Int J Clin Oncol (2017) 22:442–447
DOI 10.1007/s10147-016-1084-8

ORIGINAL ARTICLE

Single-cycle induction chemotherapy for resectable advanced hypopharyngeal cancer

Torahiko Nakashima[1] · Ryuji Yasumatsu[2] · Kaori Asai[3] · Hideoki Uryu[1] · Ryunosuke Kogo[2] · Takashi Nakagawa[2]

Received: 25 October 2016 / Accepted: 26 December 2016 / Published online: 6 January 2017

Abstract
Background The role of induction chemotherapy (IC) in the treatment of resectable advanced head and neck squamous cell carcinoma has not been elucidated, and the most effective IC regimen for chemoselection is still unknown. At our institute we have not used the triple combination of docetaxel, cisplatin, fluorouracil (TPF) for chemoselection, but rather the double combination of docetaxel + cisplatin (TP). The aim of this study is to report the outcome of patients with advanced hypopharyngeal cancer treated by single cycle of IC with TP followed by chemoradiation (CRT) or surgery.
Methods A total of 29 patients with resectable advanced hypopharyngeal cancer who were treated with a single cycle of IC were entered into the study. Responders were treated by CRT while nonresponders underwent surgery. Outcomes were analyzed using the Kaplan–Meier method.
Results A single cycle of IC with TP achieved response in 21 of the 29 patients. The major side effect was neutropenia which could be managed without delaying the sequential treatment. The 2-year overall survival and disease-specific survival were both 74.0% (stage III 100%, stage IVA 69.1%). The cumulative 2-year laryngeal preservation rate was 100% for stage III and 53.6% for stage IVA.
Conclusion A single cycle of IC with the combination of docetaxel + cisplatin may be sufficient to select advanced hypopharyngeal cancer patients with radio-sensitivity. IC intended for organ preservation strategies should be low toxic. Our strategy may be a useful for providing the benefits of IC and the opportunity for curative surgery without delay.

Keywords Hypopharyngeal cancer · Resectable · Induction chemotherapy · Cisplatin · Docetaxel

Introduction

Despite the progress which has been made in treatment modalities for head and neck cancer, patients with advanced hypopharyneal cancer still have a poor prognosis. The standard treatment for resectable advanced hypopharyngeal cancer is either chemoradiation (CRT) or upfront surgery followed by post-operative radiotherapy when necessary. In most patients, surgery includes total laryngectomy, and laryngeal preservation has been a challenge for the treatment of this disease.

The role of induction chemotherapy (IC) for resectable advanced head and neck squamous cell carcinoma (HNSCC) is still controversial. Utilizing IC to select patients who are radiosensitive and potential candidates for laryngeal preservation, a treatment approach referred to as 'chemoselection', has been recognized and is widely employed strategy [1, 2]. IC with the combination of cisplatin (CDDP) + fluorouracil (5-FU) (FP) has been reported to be useful for this chemoselection strategy [3]. However, the most effective IC regimen, i.e., the triple combination of docetaxel (DOC) + CDDP + 5-FU (TPF) or the double combinations of DOC + CDDP (TP) or FP, respectively, in

✉ Torahiko Nakashima
nakatora@kyumed.jp

[1] Department of Otorhinolaryngology, National Kyushu Medical Center, 1-8-1 Jigyohama, Chuo-ku, Fukuoka 810-8563, Japan

[2] Department of Otorhinolaryngology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

[3] Deapartment of Radiation Oncology. Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

terms of organ preservation is not yet established and still open to discussion.

At Kyushu University, a single cycle of IC with CDDP + DOC has been used for patients with resectable stage III and IVA hypopharyngeal cancer with the aim to select those who are radiosensitive and potential candidates for sequential CRT. Since the IC is intended for chemoselection, we administer DOC at 60 mg/m^2 + cisplatin at 70 mg/m^2 instead of a high-dose combination. Patients who do not respond to this IC are selected to undergo surgery. The triple combination of TPF is purposely not utilized due to its high toxicity resulting in a high incidence of delays in sequential CRT or surgery.

