European Archives of Oto-Rhino-Laryngology (2020) 277:245–254
https://doi.org/10.1007/s00405-019-05665-5

HEAD AND NECK

Single-cycle induction chemotherapy before chemoradiotherapy or surgery in functionally inoperable head and neck squamous cell carcinoma: 10-year results

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Received: 14 May 2019 / Accepted: 20 September 2019 / Published online: 3 October 2019

Abstract

Introduction The response to induction chemotherapy (IC) predicts local control after conservative treatment of laryngeal, meso- and hypopharyngeal head and neck squamous cell carcinoma (HNSCC) and can thus help to avoid surgery. Single-cycle induction chemotherapy may help to maintain a low local recurrence rate while keeping the overall toxicity manageable. However, long-term data on single-cycle IC response by tumor location is lacking.

Methods $N = 102$ patients with functionally inoperable primary HNSCC of the larynx ($n = 43$), hypopharynx ($n = 42$) or mesopharynx/tongue ($n = 17$) received one cycle of docetaxel (75 mg/m^2, d1) plus cisplatin (30 mg/m^2, d1-3) or carboplatin (AUC 1.5, d1-3) and a response evaluation 3 weeks later. Responders (≥ 30% tumor size reduction and ≥ 20% SUVmax decrease in ^{18}F-FDG PET/CT) were recommended chemoradiotherapy (CRT), and non-responders surgery.

Results The overall response rate was 72.5%. All 74 responders and 10 non-responders received primary CRT, and 18 patients received primary surgery after single-cycle IC. Overall 10-year local recurrence-free survival (LRFS) was 73.7%. Three-year LRFS was 88.2% (mesopharynx/tongue), 88.2% (larynx), and 73.3% (hypopharynx); $p = 0.17$. 3-year distant metastasis-free survival (DMFS) was 94.1% (mesopharynx/tongue), 88.0% (larynx) and 76.4% (hypopharynx); $p > 0.05$. This influenced the 3-year cancer-specific survival (CSS) for larynx (91.2%) vs. hypopharynx tumors (60.8%); $p = 0.003$, but CSS was not different to tumors in the mesopharynx/tongue (81.4%); $p > 0.05$.

Conclusions A single-cycle induction chemotherapy for HNSCC enables surgery plus adjuvant therapy as well as chemoradiotherapy. The long-term local and distant disease control was good but varied between tumors in the larynx and mesopharynx/tongue vs. hypopharynx.

Keywords Head and neck squamous cell carcinoma (HNSCC) · Induction chemotherapy · Single-cycle · Resection

Background

The value of induction chemotherapy (IC) before chemoradiotherapy (CRT) or surgery is controversial because of its additive toxicity and lack of additional oncological benefit. Although it increases the cytostatic load compared to CRT alone, it has no apparent benefits for progression or survival [1]. This also applies to patients with extensive lymph node involvement, whose have a particularly high risk of distant metastasis [2].

Evaluating the response to induction chemotherapy can, however, be useful for selecting patients for definitive conservative treatment vs. surgery [3]. Consequently, in this indication, clinicians often choose to forego additive full-dose chemoradiotherapy after 2–3 cycles of induction

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chemotherapy in favor of maintaining a lower side effect rate [4–6].

Alternatively, some investigators propose to shorten the induction protocol to a single cycle of induction chemotherapy as a chemoselection strategy in favor of the later concurrent administration of chemotherapy and radiation [7, 8]. However, experience with this chemoselection strategy is limited to case series with less than 100 patients with cancer of the larynx and/or mesopharynx [7, 8]. In 2008, our department developed a treatment protocol in which these patients receive taxane-based single-cycle neoadjuvant chemotherapy and a response-based recommendation for either surgery or CRT based on the University of Michigan treatment protocol [9].

The results of our first 10 years of experience with single-cycle induction chemotherapy in more than 100 patients will be presented in this article. In particular, we will break down the results by tumor location, because this regimen has been rejected for cancers in locations other than the larynx due to the lack of efficacy data [10].

Patients and methods

Inclusion criteria

Patients with, according to a surgical evaluation, functionally inoperable squamous cell carcinoma of the mesopharynx, larynx or hypopharynx with an eastern cooperative oncology group (ECOG) score between 0–2 and age under 78 years that were treated in our departments between May 2008 and July 20,717 were included in this retrospective study. The data was gained both from the clinical documentation and the cytostatics-providing pharmacy.

Induction chemotherapy regimen and response

Induction chemotherapy consisted of one cycle of docetaxel [75 mg/m^2, day (d) 1] plus cisplatin (30 mg/m^2, d1-3) or carboplatin (area under the curve (AUC) 1.5, d1-3). Patients with a renal clearance rate of < 60 ml/min or heart conditions that prohibit adequate hydration received carboplatin instead of cisplatin.

