Oral Oncology 78 (2018) 151–155

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Induction chemotherapy followed by concurrent chemoradiation versus concurrent chemoradiation alone in the definitive management of p16-positive oropharyngeal squamous cell carcinoma with low-neck or N3 disease

Onita Bhattasali[a], Jeannie Han[b], Lester D.R. Thompson[c], Gary L. Buchschacher Jr.[d], Iman A. Abdalla[d], Shawn Iganej[a,*]

[a] Southern California Permanente Medical Group, Department of Radiation Oncology, Los Angeles, CA, United States
[b] Southern California Permanente Medical Group, Department of Radiation Oncology, Anaheim, CA, United States
[c] Southern California Permanente Medical Group, Department of Pathology, Woodland Hills, CA, United States
[d] Southern California Permanente Medical Group, Department of Hematology/Oncology, Los Angeles, CA, United States

ARTICLE INFO

Keywords:
Oropharyngeal cancer
Squamous cell carcinoma
P16-positive
HPV-associated
Low-neck disease
N3 lymphadenopathy
Distant metastasis
Head and neck cancer
Induction chemotherapy
Chemoradiation

ABSTRACT

Objective: The addition of induction chemotherapy (ICT) to concurrent chemoradiation (CCRT) has been investigated as a method of improving outcomes among patients with locally advanced head and neck squamous cell carcinoma. Previous studies have consisted of heterogeneous populations with both p16-positive and p16-negative disease and varying extent of nodal disease burden. We evaluated the role of ICT in p16-positive oropharyngeal squamous cell carcinoma (OPSCC) at high-risk of distant failure.

Materials and methods: A retrospective review was conducted of 88 consecutive patients with p16-positive OPSCC with low-neck and/or N3 lymphadenopathy. Among these patients, 44 received ICT followed by CCRT, and 44 received CCRT alone with concurrent agents including Cisplatin, Carboplatin, and Cetuximab. Disease control and survival outcomes were reported after adjusting for age, T stage, N stage, and smoking status.

Results: Median follow-up for surviving patients was 47 (range: 13–115) months. Patients who received CCRT alone were older than those who received ICT (61 years vs. 56 years; p = 0.02); the groups were otherwise similarly balanced. 3-year distant metastasis: 38% vs. 18% (adjusted hazard ratio (HR) = 0.32 [0.13–0.82]; p = 0.02). 3-year progression-free survival: 49% vs. 74% (adjusted HR = 0.46 [0.22–0.93]; p = 0.03). 3-year overall survival: 67% vs. 83% (adjusted HR = 0.48 [0.21–1.12]; p = 0.09).

Conclusion: Among patients with p16-positive OPSCC with low-neck and/or N3 lymphadenopathy, ICT followed by CCRT may reduce the risk for distant failure over CCRT alone and lead to improved progression-free survival. Future trials should concentrate on patients at the highest risk of distant metastasis in order to appropriately assess the benefit of ICT.

Introduction

Concurrent chemoradiation (CCRT) is the standard of care for locally advanced head and neck squamous cell carcinoma (LAHNSCC) [1–3]. The addition of induction chemotherapy (ICT) to CCRT has been investigated as a method of further improving outcomes among these patients, but its application remains controversial. Several randomized clinical trials have performed a comparison of ICT followed by CCRT to CCRT alone in LAHNSCC; the majority of these studies have not demonstrated a survival benefit with the addition of ICT [4–8].