We performed a retrospective evaluation of a series of consecutive patients at a single institution who underwent a single cycle of IC (TP) followed by CRT or surgery. The purpose of the study was to elucidate the effect, toxicity, and benefits of this sequential approach for treating patients with locally advanced, operable hypopharyngeal cancer.

Patients and methods

Patient eligibility

A total of 29 consecutive patients were included in this retrospective study. All of the patients had pathologically confirmed, previously untreated stage T3 or T4 squamous cell carcinoma of the hypopharynx. Patients with synchronous double cancer were excluded from the study. Evaluation confirmed that the tumors were resectable and that total laryngectomy could be performed if upfront surgery was selected. For entry to the study, patients required a performance status of 0 or 1, adequate laboratory status, and preserved swallowing function. Patients with massive destruction of the cartilage or prominent aspiration were not enrolled. This protocol was approved by the Institutional Review board of Kyushu University Hospital. Informed consent was required according to the local guidelines. The clinical characteristics of the patients are summarized in Table 1.

Table 1 Patient demographics

Patient characteristics	Values
Age (years), range (median)	45–75 (64)
Sex	
Male	27
Female	2
Stage	
III	5
IVA	24
Subsite	
PS	25
PC	2
PW	2
T status	
T3	16
T4	13
N status	
N0	5
N1	3
N2	21

Data are presented as the number of patients unless indicated otherwise

PS Pyriform sinus, *PC* post-cricoid, *PW* posterior wall

Induction chemotherapy

After evaluation, patients with creatinine clearance of ≥60 ml/min received DOC at 60 mg/m^2 as a 1-h intravenous infusion followed by cisplatin at 70 mg/m^2 as a 2-h intravenous infusion. For patients with a creatinine clearance of 50–60 ml/min, an 80% dose of DOC + CDDP was administered. The protocol was not indicated for patients with creatinine clearance of <50 ml/min.

Response evaluation

Responses were evaluated 21–28 days after IC by endoscopy and contrast-enhanced computed tomography (CT) or magnetic resonance imaging. Biopsy was not generally performed. Gross appearance of the primary tumor by endoscopy, as assessed by a head and neck specialist, was the main factor in assessing the response. Responders were treated by CRT while nonresponders were treated by surgery [total pharyngo-laryngectomy (TPL)] or [total pharyngo-laryngo-cervical esophagectomy (TPLE)]. Response of the metastatic cervical lymph node was not included in the decision-making process. Surgery was chosen as treatment for patients with <50% shrinkage of the primary tumor.

Concurrent chemoradiotherapy

Definitive radiotherapy began within 4 weeks after IC. The patients received CDDP at 80 mg/m^2 on days 1, 22, and 43 concurrent with radiation therapy. The dose of CDDP was reduced to 80% according to renal function. Five patients for whom concurrent CDDP therapy was considered inappropriate due to of decreased renal function received daily S1(TS-1) at 65 mg/m^2 concurrent with radiation [4]. Radiation was given once daily, 5 days a week, at 1.8 Gy per fraction up to a total dose of 70 Gy.

Assessment after chemoradiotherapy

A contrast-enhanced CT scan and fluorodeoxyglucose-positron emission tomography/CT imaging was performed 7–8 weeks after CRT to evaluate the status of the primary tumor and regional lymph nodes. Patients with no disease at the primary site but with residual cervical lymph node metastasis underwent selective or modified neck dissection. Patients with pathology-proven residual disease in the primary site underwent surgery, including total laryngectomy.

The patients were followed up after definitive chemoradiotherapy. Salvage TPLE was performed when recurrent disease was found.

Statistical methods

Survival curves were estimated using the Kaplan–Meier method. The analysis of overall survival considered all causes of death, and that of disease-specific survival considered death due to hypopharyngeal cancer as events. Laryngeal preservation rate was estimated from the time to laryngectomy. Late salvage laryngectomy and death from cancer with local recurrence were counted as events.

Results

Primary tumor response and toxicity

A total of 29 advanced hypopharyngeal cancer patients were treated. The patients' characteristics are given in Table 1. Three patients required tracheostomy because of airway obstruction.

