the participating two Spanish trials [48, 49] and the EORTC trial [44], and the different follow-up treatments that were applied for the ICT responders and the ICT non-responders [50]. However, what this meta-analysis did not do, was changing the standard of care in patients with advanced HNSCC, i.e. concurrent chemoradiotherapy.

The main question that remained for most clinicians was not whether TPF was superior to PF, there was a unanimous feeling about that, but it was whether the sequential use of ICT and local therapy was superior to the concurrent use of chemotherapy and radiation. Although two previous phase III studies demonstrated benefit for ICT → RT versus RT alone, in particular in patients with inoperable/unresectable disease [51, 52], the role of ICT in connection to CCRT in patients with inoperable/unresectable disease remained controversial, due to difficulties in trial design, execution or insufficient patient accrual [53–57]. However, what most of these studies had in common was the fact that the toxicity with the combined approach was increased. Febrile neutropenia could be found as high as 11% [53] and toxic deaths have been reported even up to 6% [57]. Moreover, the use of ICT could compromise the completion of subsequent chemoradiation, which can have a deleterious effect, not only on local control, but also on survival [58]. Therefore, less toxic schemes have been investigated, such as a modified TPF regimen [59], a weekly carboplatin (AUC2) and paclitaxel (135 mg/m^2) regimen for six consecutive weeks [60] and the TPEx regimen (docetaxel and cisplatin both 75 mg/m^2 every three weeks for three cycles plus weekly cetuximab 400/250 mg/m^2) [61] are all of interest. A randomized controlled trial comparing TPF to modified TPF in fit patients is currently ongoing [62].

When to Use Induction Chemotherapy in Head and Neck Squamous Cell Cancer

For Larynx Preservation

There is an established role for ICT in larynx preservation programs for patients who otherwise would be candidates for total laryngectomy. When Wayne State University published its positive experience with the PF regimen in previously

untreated patients with head and neck cancers [21] and thereafter showed that responders nearly all (97%) were controlled by subsequent radiation, and the others did much less [25], an new concept of treatment was born, i.e. using ICT as a selection procedure. This concept was first tested in randomized trials with in the control arm patients that received the standard of care at that time, i.e. total laryngectomy with postoperative RT, and in the experimental arm patients that were treated with PF ICT followed in responders by RT and salvage surgery if required. These first generation trials are summarized in Table 11.4. The conclusions of these two trials were that the concept of larynx preservation, with the use of ICT as a selection procedure, was safe, kept the larynx in place in about two thirds of the patients and had no negative impact on survival [63–66]. The next generation of larynx preservation trials did not look only to how many larynxes could be kept in place, but took more notice of the function of the larynx. In that context a new definition of larynx preservation came forward "laryngoesophageal dysfunction-free survival" that included death, local failure, salvage laryngectomy, tracheotomy, or feeding tube at 2 years or later [67].

With the milestone of concurrent chemoradiotherapy in the second half of the 1990s (see above) next trials compared ICT followed by RT with CCRT or with alternating CT and RT [68–71]. The results of these studies are summarized in Table 11.5.

Table 11.4 Induction chemotherapy trials for larynx preservation: first generation

Study Group	Tumor size and stage	Treatment arms	No. of pts	Survival (at 5 & 10 years)	LP
VA	Larynx	TL + RND + RT	332	45% & 30%	
1991 [63]	T1-T4, N2-3	PF × 3 → RT[a]		42% & 25%	64%
EORTC	Hypopharynx	TL + RND + RT	202	33% & 14%	
1996, 2012 [64, 65]	T2-T4, N0-3[b]	PF × 3 → RT[a]		38% & 13%	62%

VA Veterans Affairs Laryngeal Cancer Study Group, *LP* larynx preservation, *TL* total laryngectomy, *RND* radical neck dissection, *RT* radiotherapy, *PF* cisplatin 100 mg/m^2 d1 + 5-FU 1000 mg/m^2, d1-5

[a]The non-responders received surgery + RT

[b]N2c was excluded

Table 11.5 Induction chemotherapy trials for larynx preservation: second generation