Previous studies addressing this question have included a heterogeneous population of all head and neck subsites with both p16-positive and p16-negative disease and varying extent of nodal disease burden. In contrast to the patterns of failure seen in p16-negative disease, distant failure constitutes a considerable portion of treatment failures in p16-positive disease [9,10]. ICT has the potential to improve distant control by eliminating micrometastatic disease; however, this benefit is only likely to be seen in those patients who are at the highest risk for distant failure. At our institution, certain patients with p16-positive oropharyngeal squamous cell carcinoma (OPSCC) with low-neck or N3

Abbreviations: ICT, induction chemotherapy; CCRT, concurrent chemoradiation; OPSCC, oropharyngeal squamous cell carcinoma; HR, hazard ratio

* Corresponding author at: Department of Radiation Oncology, Southern California Permanente Medical Group, 4950 Sunset Boulevard, Los Angeles, CA 90027, United States.
E-mail address: shawn.x.iganej@kp.org (S. Iganej).

https://doi.org/10.1016/j.oraloncology.2018.01.031
Received 19 October 2017; Received in revised form 29 December 2017; Accepted 30 January 2018

lymphadenopathy are given ICT prior to CCRT at the discretion of the treating physicians with the objective of lowering the risk of distant failure. In this study, we compared the outcomes of these patients to their counterparts who received upfront CCRT alone.

Material and methods

Study design

A retrospective review was conducted at a single institution from June 2006 to June 2015 after obtaining approval from the institutional review board. Patients eligible for inclusion had stage III-IVB (AJCC 7th Edition staging) histologically-confirmed p16-positive OPSCC with low-neck (level IV and/or Vb involvement) and/or N3 lymphadenopathy. Eighty-eight consecutive patients were identified for inclusion and were definitively managed with either ICT followed by CCRT (n = 44) or CCRT alone (n = 44). Patients who received oncologic surgery of any kind prior to definitive management were excluded from analysis, as were patients with prior head and neck radiotherapy or other known malignancies (excluding non-melanoma skin cancer) within the previous five years. Centralized pathology review was performed on all specimens, with p16 immunohistochemical staining obtained for all cases, with positive cases interpreted to be strong and diffuse, > 70% nuclear and cytoplasmic immunoreactivity [11]. A minimum of one year of follow-up was required for all surviving patients.

Treatment

Among patients who received upfront CCRT, the systemic regimens included triweekly high-dose Cisplatin (n = 19), weekly Cisplatin (n = 5), triweekly high-dose Carboplatin (n = 14), and weekly Cetuximab (n = 6). Patients in the ICT group received Docetaxel and platinum-based chemotherapy with (n = 39) or without (n = 5) 5-Fluorouracil (TPF vs. TP). Following ICT, concurrent regimens consisted of weekly Carboplatin (n = 27), triweekly high-dose Carboplatin (n = 9), weekly Cisplatin (n = 4), triweekly high-dose Cisplatin (n = 3), and weekly Cetuximab (n = 1). Radiation treatment was delivered with intensity-modulated radiation therapy (IMRT) to a planned dose of 70 Gy with simultaneous-integrated boost technique. All patients underwent weekly on-treatment examinations. A treatment break was defined as one lasting two days or longer.

Evaluation with clinical exam and nasopharyngoscopy was performed one month following completion of treatment. Subsequent follow-up was scheduled initially every two to three months and gradually transitioned to every six months until five years at which point patients had the option of annual surveillance in the head and neck clinic or routine care with their primary care provider. The most common follow-up schedule included a three-month post-treatment PET/CT or CT neck and annual chest X-ray. Additional imaging was obtained when clinically indicated i.e., patient reported symptoms or abnormal findings on examination. Post-treatment imaging studies were obtained periodically at the discretion of the treating physician. No planned neck dissections were performed.

Statistical analysis

Patient characteristics and toxicity outcomes were compared with *t*-test for continuous variables and Chi-square test for categorical variables. Outcomes were measured using the length of time from the day of treatment completion to the last day of follow-up. Endpoints analyzed included locoregional recurrence (LRR), distant metastasis (DM), progression-free survival (PFS), and overall survival (OS). Disease control and survival outcomes were estimated by the Kaplan-Meier method. Adjusted hazard ratios (HR) were calculated by a multivariate Cox proportional hazards model accounting for age, T stage, N stage, and smoking status. The statistical significance level was set at 0.05.