All of the patients received one cycle of induction chemotherapy, and the response was evaluated by an otolaryngology specialist. A single cycle of IC achieved response in 21 of 29 patients (72%). A typical endoscopic finding of a good responder is shown in Fig. 1. The 21 responders received sequential CRT, with all patients completing the program. Eight patients had <50% shrinkage of the primary tumor, and these patients were scheduled for surgery. Four patients who had residual disease in their neck underwent modified radical or selective neck dissection. Viable cancer cells were detected in the post-operative lymph node specimens all four of these patients. (Fig. 2). One patient of the

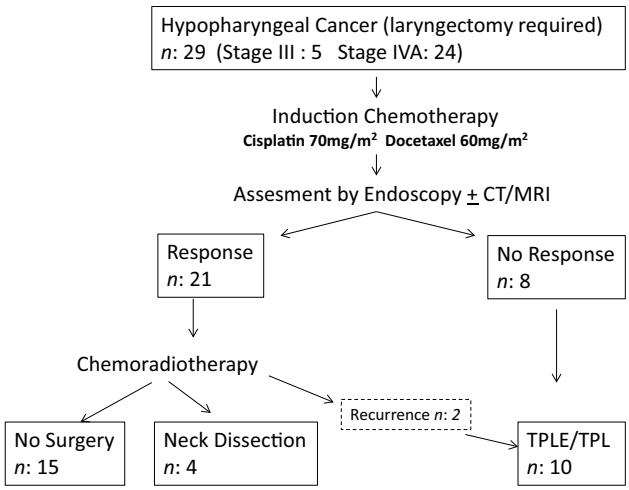

Fig. 2 Flowchart illustrating treatment of the patients. *n* Number of patients, *CT* computed tomography, *MRI* magnetic resonance imaging, *TPLE* total pharyngo-laryngo-cervical esophagectomy, *TPL* total pharyngo-laryngectomy

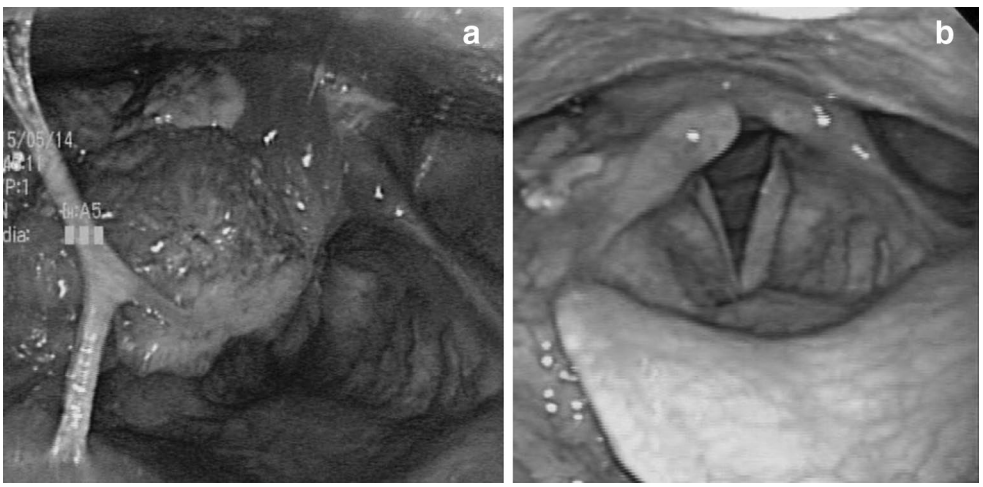

Fig. 1 Typical endoscopic finding of a responder. **a** T3 lesion is observed in the right pyriform sinus. **b** Findings following 1 cycle of IC (cisplatin + docetaxel). 90% shrinkage was obtained

Table 2 Acute toxicities during induction chemotherapy (Grades 3/4)

Acute toxicities	Number of patients (%)
Neutropenia	12 (41%)
Anemia	2 (6.9%)
Diarrhea	1 (3.4%)
Eruption	1 (3.4%)
Cholangitis	1 (3.4%)

four patients who received neck dissection could not be salvaged and died of neck recurrence.