Study Group	Tumor size and stage	Treatment arms	No.of pts	Survival (at 5 & 10 years)	LP (10 years)
RTOG 91-11	Glottic and supraglottic	PF[1] × 3 → RT	173	58% & 39%	68%[a]
2003, 2013 [70, 71]	N0-1, N2, N3	CCRT (cisplatin)	172	55% & 28%	82%[a]
	T2, T3[+], T3[-], T4	RT	173	54% & 32%	64%[a]
EORTC 24954	Larynx and hypophar.	PF[1] × 2-4 → RT	224	49% & 34%	56%[b]
2009, 2016 [68, 69]	T2-T4, N0-N2	PF[2] alternate with RT	226	52% & 32%	56%[b]

LP larynx preservation, *PF1* cisplatin 100 mg/m^2, d1 + 5-FU 1000 mg/m^2, d1–5, *CCRT* concurrent chemoradiotherapy, *RT* radiotherapy, *PF2* cisplatin 20 mg/m^2/d, d1–5 + 5-FU 200 mg/m^2/d1, d1–5, *T3+* with fixed cord involvement, *T3−* without cord fixation

[a]*LP* larynx in place, function (voice quality, swallowing function, QoL questionnaire) evaluated

[b]*LP* larynx in place, no tumor, no tracheotomy, no feeding tube

The alternating arm in the EORTC trial had a lower dose of 5-FU (total 1000 mg/m^2 instead of 5000 mg/m^2 per cycle) and a lower total dose of radiation (60Gy instead of 70 Gy). This resulted in less grade 3 or 4 mucositis (32% in the sequential arm vs 21% in the alternating arm) and late severe edema and/or fibrosis was observed in 16% of the patients in the sequential arm versus 11% in the alternating arm. No significant differences in outcome between the two arms of the study were observed. Combined with the toxicity data the results favored slightly the alternating arm. However, due to the organizational difficulties in delivering this alternating regimen in daily practice, this regimen is rarely used [66, 68, 69]. RTOG 91–11 is a crucial trial, in that it is the only trial that compares sequential treatment (PF → RT) with cisplatin-based CCRT and a RT alone arm [70, 71]. There have been several analyses reported, all showing a higher larynx preservation rate with the CCRT arm compared with the ICT arm or the RT alone arm. At the long-term follow-up analysis, both chemotherapy regimens significantly improved laryngectomy-free survival (LFS; primary endpoint) compared with RT alone. Overall survival did not differ significantly, although there was a possibility of worse outcome with CCRT relative to ICT (HR, 1.25; 95% CI, 0.98 to 1.61; P = .08). No difference in late effects was detected, but for deaths not related to the study cancer, there was a significant disadvantage for the CCRT group compared to the ICT group (52.8% vs 69.8%, respectively, p = 0.03).

With the revival of ICT in the first decade of the twenty-first century, it was to expect that the comparison of TPF versus PF would also be studied in the larynx preservation setting. This was executed by the GORTEC (Groupe Oncologie Radiotherapie Tete Et Cou) in a phase III protocol [72]. Protocol 2000–1 was conducted in 220 patients with locoregionally advanced laryngeal and hypopharyngeal cancer, who were eligible for total laryngectomy. The European TPF schedule was compared with the standard PF regimen and three cycles at a 3-week interval were planned. The primary endpoint of the study was larynx preservation and larynx preservation was defined as a larynx in place without tumor, tracheostomy or feeding tube. Ultimately, 213 patients were treated with a median follow-up of 105 months [72, 73]. The larynx preservation rate was significantly higher with TPF than with PF (at 10 years 70.3% versus 46.5%, P = .01 in the TPF vs PF arms, respectively). The 10-year laryngeal dysfunction-free survival was 63.7% with TPF and 37.2% with PF, which was again significantly different [73]. There was no significant difference in 5-year or 10-years OS, or disease-free survival (DFS). Statistically fewer grade 3–4 late toxicities occurred with the TPF regimen compared with the PF arm (9.3% vs 17.1%, P = .038). Support for this observation comes from a subgroup analysis of the TAX 324 study, that included only patients with advanced laryngeal and hypopharyngeal cancer. Among those that had operable disease (TPF, n = 67; PF, n = 56), LFS was significantly greater with TPF (HR: 0.59; 95% CI: 0.37–0.95; P = 0.030). Three-year LFS with TPF was 52% versus 32% for PF [74].

For larynx preservation ICT with TPF is one of the two approaches that can be considered as a standard approach for patients with advanced laryngeal or hypopharyngeal cancer, who are not eligible for partial laryngectomy. The

other approach is cisplatin-based CCRT. Overall, T4 disease and tumors extending to the post-cricoid area are not eligible for larynx preservation. It is unclear for the moment which option is best. The two approaches are presently being compared in the ongoing SALTORL trial (GORTEC 2014–03).