Table 1
Patient characteristics.

	CCRT alone	ICT + CCRT	p-value
Median follow-up of surviving patients (months)	36 (13–115)	51 (16–78)	
Median age (years)	61 (35–83)	56 (41–74)	**0.02**
Sex			*> 0.99*
Male	38 (86%)	39 (89%)	
Female	6 (14%)	5 (11%)	
Subsite			0.57
Tonsil	19 (43%)	21 (48%)	
Base of tongue	24 (55%)	23 (52%)	
Soft palate	1 (2%)	0 (0%)	
Current smoker	10 (23%)	8 (18%)	0.79
≥3 drinks per day	9 (20%)	9 (20%)	> 0.99
T stage			0.61
T1	6 (14%)	5 (11%)	
T2	15 (34%)	15 (34%)	
T3	11 (25%)	7 (16%)	
T4	12 (28%)	17 (39%)	
N stage			0.49
N2b	14 (32%)	15 (34%)	
N2c	12 (27%)	16 (36%)	
N3	18 (41%)	13 (30%)	
TNM stage			0.38
IVA	24 (55%)	29 (66%)	
IVB	20 (45%)	15 (34%)	
Low-neck disease	35 (80%)	37 (84%)	0.78
Low-neck and N3 disease	9 (20%)	6 (14%)	0.57

Results

Patient and tumor characteristics

Median follow-up for surviving patients was 47 (range: 13–115) months. Patients who received CCRT alone were older than those who received ICT (61 years vs. 56 years; p = 0.02). Patient groups were otherwise similarly balanced with respect to tumor and nodal stage, presence of low-neck disease, and alcohol and tobacco history. Patient characteristics are listed in Table 1.

Disease control and survival outcomes

Disease control and survival outcomes were estimated by the Kaplan-Meier method, and adjusted HR were calculated to account for confounding factors including age, T stage, N stage, and smoking status. There was no difference observed in LRR rates between patients who received CCRT alone vs. ICT. 3-year LRR: 19% vs. 14% (HR = 0.89 [0.31–2.56]; p = 0.84; adjusted HR = 1.18 [0.38–3.63]; p = 0.78), respectively (Fig. 1). Patients who received CCRT alone experienced a higher rate of distant failure (Fig. 2). 3-year DM: 38% vs. 18% (HR = 0.34–0.15–0.74]; p = 0.009; adjusted HR = 0.32 [0.13–0.82]; p = 0.02). Distant failures were predominantly in isolation, and the most common sites of failure were the lungs followed by the mediastinal and hilar lymph nodes (Table 2). On unadjusted analysis, PFS and OS were inferior in patients who received CCRT alone (Figs. 3 and 4). 3-year PFS: 49% vs. 74% (HR = 0.41 [0.22–0.78]; p = 0.007). 3-year OS: 67% vs. 83% (HR = 0.44 [0.21–0.96]; p = 0.04). After adjusting for confounding variables, ICT was associated with superior PFS (adjusted HR = 0.46 [0.22–0.93]; p = 0.03), but there was no difference in OS (adjusted HR = 0.48 [0.21–1.12]; p = 0.09) between the two groups. Disease control and survival outcomes are outlined in Table 3.

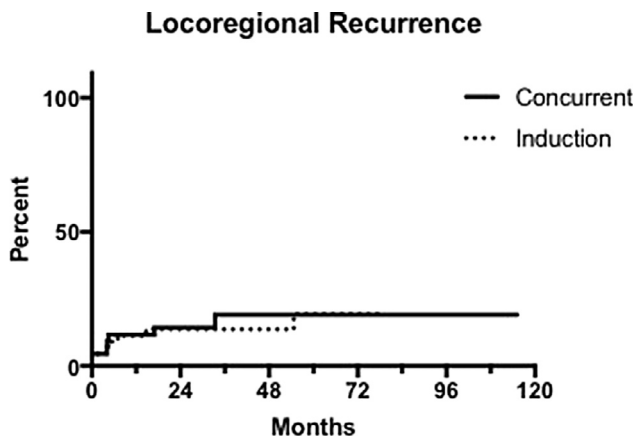

Fig. 1. Locoregional recurrence.