During induction chemotherapy, 12 patients (41%) experienced Grade 3/4 leukopenia (Table 2). The adverse events were all managed, including three patients who used granulocyte colony stimulating factor. There was no severe side effect which caused a delay of the sequential CRT or surgery.

Survival

The mean follow-up time was 25.8 (range 6–74) months. The estimated 2-year overall survival was 74.0% (stage III 100%, stage IVA 69.1%) (Fig. 3a). Distant metastasis was the most common cause of failure (6 patients) affecting overall survival. None of the patients who developed distant metastases were controlled. The estimated 2-year disease-specific survival was 74.0% (stage III 100%, stage IVA 69.1%) (Figure 3b).

Larynx preservation

Ten patients (34%) underwent surgery (TPL/TPLE), among whom eight patients received surgery sequentially to IC following the planned assessment. All eight patients who received surgery underwent post-operative CRT due to multiple lymph node metastasis or extra-capsular invasion of the lymph nodes. Two patients received surgery for eventual recurrence. The salvage surgeries were uneventful without severe complications. The cumulative laryngeal preservation rate (2 years) was 100% for stage III hypopharyngeal cancer and 53.6% for stage IVA. The preservation rate was 87.5 and 30.8% for patients with T3 and T4 tumors, respectively (Fig. 4).

Discussion

The treatment strategy for resectable, hypopharyngeal patients is still controversial. For locally advanced cases that require total laryngectomy, the treatment options are (1) upfront surgery, (2) CRT, or (3) sequential therapy starting from IC [5]. Laryngeal preservation has been a challenge in the treatment of this disease. CRT with CDDP has been the preferred treatment for patients with advanced hypopharyngeal cancer who want to preserve their larynx [5]. However, these patients sometimes suffer from severe treatment-associated toxicity, including dysphagia and aspiration. In laryngeal cancer, the long-term follow-up results of patients treated by CRT with CDDP indicate that death from causes unrelated to the primary cancer are not negligible [6], suggesting that CRT can reduce the long-term quality of life of these patients. There is still no gold standard strategy for the treatment of locally advanced, resectable hypopharyngeal cancer patients.

The concept of IC has been studied and considered for various purposes, including organ preservation (chemoselection), improvement of overall survival, and reduction of distant metastasis. Lefebvre et al. [7] compared the treatment results of the sequential (IC followed by CRT)

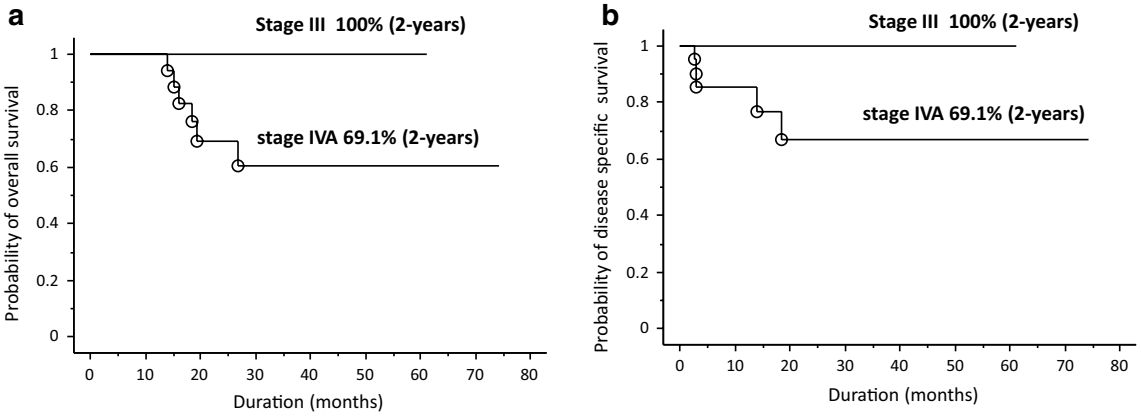

Fig. 3 Kaplan–Meier analysis of overall survival (**a**) and disease-specific survival (**b**). Estimated 2-year overall survival for stage III and IVA patients was 100 and 69.1%, respectively. Estimated 2-year disease specific survival for stage III and IVA patients was 100 and 69.1%, respectively