For Treatment Intensification

As mentioned earlier, the main question that remained for most clinicians was whether the use of TPF before the cisplatin-based CCRT would lead to survival benefit. The background for that can be found in the individual patient-based meta-analysis (MACH-NC) by Pignon et al., initially published in 2000, but updated in 2009 [75]. In that analysis, a 6.5% 5-year absolute survival benefit was demonstrated for the concurrent chemotherapy/RT approach [75]. No overall survival benefit was observed with the ICT schedules, although a marginal improvement was noticed in trials that made use of the PF combination. Patterns of failure differed between the two approaches. ICT significantly improved the rate of distant metastases (HR, 0.73; 95% confidence interval [CI] 0.61 to 0.88; p = .001), but did not influence locoregional failure. However, CCRT markedly improved locoregional control (HR, 0.74; 95% 0.70 to 0.79; p < .001) with a significant but less impressive improvement in distant control (HR, 0.88; 95% CI, 0.77 to 1.00; p = .04). It seemed therefore reasonable to assume that combining both approaches could have a complementary effect on outcome. The five randomized controlled trials that compared ICT → CCRT versus CCRT alone are summarized in Table 11.6 [53–57]. Four of the five trials showed no impact of ICT on survival. The Italian study (with two types of concomitant regimens, cisplatin/5-FU + RT or cetuximab + RT) did show a survival benefit, but subgroup analysis did not show benefit for patients who received potentiation with cisplatin and fluorouracil. Two trials had accrual problems and stopped early before reaching the required number of patients, and two studies had difficulties in trial design or trial performance. Therefore, the role of ICT given before CCRT on the basis of these five trials still remains controversial.

Two meta-analyses on the usefulness of ICT before CCRT in patients with LA-HNSCC concluded that, although ICT reduced the occurrence of distant failures, this did not translate into a significant survival benefit [76, 77]. However, the most recent systematic review and Bayesian network meta-analysis, comprising 57 trials and 15,723 patients indicated that IC with TPF was significantly superior against CCRT with cisplatin (HR 0.73 95% credible interval [CrI] 0.58–0.92) [78]. Therefore, it seems that over time, more data are pointing at a real value of the TPF regimen when used in addition to cisplatin-based CCRT. **However, as indicated above, individual randomized studies so far have not given an clear answer as to whether ICT is useful for treatment intensification in daily practice. Therefore, further positioning of ICT with CCRT as standard treatment for LA-SCCHN will come from more RCTs directly comparing ICT→ CCRT with CCRT in the appropriate patient population.**

Table 11.6 Randomized trials of induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced HNSCC

Investigators/Trial	Population	Regimens	Survival↑	Tox↑
Hitt et al/TTCC [53]	439 pts, stage III/IV	TPF (or PF)x3→CCRT(P)	No	Yes
	Prim. endpoint: PFS	CCRT (cisplatin)		
Haddad et al/ PARADIGM [54]	145 pts, N2 and N3	TPFx3→CCRT (C or Doce)	No	Yes
	Prim. endpoint: OS	CCRT (cisplatin)		
Cohen et al/DeCIDE [55]	285 pts, N2 and N3	TPFx2→CCRT (THF)	No	Yes
	Prim. endpoint: OS	CCRT (THF)		
Ghi et al./GSTTC [56]	421 pts, stage III/IV	CCRT(PF) w/wo prior TPF	Yes[a]	Yes[b]
	Prim. endpoint: OS	BRT(cet.) w/wo prior TPF		
Geoffrois et al./GORTC 2007-02 [57]	370 pts, N2b/c, N3	TPFx3→BRT (cetuximab)	No	Yes
	Prim. endpoint: 2-yPFS	CCRT (carbo/5-FU)		

T docetaxel, *P* cisplatin, *F* 5-fluorouracil, *CCRT* concurrent chemoradiotherapy, *C* carboplatin, *Doce* docetaxel, *Cet* cetuximab, *THFX* docetaxel, fluorouracil and hydroxyurea, *BRT* bioradiation with cetuximab

[a]PFS and OS were significantly better in the ICT arms, but subgroup analysis did not show any benefit for patients who received radiation with cisplatin and 5-FU after TPF