Tumor response assessment and definitive treatment recommendation

Tumor assessments were performed before (baseline) and 21–27 days after single-cycle induction chemotherapy. Each patient was evaluated by panendoscopy, ^{18}F-fluordesoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and, if indicated, contrast-enhanced computed tomography (CT) following a standard protocol.

Definitive treatment recommendations for the individual patients were based primarily on the endoscopic findings and, secondly, on the changes in glucose metabolism detected by ^{18}F-FDG PET/CT. A ≥ 30% decrease in endoscopic tumor size and a ≥ 20% maximum standardized uptake value (SUVmax) decrease in ^{18}F-FDG PET/CT standard uptake were the justification criteria for conservative treatment. Biopsy results were not considered in the decision-making process. The individual treatment recommendations were not binding on the patients, so they were free to ignore the recommendation and choose definitive CRT in the case of non-response or resection despite response. The uncertainties regarding the selection process were personally explained to each patient several times at multidisciplinary tumor board meetings.

Chemoradiotherapy

The CRT regimen consisted of conventionally fractionated radiotherapy (RT) to a total dose of 70–72 Gray (Gy) with target volume adaptation after 50 Gy and 60 Gy or, after 30 Gy, hyperfractionated accelerated RT with 1.4 Gy twice daily to a total dose of 70–72 Gy and chemotherapy with cisplatin (20 mg/m^2, d1-4, d29-32) or carboplatin (AUC 1, d1-4, d29-32) in combination with paclitaxel (d2, 5, 8, 11, 25, 34, 36 and 43) [9]. The switch from docetaxel to paclitaxel for CRT was due to more established treatment protocols for paclitaxel during concurrent chemoradiation, but there was only a federal drug approval for docetaxel for ICT [11]. Patients unable to undergo chemotherapy due to impaired hematopoiesis received cetuximab instead of paclitaxel.

Tumor resection and adjuvant therapies

Resection of the primary tumor, including neck dissection, with due regard to the use of organ-preserving techniques was the recommended treatment for non-responders. The intensity of the adjuvant therapies was determined by tumor stage. CRT was generally performed using the cytostatic agents cisplatin (20 mg/m^2, d1-5, d29-33) or carboplatin (AUC 1, d1-5, d29-33) and 5-fluorouracil (5FU; 800 mg/m^2, d1-5, d29-33).

Neck dissection after CRT

Patients with sonographic signs of vital lymph node metastases 6–10 weeks after definitive CRT and complete regression of the primary tumor received salvage neck dissection on the affected side of the neck. This was part of the treatment concept and was not classified as treatment failure.

Salvage surgery

Salvage surgery was to be attempted in patients with partial regression of the primary tumor 6–10 weeks after chemoradiotherapy. If the tumor was even vaguely suspicious, biopsy specimens were collected during panendoscopy.

Isolated local recurrences were treated by salvage surgery, if resectable. Organ removal due to functional issues was permitted but avoided when possible.

Statistical analysis

The endpoints of this retrospective study were overall survival (OS), cause-specific survival (CSS), disease-free survival (DFS), local control (LC), regional control (RC), and distant metastasis-free survival (DMFS). Cause-specific survival included death from head and neck squamous cell carcinoma (HNSCC), and disease-free survival was defined as the length of time after the end of primary treatment until the development of recurrence of the HNSCC. Head and neck tumors arising in other locations were not classified as local recurrences.

Survival time with an intact organ was defined as the time to organ removal, local recurrence or death. All time-dependent probabilities were calculated by Kaplan–Meier estimation and compared by log-rank test. If significant univariate differences were detected, multivariate tests of independence were also performed. Frequencies were compared using the chi-square test. Baseline characteristic of patients in the location groups were compared using the chi-square test and Kruskal–Wallis test.

Results

Patient characteristics

From May 2008 to July 2017, single-cycle induction chemotherapy was administered to 104 HNSCC patients at our department, 102 of whom returned for re-evaluation 3 weeks later. Two patients declined further diagnostic and treatment measures citing the good reduction of their symptoms; these two subjects survived for at least 3 months according to our records. The remaining 102 patients (19 women and 83 men) were included in the analysis. The cohort contained almost equal numbers of patients with carcinomas of the hypopharynx and larynx—the most common tumor locations. Over two thirds of the patients had few comorbidities (Charlson-Comorbidity-Index $2 \leq$), approximately one third had medium or many comorbidities (Charlson-Comorbidity-Index > 2). There were no differences between the tumor location groups at baseline (Table 1). Median follow-up was 41.0 months. Before or during therapy, 93 patients received a percutaneous endoscopic gastrostomy (PEG) tube to prevent nutrition issues due to dysphagia.