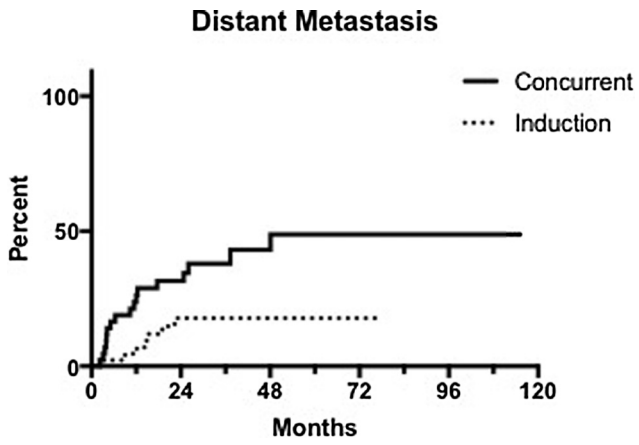

Fig. 2. Distant metastasis.

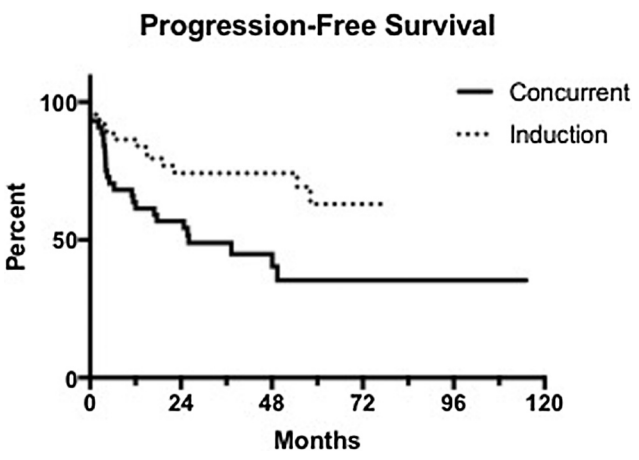

Fig. 3. Progression-free survival.

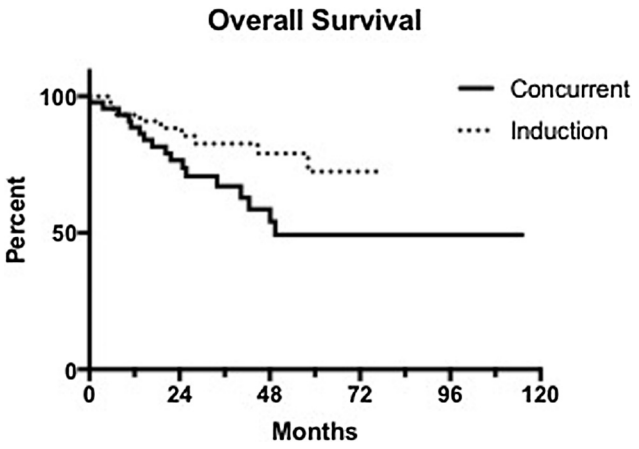

Fig. 4. Overall survival.

Table 2
Sites of first distant failure.