[b]More severe neutropenia in the ICT arms, other toxicities were not significantly different

Results from the DeCIDE trial and the GORTEC 2007–02, showing fewer distant metastases in the ICT arm of the studies, suggest that there still may be patients at very high risk for developing distant metastases who could benefit from ICT. Some improvement in the N-staging in the most recent American joint Committee in Cancer staging system has been made. Features such as low neck nodes and matted nodes (a proxy for extranodal extension) are of interest in that respect. In a retrospective analysis of 321 patients treated with three cycles docetaxel/cisplatin ICT followed by CCRT (weekly cisplatin), Kim et al. reported that lower neck node involvement (level IV, Vb, and supraclavicular regions) ($p = 0.008$) and poor response to ICT ($p < 0.001$) were associated with a significantly inferior distant metastasis-free survival [79].

In contrast to the patterns of failure seen in p16-negative disease, distant failure constitute a considerable portion of treatment failures in patients with p16-positive disease [80]. The Toronto group, in their analysis, pointed at patients with T4 and N3 disease being at high risk for distant failure. In a retrospective study, comprising patients with p16-positive OPSCC with low-neck (level IV and/or Vb) and/or N3 lymphadenopathy, being at high risk of distant failure, 44 receiving ICT (docetaxel/platinum w/wo 5-FU) followed by CCRT (43 receiving platinum, 1 cetuximab) were compared with 44 patients receiving CCRT alone (38 receiving platinum, 6 cetuximab) [81]. The median age of the patients in the CCRT group was somewhat

higher (61 vs 56 years, p = 0.02). Disease control and survival outcomes were reported after adjusting for age, T-stage, N-stage and smoking status. A significant difference in distant metastases (adjusted HR 0.32, p = 0.02) and PFS (adjusted HR 0.46, p = 0.03) was observed, while OS showed a trend (adjusted HR 0.48, p = 0.09), all in favor of ICT at 3 years [81]. Finally, also protein expression biomarkers of aggressive disease could be of use in identifying patients who could benefit from ICT [82]. Examples are elevated expression of cyclin D1 and GDF15 expression as predictive markers for benefit of TPF, and acetylated tubulin as a marker for sensitivity to taxane chemotherapy [83–85]. There are also indications that excision repair cross-complementing 1 (ERCC1) expression may be of importance [86, 87]. Bišof et al. [86] reported, based on a meta-analysis of 1288 HNSCC patients who had been treated with platinum-based chemotherapy, that ERCC1 might be a predictive and prognostic factor for individualized therapies for HNSCC patients. In a study of 64 patients with oro- and hypoharyngeal cancers, who received PF induction chemotherapy before definitive local treatment, Hasegawa et al. concluded that ERCC1 was predictive for response to PF and could select those who were candidates for organ preservation [87]. The study included four clinical variables (age, sex, T-class and N-class) and 22 biomarkers which were tested on pretreatment biopsies. In multivariate analysis, next to T-class, ERCC1 expression came forward as the only independent predictive marker for response. The investigators considered that both a DNA repair pathway and an apoptosis pathway are pivotal to the mechanism underlying response to chemotherapy and suggested that further studies on ERCC1 polymorphisms and mutations and assessing apoptotic response associated with p53 activation in HNSCC were needed to clarify genetic associations with response to chemotherapy in HNSCC patients [87].

For Borderline Resectable or Unresectable Oral Cavity Cancer

Oral cavity cancer is one of the most common malignancies worldwide with geographic variation in incidence and mortality [88]. Higher incidence rates are observed in developing countries compared to developed countries. Bangladesh, Pakistan and India have the highest incidence rates of oral cavity cancer where it is the most common cancer in males and the second in females after breast cancer. As result of delay in presentation, most patients in these countries are diagnosed with advanced disease [89]. Surgery is usually the preferred upfront treatment in patients with oral cavity cancer. However, surgical resection cannot be achieved in many cases with advanced disease without major impact on patient's quality of life. The optimal care of these patients is challenging when surgical treatment is not possible. This is nicely summarized in the recent publication by Alzahrani et al. [89].