Response to single-cycle IC

Of the 102 included patients, 91 (89.2%) received single-cycle IC with docetaxel plus cisplatin, and the other 11 (10.8%) received docetaxel plus carboplatin. No patient died immediately after or as a result of single-cycle IC. Three weeks after single-cycle IC, 74 (72.5%) patients were classified as responders and 28 (27.5%) as non-responders based on the metabolic and clinical response criteria, i.e., 74 patients showed both a metabolic and an endoscopic response. No patient showed clinical progression of the primary tumor. All tumor locations had a similarly high likelihood of response to single-cycle IC (71 to 74%). Conversely, the likelihood of response decreased with T stage: 30 of 32 cases (93%) for T2 ≥ 28 of 42 cases (66%) for T3 ≥ 14 of 25 cases (56%) for T4 ($p = 0.02$).

Ultimately, 74 of 102 patients (72.5%) met the eligibility criteria and received primary CRT. Of the 28 patients formally classified as non-responders, 18 (17.6%) received surgery and 10 (9.8%) received chemoradiotherapy. Statistically, there were no differences in treatment assignments between tumor locations; overall $p > 0.05$ (Table 1).

Feasibility of chemoradiotherapy

It was possible to deliver CRT to a total dose of at least 68 Gy in all cases except one ($N = 84$). The exception was a woman with p16-positive oropharyngeal cancer who chose to discontinue RT at a dose of 58 Gy. One patient (male) achieved an equivalent dose in 2 Gy fractions (EQD2) of > 68 Gy on an initial hypofractionated regimen. Conventionally fractionated radiotherapy was administered in 37 (44%) cases and accelerated hyperfractionated radiotherapy was given after 30 Gy in 47 (56%) cases.

Radiotherapy was administered with no treatment break or a 1-day break in 75 cases (89.3%), with a 2–3-day treatment break in 6 cases (7.2%), and with a treatment break of 4–5 days in 3 cases (interruptions for device maintenance and holidays were also counted as breaks).

Regarding chemotherapy, there were no unplanned breaks in IC. During primary CRT, 81% of patients received the full dose of the respective platinum drug, whereas only 50% of patients received the full dose of paclitaxel. One patient received cetuximab during RT (Table 2).

Acute toxicity of single-cycle IC and CRT

Grade III and IV leukopenia occurred in 22 of 91 cases and was thus the most common side effect of single-cycle induction chemotherapy. Granulocyte-colony stimulating

Table 1 Patient characteristics: characteristics of the overall population and subpopulations of patients with squamous cell carcinoma of the mesopharynx/tongue, hypopharynx and larynx

Characteristics	Number	Mesopharynx/tongue ($n=17$)	Hypopharynx ($n=42$)	Larynx ($n=43$)	p value
Sex					0.35
Male	83 (81%)	13 (76%)	37 (88%)	33 (77%)	
Female	19 (19%)	4 (24%)	5 (12%)	10 (23%)	
Age (years)					0.13
Median	58.5 years	60 years	56 years	60 years	
Range	35–78 years	43–71 years	44–76 years	35–78 years	
Charlson-comorbidity-index					0.30
1–2 points	71 (69.6%)	13 (76.5%)	32 (76.2%)	26 (60.5%)	
3–4 points	28 (27.5%)	4 (23.5%)	8 (19.0%)	16 (37.2%)	
≥5 points	3 (2.9%)	0	2 (4.8%)	1 (2.3%)	
Stage, UICC-TNM 2010					
T1	1 (1%)	0	0	1 (2%)	0.64
T2	34 (33%)	8 (47%)	11 (26%)	15 (35%)	
T3	42 (41%)	3 (18%)	21 (12%)	18 (42%)	
T4	25 (25%)	6 (35%)	10 (24%)	9 (21%)	
N0	31 (30%)	3 (18%	11 (26%)	17 (40%)	0.10
N1	16 (16%)	2 (12%)	7 (16%)	7 (16%)	
N2a	2 (2%)	0	1 (2%)	1 (2%)	
N2b	25 (24%)	5 (29%)	11 (26%)	9 (21%)	
N2c	27 (27%)	7 (41%)	11 (26%)	9 (21%)	
N3	1 (1%)	0	1 (2%)	0	
UICC					0.09
II	11 (11%)	2 (12%)	2 (5%)	7 (16%)	
III	23 (22%)	2 (12%)	9 (21%)	12 (28%)	
IVa	67 (66%)	13 (76%)	30 (72%)	24 (56%)	
IVb	1 (1%)	0	1 (2%)	0	
Grade					0.45
1	4 (4%)	0	1 (2%)	3 (7%)	
2	50 (49%)	7 (41%)	24 (57%)	19 (44%)	
3	48 (47%)	10 (59%)	17 (40%)	21 (49%)	
Definitive therapy after single-cycle IC					0.79
Primary surgery	18 (18%)	4 (24%)	7 (17%)	7 (16%)	
Chemoradiation	84 (82%)	13 (76%)	35 (83%)	36 (84%)	
Responders	74	12 (71%)	30 (71%)	32 (74%)	0.94
Non-responders	28	5 (29%)	12 (29%)	11 (26%)	