	CCRT alone	ICT + CCRT
Patterns of distant failure		
Total distant failures	17 (39%)	7 (16%)
Isolated distant failures	13 (30%)	4 (9%)
Sites of first distant failure		
Lung	16 (36%)	6 (14%)
Mediastinal nodes	8 (18%)	4 (9%)
Hilar nodes	5 (11%)	1 (2%)
Axillary nodes	2 (5%)	0 (0%)
Abdominal/pelvic nodes	0 (0%)	2 (5%)
Liver	2 (5%)	3 (7%)
Spleen	0 (0%)	1 (2%)
Bone	2 (5%)	0 (0%)
Skin	1 (2%)	0 (0%)

Toxicity

Among patients in the ICT group, 34 (77%) patients received the planned three cycles, and 10 (23%) patients received two cycles. Reasons for not receiving all three cycles included treatment-related toxicity, performance status, or suboptimal response to ICT. Patients who received CCRT alone were more likely to require a feeding tube compared to patients who received ICT (57% vs. 27%; $p = 0.009$). There was no difference between CCRT alone and ICT in the percentage of patients who required a treatment break (27% vs. 18%; $p = 0.45$).

Discussion

The study of ICT in the management of LAHNSCC has been met with conflicting results. A meta-analysis by Pignon et al. demonstrated a survival benefit for CCRT which was not observed for ICT compared to radiation alone [3]. Consequently, CCRT was established as the standard of care for LAHNSCC. However, the publication of TAX 324 sparked renewed interest in ICT when encouraging patient outcomes were reported using TPF followed by CCRT [12]. It was hypothesized that the combination of ICT and CCRT was the reason for such favorable outcomes.

Since then, multiple randomized clinical trials have been published evaluating the addition of ICT to CCRT. The PARADIGM trial randomized unresectable (T3-4 or N2-3 disease excluding T1N2 disease) LAHNSCC patients to ICT with TPF followed by CCRT vs. CCRT alone with high-dose Cisplatin with accelerated radiotherapy [6]. Choice of concurrent regimen in the ICT arm was response-driven with complete responders receiving weekly Carboplatin and partial responders receiving weekly Docetaxel with accelerated radiotherapy. No difference was observed in overall survival; however, the trial was terminated early due to poor accrual, and as such, there was insufficient power to interpret the study results.

The DECIDE trial evaluated the role of ICT in patients with LAHNSCC with N2 or N3 disease [5]. Patients in this study received twice-daily radiotherapy with Docetaxel, 5-Fluorouracil, and Hydroxyurea with or without two cycles of induction TPF. While this study found that ICT reduced the rate of DM, there was no survival benefit observed among all-comers. There was, however, a trend toward improved OS in the subgroup of patients with N2c-N3 disease who

Table 3
Disease control and survival outcomes at 3 years.

	CCRT alone	ICT + CCRT	Hazard ratio (HR)	p-value	Adjusted HR	p-value
Locoregional recurrence	19%	14%	0.89 [0.31–2.56]	0.84	1.18 [0.38–3.63]	0.78
Distant metastasis	38%	18%	0.34 [0.15–0.74]	**0.009**	0.32 [0.13–0.82]	**0.02**
Progression-free survival	49%	74%	0.41 [0.22–0.78]	**0.007**	0.46 [0.22–0.93]	**0.03**
Overall survival	67%	83%	0.44 [0.21–0.96]	**0.04**	0.48 [0.21–1.12]	0.09

received ICT. Unfortunately, this study was also closed prior to the planned accrual number and was underpowered for analysis of the final sample size. Furthermore, only two cycles of ICT were used which may have impacted the survival outcomes.

A three-arm study was conducted by the Spanish Head and Neck Cancer Cooperative Group comparing CCRT with high-dose Cisplatin alone or following ICT with either PF or TPF in patients with stage III-IV unresectable LAHNSCC [4]. Again, no survival benefit was demonstrated with the addition of ICT. It is important to note that both the DECIDE and PARADIGM trials included N2a-b disease, and the Spanish study included stage III disease. Patients with a lower burden of disease may not benefit from the addition of ICT, and the inclusion of these subgroups may have masked a benefit that would otherwise have been seen if the appropriate patient population was selected.