The role of induction chemotherapy in patients with resectable oral cavity cancer has been tested in two RTCs and both trials showed a negative outcome [90–92]. Licitra et al. [90] reported on 195 patients with resectable oral cavity cancer (stage

T2-T4 (>3 cm), N0-N2, M0), who were randomized to receive three cycles of PF before surgery versus surgery alone. High-risk patients (positive resection margins, extracapsular nodal spread, nodal disease [N2 or N3], vascular invasion, or perineural invasion) underwent adjuvant RT. There were three toxic deaths in the chemotherapy arm, but ICT did not lead to an improvement in OS (at 5 years 55% in both arms), locoregional relapse or distant failure. An update of this study with a median follow-up of 11.5 years showed similar results with regard to clinical outcomes [91]. Interestingly, in the late follow-up of the patients in this trial, the control group showed a higher incidence of fibrosis (40% vs 22% in chemotherapy arm) and more grade 2 dysphagia (14% versus 5% in the chemotherapy arm), which the authors ascribed to less extensive surgery carried out in the chemotherapy group (31% versus 52% in control group) and less patients receiving postoperative RT (33% versus 46% in control group). Zhong et al. [92] randomized 256 patients with stage III or IVA oral squamous cell cancer to receive 2 cycles of TPF followed by surgery and adjuvant RT or surgery and adjuvant RT alone, again showing no difference in survival. A recent meta-analysis of individual patient data of these earlier mentioned two studies confirmed the lack of clinical benefit from ICT [93]. Contrary to that, for cN2 patients, an OS benefit was found in favor of ICT ($p = 0.04$)**. Taken together, it can be concluded that there is no evidence for routine use of ICT in resectable oral cavity cancer.**

The main goal of using induction chemotherapy before surgery is to convert borderline resectable disease or clearly unresectable disease to technically resectable disease. Although there are no randomized trials to prove this concept, there are studies, most of them coming from India (not surprising with 64% of patients have clinical stage IV disease versus 2.2% in the US), that lead to the same conclusion, i.e. about 30% will become resectable, and patients in whom this is possible will do better than those in whom this not possible [94–98]. Similar results have been reported by our colleagues in Taiwan [99]. Extension of the tumor to the base of skull, prevertebral muscles and encasement or invasion of the carotid artery are absolute contraindication to surgery. In addition, Patil et al. [96] adopted criteria specifically for oral cavity cancer. These include: (1) buccal mucosa primary with diffuse margins and peritumoral edema, going up to or above the level of zygomatic arch and without any satellite nodules, (2) tongue primary (anterior two-thirds) with the tumor extending up to or below the level of the hyoid bone, (3) extension of tumor of anterior two-thirds of the oral tongue to the vallecula, (4) extension of tumor into the high infratemporal fossa, as defined by extension of tumor above an axial plane passing at the level of the sigmoid notch, and (5) extensive skin infiltration impacting the achievement of negative margin. The Indian studies mentioned above are summarized in Table 11.7. Febrile neutropenia in some of these studies was reported to be a major problem. **Nevertheless, according to in particular our Indian colleagues, who see these far advanced stages of disease much more frequently than we do in the higher income countries, ICT may be considered in patients with unresectable or borderline resectable oral cavity cancers, as it may increase the chance of resectability and subsequently might improve outcomes.**

Table 11.7 Induction chemotherapy in unresectable/borderline resectable locally advanced OSCC*

Investigators	No.of pts	Disease stage (T)	Treatments	Outcomes
Rudresha et al. [94]	116	IV (T4b)	TPF or TP (2–3x) → S	Resect. 19%; mOS 19.7 mo; mOS with NST 7.1 mo
Joshi et al. [95]	110	IV (T4b)	TPF or TP (2–3) → S	Resect. 30.9%; mOS 18.0 mo; mOS with NST 6.5 mo
Patil et al. [96]	721	IV (T4a/ T4b)	TP or TPF (2x) → S	Resect. 43%; mOS 19.6 mo; mOS with NST 8.16 mo; 24 mo LRCT rate 32% vs 15%
Rudresha et al. [97]	80	IV (T4a)	TP (2–3) → S	Resect. 23.8%; mOS 16.9 mo; mOS with NST 8.8 mo

OSCC oral squamous cell carcinoma, *TPF* docetaxel/cisplatin/5-FU, *TP* taxane/platinum, *mOS* median overall survival, *NST* nonsurgical treatment, *LRCT* locoregional control, *Resect*. resectable, *Patil's criteria