IC induction chemotherapy

factor (G-CSF) prophylaxis was, therefore, added to the regimen and prevented the development of grade IV leukopenia in the subsequent 11 patients. Two patients had grade 3 renal failure. No patients died as a result of single-cycle IC (Table 3).

Infections, higher grade leukopenia and dermatitis were the leading side effects during CRT but again, no patient died as an immediate consequence of chemoradiotherapy within 30 days of the end of treatment.

Surgical treatment of 18 non-responders

Ten non-responders underwent laryngectomy and the other eight received organ-sparing surgery. Subsequently, 3 patients received adjuvant RT, 13 received adjuvant CRT, and 2 received no adjuvant therapy (one had tumor stage ypT1 and was ineligible for adjuvant therapy; the other developed early recurrence and died of related complications).

Table 2 Feasibility of chemoradiotherapy (CRT) after single-cycle induction chemotherapy (IC)

Single-cycle IC ($n=102$)	Number of patients	Percent (%)
Cisplatin	91	89.2
Carboplatin	11	10.8
Neoadjuvant CRT ($n=84$)		
Cisplatin	71	84.5
Carboplatin	12	14.3
Other	1	1.2
Dose		
Full dose (8 doses)	68	80.9
> 75% (≥ 6 doses)	10	11.9
> 50% (≥ 4 doses)	5	6.0
< 50% (< 4 doses)	1	1.2
Paclitaxel		
Full dose (8 doses)	42	50.0
> 75% (≥ 6 doses)	25	29.8
> 50% (≥ 4 doses)	11	13.0
< 50% (< 4 doses)	6	7.1
Radiotherapy dose		
≥ 70 Gy	76	90.5
< 70 Gy (at least 58 Gy)	8	9.5
Delay in chemoradiotherapy		
No delay	59	70.2
Delay ≤ 2 days	19	22.6
Delay > 2 days	6	7.1

Table 3 Toxicity of single-cycle induction chemotherapy (IC) and chemoradiotherapy

Toxicity	Number and percentage (%) of patients		
	Grade 2	Grade 3	Grade 4
Single-cycle IC ($n=102$)			
Infection	6 (5.9)	10 (9.8)	0
Leukopenia	19 (18.6)	18 (17.6)	4 (3.9)
Prophylactic G-CSF	11 (10.7)		
Therapeutic G-CSF	8 (7.8)		
Anemia	1 (1.0)	2 (2.0)	0
Need for transfusions	1 (1.0)		
Thrombocytopenia	1 (1.0)	0	1 (1.0)
Creatinine elevation	4 (3.9)	2 (2.0)	0
Chemoradiotherapy ($n=84$)			
Infection	29 (34.1)	38 (44.7)	0
Leukopenia	27 (31.7)	23 (27.1)	1 (1.1)
Prophylactic G-CSF	0		
Therapeutic G-CSF	7 (8.2)		
Anemia	15 (17.7)	26 (30.6)	0
Need for transfusions	27 (31.8)		
Thrombocytopenia	3 (3.5)	4 (4.7)	1 (1.2)
Creatinine elevation	9 (10.6)	1 (1.2)	0
Dermatitis	43 (50.6)	13 (15.3)	0
Mucositis	46 (54.1)	12 (14.1)	0

Local and regional tumor control

Of the 102 patients, 71 (69.6%) remained disease-free and 31 (30.4%) experienced disease recurrence. Relapses consisted of isolated local recurrence in 13 patients (12.7%), isolated lymph node recurrence in 2 patients (2.0%), combined local and lymph node recurrence in 1 patient (< 1%), local recurrence with distant metastases in 4 patients (3.9%), isolated distant metastasis in 10 patients (9.8%), and local and regional recurrence in combination with distant metastasis in 1 patient (< 1%).