Only one randomized trial has demonstrated a survival benefit with the addition of ICT in LAHNSCC. The recent study published by Ghi et al. included a 2 × 2 factorial design of patients with LAHNSCC and evaluated the addition of ICT with TPF to either Cetuximab or PF-based radiotherapy [8]. This trial found that the addition of ICT resulted in improved OS, PFS, and LRC. The authors also noted that compliance to concomitant therapy was not impacted by receipt of ICT. One study of particular interest is GORTEC 2007-02 which focused on patients with LAHNSCC with palpable N2b-N3 disease [13,14]. The trial randomized patients to 5-Fluorouracil and Carboplatin-based CCRT vs. induction TPF followed by Cetuximab-based radiotherapy, and the preliminary results have been presented in abstract form. The study investigators found that ICT resulted in superior distant control in this group of patients with a higher burden of nodal disease. The primary endpoint, however, was PFS, for which no benefit was seen at the time of initial report.

In order to minimize the patient heterogeneity seen in the aforementioned trials, our study evaluated outcomes solely among patients with p16-positive OPSCC. Similar to nasopharyngeal carcinoma, p16-positive OPSCC represents a highly chemosensitive disease [15]. Recently, a phase III randomized controlled trial published by Sun et al. found that the addition of induction TPF to CCRT in locally advanced nasopharyngeal carcinoma in an endemic population resulted in superior distant control and consequently improved failure-free and overall survival [16]. It is conceivable that a similar outcome could be expected in p16-positive OPSCC if the appropriate patient population is selected. In multivariate analysis, our study found that ICT was associated with superior distant control and PFS but failed to demonstrate a difference in OS. It is possible that the small sample sizes in this study precluded observation of a survival difference, and a larger study focusing on this population may show a survival benefit with ICT.

Additionally, in contrast to what is observed in p16-negative OPSCC, isolated distant recurrences constitute a significant portion of treatment failures in locally advanced p16-positive OPSCC and may, therefore, provide a better opportunity for improving overall outcomes through ICT. Finally, only patients with low-neck or N3 lymphadenopathy were analyzed in this study. Patients with low-neck and N3 disease have previously been shown to be at an elevated risk of distant failure [17,18]. By excluding lower risk patients without these characteristics, the benefit of ICT may become more detectable.

A higher rate of PEG tube placement was observed in the CCRT alone group. This may have been due to employment of less intensive concurrent regimens in patients who received ICT. Although numerically a higher rate of patients appeared to require treatment breaks in patients who received CCRT alone, there was no significant difference between groups. Again, less intensive concurrent regimens in the ICT group may have led to these findings.

Limitations of this study include its retrospective nature and the small sample sizes within the comparison groups. Additionally, there was heterogeneity of concurrent regimens employed in the CCRT alone group. Presently, high-dose Cisplatin is listed as the National Comprehensive Cancer Network (NCCN) category one preferred recommendation for concurrent agent in definitive management of LAHNSCC. Although weekly Cisplatin and Cetuximab are also listed as acceptable regimens, there is no published randomized data suggesting that these agents have equivalent efficacy compared to high-dose Cisplatin. While high-dose Cisplatin was the most commonly used concurrent agent in the CCRT alone group, it is possible that, in this group of patients with the highest burden of nodal disease, alternative agents may be inadequate in achieving disease control. Furthermore, a small percentage of patients in the ICT group received only doublet chemotherapy with TP which may be inferior to TPF ICT.

To conclude, this study suggests that ICT followed by CCRT may reduce the occurrence of DM and improve PFS over CCRT alone in patients with p16-positive OPSCC with low-neck or N3 lymphadenopathy who are at high risk of distant failure. Future randomized studies should concentrate on patients at the highest risk of developing distant metastases in order to assess the potential benefit of ICT in this population.

Conflict of interest

None declared.

Acknowledgements

The authors would like to thank Hannah B. Herrera for her research assistance.

Role of the Funding Source

This work was supported by a grant from the Regional Research Committee of Kaiser Permanente Southern California [KP-RRC-20160901]. The committee was not involved in the preparation of this manuscript.