As a Selection Tool for RT Dose de-Escalation in HPV-Positive OPSCC

Treatment of patients with HPV-positive OPSCC is rapidly evolving and challenging the standard of care of definitive RT with concurrent cisplatin [100]. Several de-escalation approaches are under study, among which are radiation alone instead of radiation combined with cisplatin, radiation combined with cetuximab instead of radiation combined with cisplatin, transoral surgery followed or not by postoperative RT and ICT followed by decreased radiation dose and/or volumes for good responders. In the latter setting, ICT is used as a tool to stratify patients by treatment response. De-escalation approaches are getting major attention in patients with locoregionally advanced OPSCC, because these patients have overall a better prognosis and if treated curatively with current standard treatment (CCRT), are confronted with possible long-term toxicity issues, such as feeding tube dependency ≥2 years post RT, pharyngeal dysfunction (dysphagia), laryngeal dysfunction, mucositis, or other toxicities (e.g. infection, fistula, weight loss etc). Three US trials have reported on ICT approaches, i.e. ECOG 1308 (NCT 01084083), the Quarterback trial (NCT 01706939) and the OPTIMA HPV trial (NCT 02258659).

ECOG 1308 was a single arm phase II study in which patients with HPV-associated OPSCC (the majority having T1-3N0-N2b disease and a history of ≤10 pack-years of smoking) were treated with three cycles paclitaxel, cisplatin and cetuximab, followed by cetuximab concurrently with intensity-modulated radiation therapy (IMRT). The purpose of the study was to evaluate whether a clinical CR to ICT could select patients for reduced radiation dose as a means of sparing late sequelae [101]. Patients with CR at the primary received a reduced RT dose (54 Gy instead of 69.3 Gy). Involved lymph nodes received 69.3 Gy unless they also were judged to have completely responded. The primary end point was 2-year PFS. Of the 90 patients enrolled, 80 were evaluable and 77 received three cycles of ICT. Fifty-six patients (70%) had a CR to the ÌCT at the primary site and 51 patients continued

to cetuximab with IMRT 54 Gy. At a median follow-up of 35.4 months, the 2-year PFS and OS rates were 80% and 94% among those 51 patients. These figures were most promising (96% and 96%, respectively) for the more favorable group of patients (i.e. having <T4, < N2c and ≤ 10 pack-years of smoking). At 12 months, significantly fewer patients treated with the reduced RT dose had difficulty swallowing solids (40% v 89%; P = .011) or had impaired nutrition (10% v 44%; P = .025). The authors concluded that a reduced-dose IMRT with concurrent cetuximab was worthy of further study in favorable-risk patients with HPV-associated OPSCC.

The Quarterback trial, a phase III trial in patients with locally advanced p16-positive OPSCC and ≤ 20 pack years smoking, made use of three cycles of the American TPF regimen and clinical responders who were HPV-positive by type-specific PCR were randomized 1:2 to standard-dosed (sd) IMRT (70 Gy) or reduced-dosed (rd) IMRT (54 Gy), both combined with weekly carboplatin at AUC 1.5. The endpoints of the study were 3-year PFS and OS. The planned number of patients was 365 with 240 in the experimental arm. The original statistical plan was revised because of poor accrual. The trial terminated after 20 evaluable patients were randomized and treated (8 with sdCCRT and 12 rdCCRT). Sixteen (80%) were HPV16-positive and 4 (20%) had other high-risk (HR) variants. Fourteen (70%) had high risk features: T4, N2c, or N3. Median follow up was 56 months (range 42–70). Three-year PFS/OS for sdCCRT and rdCCRT were 87.5% vs 83.3% (log-rank test, p = 0.85), respectively. All three failures were locoregional within 4 months of completion of CCRT, 2 were in HR variants. As mentioned by the authors, the small sample size limits the interpretation of the outcome, but the study supports the potential clinical benefit of radiation dose reduction after ICT as a treatment strategy [102].