Local control was 81.3% ± 4.2% at 3 years and 73.7% ± 6.7% at 10 years, and the locoregional control rate at 3 years was 80.2% ± 4.2%. Local control was independent of the initial tumor stage and grade (T1/2 vs. T3/4, $p=0.057$, and N0-N2a vs. N2b-N3, $p=0.511$, G1 vs. G2/3, $p=0.324$). Local control in patients who received surgery after IC was no different from that in those who received definitive CRT instead ($p=0.5$). The 3-year local control rate by tumor location was 88.2% ± 7.8% for mesopharyngeal carcinoma ($N=17$), 85.6% ± 6.0% for laryngeal carcinoma ($N=43$), and 73.7% ± 7.3% for hypopharyngeal carcinoma ($N=42$); $p=0.17$ for larynx vs. hypopharynx (Fig. 1). 3-year locoregional control rates for the three locations were 88.2% ± 7.8%, 73.7% ± 7.3% and 82.9% ± 6.4% ($p>0.05$), respectively.

In the definitive CRT group, the 3-year local control rate was 74.8 ± 8.0% for conventionally fractionated radiotherapy vs. 86.3 ± 5.2% for hyperfractionated accelerated radiotherapy ($p=0.268$), and 82.8 ± 4.8% with cisplatin vs. 73.3 ± 13.2% with carboplatin ($p=0.67$).

Organ preservation

Of the 84 patients who received primary CRT after single-cycle IC, 15 developed local recurrences (17.8%). Out of these 15 patients, 6 were treated by laryngectomy and one by partial glossectomy; the other 8 recurrences were locally or functionally inoperable. No laryngectomy was performed for functional reasons after CRT. Two patients developed local recurrences after organ-sparing surgery and then became inoperable due to distant metastasis.

The absolute number of patients with widely resected tumors and lasting organ loss was 17 (16.6%). Organ recurrence-free survival was 73.1% ± 4.6% at 3 and 5 years, respectively, and 67.9% ± 6.6% at 10 years. Local recurrences and organ removal surgery mainly occurred around 2.5 years after primary therapy (Fig. 2).

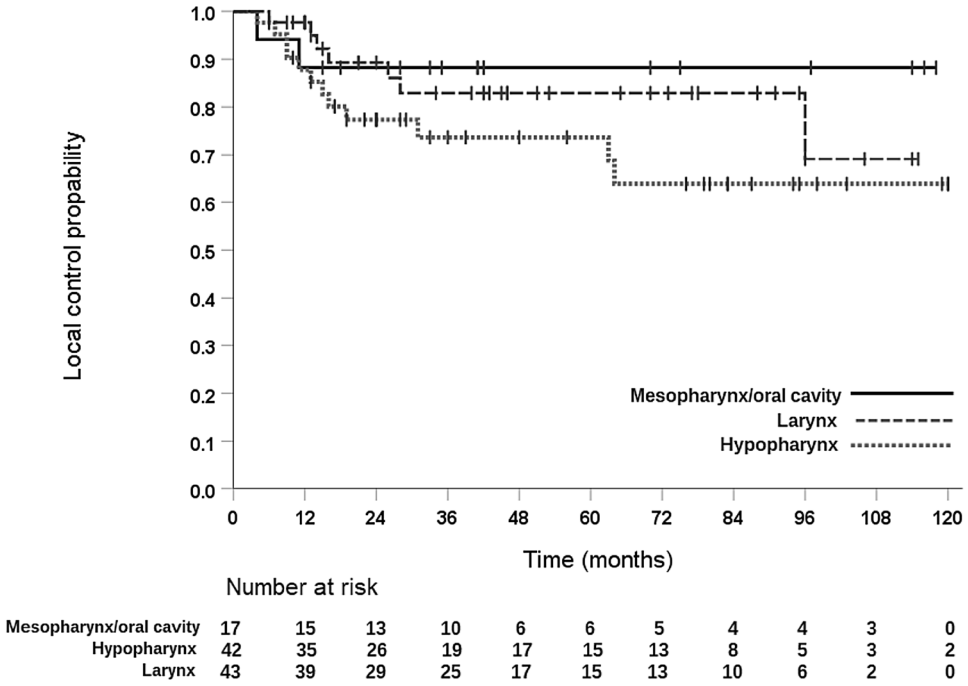

Fig. 1 Local control probability (solid line: mesopharynx and oral cavity, dashed line: larynx, dotted line: hypopharynx)