References

[1] Denis F, Garaud P, Bardet E, et al. Final results of the 94-01 French head and neck oncology and radiotherapy group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol: Off J Am Soc Clin Oncol 2004;22(1):69–76.
[2] Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol: Off J Am Soc Clin Oncol 2003;21(1):92–8.
[3] Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiotherap Oncol: J Europ Soc Therapeut Radiol Oncol 2009;92(1):4–14.
[4] Hitt R, Grau JJ, Lopez-Pousa A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy

alone as treatment of unresectable head and neck cancer. Annal Oncol: Off J Europ Soc Med Oncol 2014;25(1):216–25.
[5] Cohen EE, Karrison TG, Kocherginsky M, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. J Clin Oncol: Off J Am Soc Clin Oncol 2014;32(25):2735–43.
[6] Haddad R, O'Neill A, Rabinowits G, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. Lancet Oncology 2013;14(3):257–64.
[7] Budach W, Bolke E, Kammers K, et al. Induction chemotherapy followed by concurrent radio-chemotherapy versus concurrent radio-chemotherapy alone as treatment of locally advanced squamous cell carcinoma of the head and neck (HNSCC): A meta-analysis of randomized trials. Radiotherap Oncol: J Europ Soc Therapeut Radiol Oncol 2016;118(2):238–43.
[8] Ghi MG, Paccagnella A, Ferrari D, et al. Induction TPF followed by concomitant treatment versus concomitant treatment alone in locally advanced head and neck cancer. A phase II-III trial. Annal Oncol: Off J Europ Soc Medical Oncology 2017;28(9):2206–12.
[9] Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. New England J Med 2010;363(1):24–35.
[10] O'Sullivan B, Huang SH, Siu LL, et al. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. J Clin Oncol: Off J Am Soc Clin Oncol 2013;31(5):543–50.
[11] Lewis JS, Jr., Chernock RD, Ma XJ, et al. Partial p16 staining in oropharyngeal squamous cell carcinoma: extent and pattern correlate with human papillomavirus RNA status. Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc 2012;25(9):1212–20.
[12] Lorch JH, Goloubeva O, Haddad RI, et al. Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX 324 randomised phase 3 trial. Lancet Oncology 2011;12(2):153–9.
[13] Geoffrois L, Martin, L., Garaud, P., De Raucourt, D., Miny, J., Maingon, P., Lafond, C., Tuchais, C., Sire, C., Babin, E., Coutte, A., Tao, Y., Rolland, F., Girard-Calais, M., Bourhis, J., Vautrin, C. Impact of p16 expression on induction taxotere-cisplatin-5 FU (TPF) followed by cetuximab-radiotherapy in N2b–N3 head and neck squamous cell carcinoma (HNSCC): Results of GORTEC 2007–02 phase III randomized trial. 2017 ASCO Annual Meeting: J Clin Oncol, 2017.
[14] Geoffrois L, Martin L, Garaud P, et al. Induction docetaxel platinum 5-FU (TPF) followed by cetuximab-radiotherapy (cetux-RT) versus concurrent chemo-radiotherapy (CT/RT) in patients with N2b/c-N3 non operated stage III-IV squamous cell cancer of the head and neck (SCCHN): Results of the GORTEC 2007–02 phase III randomized trial. 2016 ASCO Annual Meeting: J Clin Oncol, 2016.
[15] Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Nat Cancer Institute 2008;100(4):261–9.
[16] Sun Y, Li WF, Chen NY, et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. Lancet Oncology 2016;17(11):1509–20.
[17] Riaz N, Setton J, Tam M, et al. Patients with low lying lymph nodes are at high risk for distant metastasis in oropharyngeal cancer. Oral Oncology 2014;50(9):863–8.
[18] Ballonoff A, Raben D, Rusthoven KE, et al. Outcomes of patients with n3 neck nodes treated with chemoradiation. Laryngoscope 2008;118(6):995–8.