In the OPTIMA HPV trial, patients were classified as low-risk (LR) (≤T3, ≤N2B, ≤10 pack year history) or high-risk (HR) (T4, ≥N2c, >10 pack year history). Patients received ICT of three cycles of dose dense carboplatin and nab-paclitaxel. LR patients with 50% response received 50 Gray (Gy) RT (RT50) while LR patients with 30%–50% response or HR patients with 50% response received 45 Gy CCRT (CCRT45). Patients with lesser response received standard-of-care 75 Gy CCRT (CCRT75). The primary end point was 2-year progression-free survival compared with a historical control of 85%. Secondary end points included overall survival and toxicity. Sixty-two patients (28 LR/34 HR) were enrolled [103]. Of the LR patients, 71% received RT50 while 21% received CRT45. Of the HR patients, 71% received CRT45. With a median follow-up of 29 months, 2-year PFS and OS were 95% and 100% for LR patients and 94% and 97% for HR patients, respectively. The overall 2-year PFS was 94.5% and within the 11% non-inferiority margin for the historical control. Grade ≥ 3 mucositis occurred in 30%, 63%, and 91% of the RT50, CCRT45, and CCRT75 groups, respectively (P = 0.004). Rates of any PEG-tube use were 0%, 31%, and 82% for RT50, CCRT45, and CCRT75 groups, respectively (P < 0.0001) [103]. This decreased over time, being at 12 months 0%, 4% and 9%, respectively. Updated information was presented at ASCO 2020, now including 107 patients that were treated according to the same lines and now with a median follow-up of

36 months [104]. Overall, 94% of patients were alive at last follow-up (98% LR; 89% HR). Three patients developed a recurrence (2 HR and 1 LR); 2 local and 1 at distance. This OPTIMA approach demonstrated excellent oncologic and functional outcomes with long-term follow-up.

Despite these promising results, clinicians should refrain from de-escalation approaches outside clinical trials for this moment, because the safety of these approaches are still unclear. This has been reinforced by unexpected negative outcomes of two RCTs, in which cetuximab plus RT was compared with the standard-of-care cisplatin-based CCRT in p16-positive OPSCC [105, 106]**.**

Oligometastatic Disease

Another area of potential interest for the applicability of induction chemotherapy is oligometastatic disease. It is estimated that 5–47% (mean 15%) of patients will have distant metastases during the course of the disease [107]. The Surveillance Epidemiology and End Results (SEER) database revealed that 19% of patients with oral cavity or pharynx cancer presented with distant metastases at diagnosis [108]. The most common site of metastases from HNSCC is the lung accounting for up to 70% to 85%, followed by metastases to the bone (up to 20%) and liver (up to 10%). Other organs such as the brain, mediastinum, skin and bone marrow occur even more rarely [109]. There are different definitions of oligometastases for different cancers, but a consensus definition is five or fewer sites of metastatic disease [109]. Patients with oligometastatic HNSCC can be divided in two groups; (1) those who present with metastatic disease at initial diagnosis, i.e. synchronous distant metastases, and (2) those who have developed the metastatic lesions during their surveillance after their definitve treatment, the so-called metachronous distant metastases, with or without locoregional disease relapse.

Considering all patients with metastatic HNSCC as one group that should be treated with systemic therapy for palliation might not be correct. The contemporary standard of care systemic therapies result in a median survival of 10.1 to 13.6 months and it is unclear yet whether the treatment with immune checkpoint inhibitors will lead to cure [40, 110]. However, metastatic disease in HNSCC covers a wide range of disease presentations, depending not only on the site from which these metastases are originating, but also on the tumor biology and kinetics, whereby metastatic disease may vary from widely disseminated disease to oligometastatic disease.

Oligometastatic disease is a moving concept not only defined by its phenotypic metastatic burden but also by the ability to perform metastatic-directed treatments [107]. Advances in minimally invasive surgery and whole body stereotactic hypofractionated radiation therapy have opened an avenue to treat metastases in a safe, well-tolerated and relatively cost-effective manner. In a retrospective series from Germany, the authors noted a significant survival benefit for HNSCC patients who

received a specific therapy regarding distant metastases irrespective of localization as compared to a matched control cohort [111]. An analysis of patients with metastatic HNSCC in the National Cancer Database (NCDB) revealed that the patients who received high-intensity local treatment (defined as radiation doses ≥60 Gy or oncologic resection of the primary tumor) and systemic therapy had a 13% improvement in 2-year overall survival(OS) compared to patients receiving systemic therapy alone [112]. It is beyond the scope of this chapter on induction chemotherapy to discuss extensively the treatment of oligometastatic disease and the participation of local therapies therein. Suffice to say that currently, due to the lack of randomized but also sufficiently powered prospective trials, no firm recommendations can be given on how to optimally treat oligometastatic disease. However, ablative techniques have already penetrated into routine clinical practices in high-volume centers [113].