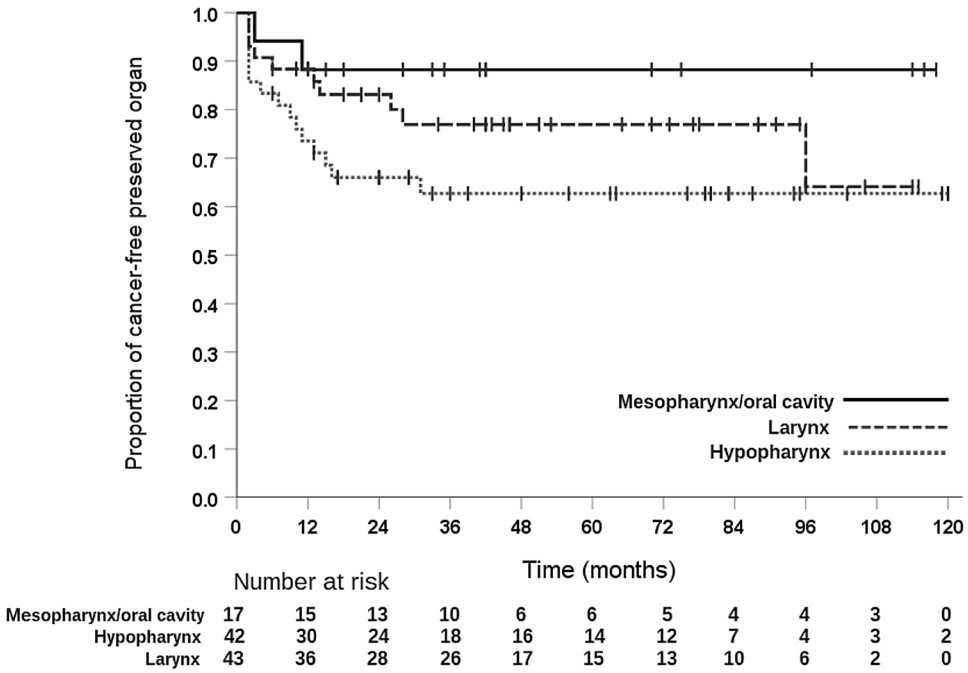

Fig. 2 Proportion of cancer-free organs in situ (solid line: mesopharynx and oral cavity, dashed line: larynx, dotted line: hypopharynx)

The overall rate of carcinoma-free, functionally intact survival without a permanent tracheostomy was 44.1% (45/102) after treatment, and the rate in laryngeal or hypopharyngeal cancer patients was 46% (33/71) after CRT.

Neck dissection

After receiving CRT, 7 of 84 patients (8.3%) developed vital regional lymph node metastases that were treated by neck

dissection.

Distant metastasis-free survival and disease-free survival

Distant metastasis-free survival was 84.6 ± 4.0% and 83.0% ± 4.2% at 3 and 5 years, respectively. The probability of distant metastasis (DM) was independent of T stage (T1/2 vs. T3/4, $p = 0.39$), N stage ($p = 0.414$), and tumor grade ($p = 0.371$). Distant metastasis-free survival by tumor location was 94.1 ± 5.7% for mesopharynx, 76.4 ± 7.5% for hypopharynx, and 88.0 ± 5.7% for larynx tumors ($p > 0.05$ in each case).

Overall 3-year and 5-year disease-free survival (DFS) was 71.1 ± 4.7% and 69.7 ± 4.8%, respectively. Patients with HNSCC of the mesopharynx had the best disease-free survival (82.2 ± 9.3% at 3 years), followed by larynx (78.0 ± 7.0% at 3 years), and hypopharynx HNSCC patients (59.3 ± 7.9% at 3 years; $p = 0.08$).

Cancer-specific and overall survival

On the cutoff date of 1 June 2018, 55 of the 102 patients (53.9%) were alive and 47 (46.1%) were deceased. Twenty-four patients (23.5%) died of the initially treated primary tumor. The other 23 (22.5%) died of causes unrelated to primary tumor recurrence: secondary tumors ($n = 5$), pneumonia or aspiration ($n = 7$), prolonged, severe weight loss ($n = 3$), liver cirrhosis ($n = 1$), and unknown causes in the absence of recurrence ($n = 7$).

Cancer-specific survival (CSS) was 76.4% ± 4.5%, 75.0 ± 4.7% and 67.3 ± 7.1% for 3, 5 and 10 years, respectively. Carcinomas of the hypopharynx were associated with worse CSS than those in other locations: 3-year CSS of 60.8% ± 8.0% (hypopharynx) vs. 81.4 ± 9.7% (mesopharynx) vs. 91.2% ± 4.9% (larynx); $p < 0.003$ for hypopharynx vs. larynx and $p = 0.107$ for hypopharynx vs. mesopharynx (Fig. 3). Tumor location and response were independent factors associated with cancer-specific survival. For example: location (HR: 1.5, $p = 0.006$) and response (HR: 1.1, $p = 0.028$) for squamous cell carcinoma (SCC) of the larynx vs. hypopharynx.

Three-, 5- and 10-year overall survival was 68.2 ± 5.1%, 54.5 ± 5.5% and 34.6 ± 6.9%, and the there was a significant difference between surgery and CRT (at 3 years: 72.8 ± 5.1% vs. 46.5 ± 12.4%; $p = 0.018$). Again, patients with SCC of the hypopharynx had the worst survival (54.3% ± 8.0% vs. 80.0% ± 6.4% for larynx, $p = 0.28$; Fig. 4).

Discussion

The results of treatment of more than 100 patients with single-cycle induction chemotherapy for treatment selection purposes are summarized below.

A single cycle of induction chemotherapy made it possible to deliver full-dose chemoradiotherapy as planned, i.e., more than 90% of patients received a cumulative cisplatin dose of ≥ 200 mg/m^2. Full-dose radiotherapy was also possible. This is particularly important, because multiple cycles of TPF [docetaxel, cisplatin, 5-fluorouracil (5-FU)]

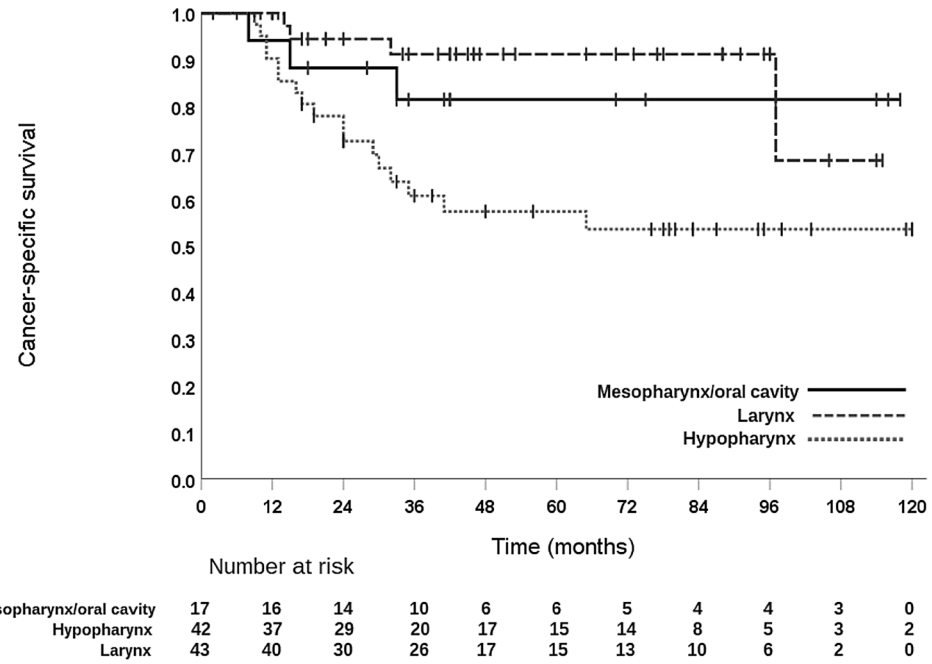

Fig. 3 Cancer-specific survival (solid line: mesopharynx and oral cavity, dashed line: larynx, dotted line: hypopharynx)

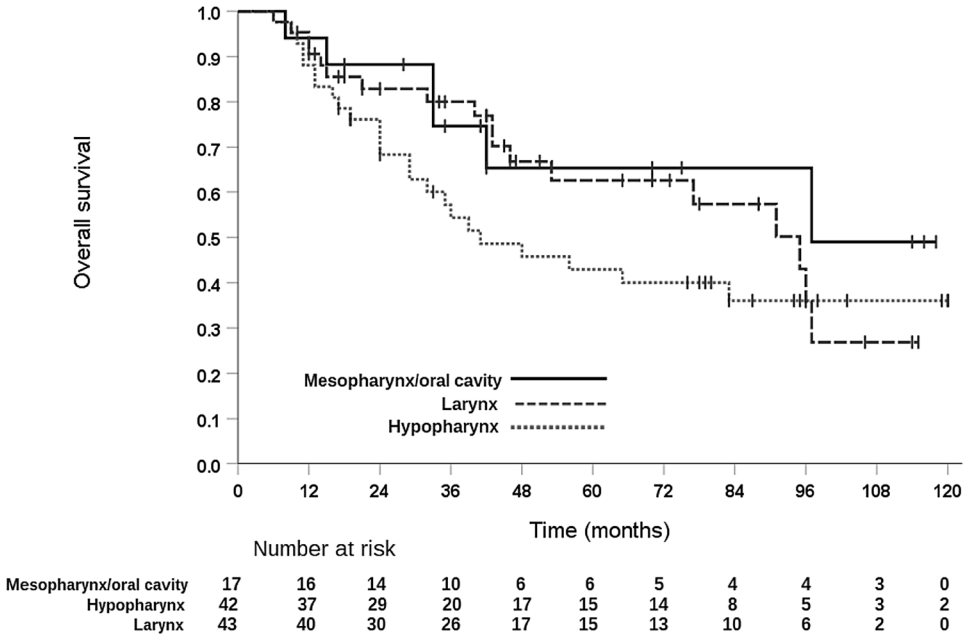

Fig. 4 Overall survival (solid line: mesopharynx and oral cavity, dashed line: larynx, dotted line: hypopharynx)