The role of induction chemotherapy in this context is primarily concerning synchronous metastatic disease at first diagnosis. Singular cases can be found in the literature were upfront chemotherapy is given with curative intent. Therefore strategies combining induction chemotherapy and upfront metastasis-directed treatments prior to locoregional therapy for the primary tumor can be anticipated [82].

Where to Use Induction Chemotherapy

Toxicity is an issue of ICT, in particular when there is not much experience with the contemporary ICT regimens. With the European TPF regimen, as given in TAX 323/EORTC 24971 [44], i.e. with prophylactic antibiotics [ciprofloxacin from day 5–15] in each cycle and dexamethasone given before the start of each cycle to prevent docetaxel-related hypersensitivity reactions, skin toxicity and fluid retention, common (≥5%) grade 3–4 adverse events included: neutropenia (76.9%), leukopenia (41.6%), alopecia (11.6%), anemia (9.2%), infection (6.9%), febrile neutropenia (5.2%) and thrombocytopenia (5.2%). 6.2% of patients discontinued treatment due to adverse events and there were 2.3% toxic deaths. With the American TPF, as given in TAX 324 [43], premedication, prophylactic antibiotics and dexamethasone were given in the manner as in TAX 323/EORTC 24971, common (≥5%) grade 3–4 adverse events included: neutropenia (83%), stomatitis/mucositis (21%), nausea (14%), dysphagia (13%), anemia/febrile neutropenia/neutropenia infection/anorexia (each 12%), vomiting (8%), diarrhea (7%), infection (6%), and lethargy [5]. 6% of patients discontinued treatment due to adverse events related to treatment and there <1% deaths due to toxic effect of study medication.

Crucially in the safe use of TPF regimens is that it is being administered by experienced oncologists, familiar with the necessary protocols and supportive care requirements to ensure patient safety and maximize adherence throughout the treatment [114]. Adequate fluid management, especially on days 1–2 during TPF

administration is crucial in preventing renal toxicity, hypovolemia, and severe fatigue. Discussing the patient in multidisciplinary team (MDT) meetings is strongly advised, considering also additional matters such as patient's psychological and nutritional status, potential for palliative care, addiction services, and speech therapy. The importance of MDT meetings have been extensively discussed during THNO-5 [115]. MDT meetings have emerged as a practical necessity for optimal coordination among health professionals and clear communication with patients, and increasingly more attention is paid to psychological aspects, quality of life, patient's rights and empowerment, and survivorship. Moreover, it has become more and more clear that treatment in higher volume centers, and experience of the center in trial participation correlate with outcomes [116, 117].

Conclusions

For more than 10 years the PF regimen has been replaced by the TPF regimen as the standard ICT regimen [43, 44]. ICT has an established role for organ preservation in advanced laryngeal and hypopharyngeal cancer and the TPF regimen has been validated in that setting. There remains uncertainty about the benefit of the sequential approach of ICT followed by CCRT, despite the fact that ICT significantly reduces the occurrence of distant metastases. It seems therefore appropriate to further study ICT in patients who have the highest risk to develop distant metastases, in particular patients with low neck nodes and matted nodes. Moreover, further studies in patients with HPV-associated OPSCC at risk for distant failure (T4 or N3 disease) could be considered for that also. Retrospective data from India suggest that ICT may play an important role in converting borderline resectable disease or clearly unresectable disease to technically resectable disease. Therefore, larger randomized trials in patients with borderline resectable cancer of the oral cavity are needed to establish the benefit of induction chemotherapy in this setting. Data are available that suggest that ICT can be used as a tool to select HPV-associated OPSCC patients for dose and volume de-escalation of RT, and retaining excellent oncologic and functional outcomes. These approaches still need to be confirmed in adequately sized clinical trials. Outside clinical trials, the utility of ICT is restricted to uniquely pragmatic clinical scenarios, such as unavoidable delay in radiation or in the situation that RT is not tolerated or feasible. This can happen when there is severe pain from advanced disease or there is impending airway compromise or neurologic dysfunction that necessitates rapid initiation of treatment [82]. Future areas of research are the role of ICT in strategies whereby ICT is combined with upfront metastases-directed treatments, the usefulness of targeted agents or immune checkpoint inhibitors in the induction setting; studies in that direction have started. Finally, the application of radiographic, proteomic and genomic biomarkers will get attention to further define prognostic groups and guide treatment selection with greater precision.

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