are associated with long-term impairment of bone marrow reserve, which means that definitive radiochemotherapy can only be administered with cetuximab [2, 12] or with only one cycle of chemotherapy [13] or with carboplatin or docetaxel alone [14]. Secondly, multi-cycle induction chemotherapy is associated with a mortality rate of 1–4% and a morbidity rate of 10%, which prevents further treatment [2, 15]. This level of mortality and morbidity is hardly acceptable in cases, where subsequent definitive treatment could, at least, achieve control of the primary tumor. All patients treated with the proposed single-cycle IC regimen proceeded to concurrent chemoradiotherapy or surgery, and none of them died within 30 days of single-cycle induction chemotherapy. Side effects of the CRT were manageable, and due to early PEG tube application, unfavorable nutrition issues were avoided [16, 17]. Therefore, it appears that a single cycle of induction chemotherapy is the optimal length of induction chemotherapy required to minimize treatment toxicity.

A second key finding was that a single cycle of docetaxel plus cisplatin (TP) is equivalent to a single cycle of cisplatin plus 5-fluorouracil (PF) with respect to inducing remission, i.e., neither regimen is inferior or superior to the other. Similar to the results of Urba et al. [8], 72 to 75% of our patients responded to single-cycle neoadjuvant chemotherapy. Like us, they also used an endoscopic response criterion. By definition, the metabolic criterion played a subordinate role in making the recommendation for definitive treatment because of its low level of evidence. If a high number of responders is important, this can only be achieved with three cycles of a triple combination induction chemotherapy regimen [15, 18]. However, besides having the disadvantages mentioned above, it has no additive value for overall survival [18]. In another German study of induction chemotherapy with TPF, the triple combination was unfeasible due to unacceptable adverse effects in many cases, and therefore, subsequent patients received only the double combination of TP before definitive treatment [6]. In summary, as determined also based on endoscopic response criteria, TP is equivalent to single-cycle PF and is thus appropriate for induction chemotherapy. Further criteria to predict tumor response, such as the p16 status, weren't used but could be a possibility in the future [19].

Our third conclusion relates to potential differences in the efficacy of single-cycle IC between tumor locations. Our data showed that single-cycle IC leads to an equivalent response pattern. In cases with comparable starting conditions, the duration of the local and systemic success of treatment varies. Mesopharyngeal carcinomas had the best outcomes. Interestingly, the 15% difference in functional-organ preservation rates between laryngeal and hypopharyngeal cancer patients was persistent, resulting in better long-term local tumor control. The organ preservation rate achieved in our laryngeal cancer patients is comparable to that in the RTOG 94–11 study [4] and better than that obtained in the University of Michigan study [8]. The long-term organ preservation rate of our hypopharyngeal cancer patients, which wasn't analyzed separately in previous studies, is just over 60%.

Differences in local tumor control between tumor locations continued in long-term tumor control and the probability of death due to the tumor disease. The third conclusion is that, given the same response to single-cycle neoadjuvant

chemotherapy, tumors in different locations benefit differently from single-cycle induction chemotherapy.

Conclusions

Overall, in combination with the findings of the University of Michigan study and the DELOS study, the evidence provided by this study demonstrates that one cycle of neoadjuvant chemotherapy is adequate to achieve sufficient tumor remission for definitive therapy. Whether TP has advantages over PF can still be disputed, but TP is a good alternative. Subsequent CRT is neither prevented nor delayed, nor compromised by radiotherapy. Unlike the PACCis study [20], it was possible to deliver comparable cisplatin and taxane doses in the present study. Compared with previous organ preservation studies, the affected organ could be preserved and remained in situ in a larger percentage of our patients. This is particularly true of patients with cancer of the larynx and mesopharynx. Identically treated carcinomas of the hypopharynx had less favorable outcomes. In the end, larynx preservation was possible in 60% of these patients.

Acknowledgements The present work was performed by Marius Breheret in fulfillment of the requirements for the degree of Doctor of Medicine (Dr. med.).

Compliance with ethical standards

Conflict of interest Torsten Kuwert receives honoraria from Siemens Healthineers for lectures. The Erlangen Clinic of Nuclear Medicine has a research cooperation with that company on the field of SPECT/CT. Markus Hecht reports advisory board services for Merck Serono, MSD and BMS, travel support from Merck Serono, MSD and TEVA and research funding from AstraZeneca, MSD and Novartis.

Informed consent Written informed consent was obtained from all individual participants included in the study. Due to using the established standard protocol in our departments and retrospective method, formal consent for this type of study is not required.

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