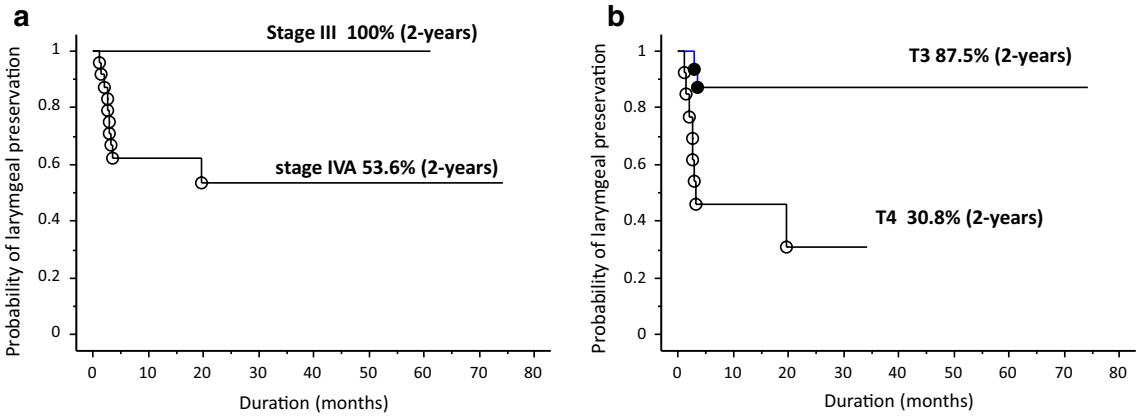

Fig. 4 Kaplan–Meier analysis of laryngeal preservation. Late salvage laryngectomy and death from cancer with local recurrence were counted as events. Estimated 2-year preservation for stage III and IVA tumors was 100 and 53.6%, respectively. Estimated 2-year preservation for patients with T3 and T4 tumors was 87.5 and 30.8% respectively

approach and the upfront surgery approach in resectable hypopharyngeal cancer patients. These authors demonstrated that IC (3 cycles of CDDP + 5-FU) followed by CRT did not compromise the survival of these patients while enabling retainment of the larynx [7]. The clinical usefulness of a single cycle of IC with FP for chemoselection in laryngeal cancer patients has been reported by Urba et al. [3]. Single-cycle IC with FP followed by CRT is also an effective treatment for human papillomavirus-positive oropharyngeal cancer patients [8].

The addition of DOC to the dual therapeutic combination of FP, resulting in the triple combination of TPF, for IC has been reported to improve the overall survival rates of advanced HNSCC patients. The TPF regimen is recognized as a standard treatment regimen of IC [9, 10]. A randomized trial reported by Pointraeu et al. compared the TPF and the FP regimens in hypopharyngeal cancer patients as IC regimens with respect to preservation of the larynx. The 3-year larynx preservation rate was superior in the TPF group but there was no difference in survival rates [11]. However, no direct comparison of the TPF regimen and the TP regimen in this context has been made.

Recently, Popovtzer et al. studied a series of 27 patients with advanced laryngeal cancer and reported that single-cycle IC by TPF was sufficient to identify those patients amenable to organ preservation [12]. At our institution, we utilize single-cycle IC of TP in advanced hypopharyngeal cancer patients for the purpose of chemoselection. We do not use the TPF regimen because of its toxicity and the possibility of having to delay subsequent treatment. Although our study involves only a small number of patients, the survival rate and laryngeal preservation rate were satisfactory compared to recent reports using TPF for IC [12–14]. A study comparing TPF and TP as an IC setting is necessary to prove the non-inferiority of TP chemotherapy.

From the point of view of a surgical oncologist, we should disregard the opportunity of a curative operation, which may be the only option to cure the disease. However, we occasionally have patients who are forced to delay their curative operation due to the toxicity of the primary treatment. IC with the aim of chemoselection should be performed within a short period with an effective regimen that has minimum toxicity and which does not impair the general condition of the patient. The major toxicity of our protocol is neutropenia, which can be managed by granulocyte-colony stimulating factor. Assessment after the single cycle of IC does not delay the following treatment and is well tolerated. On the other hand, late adverse events could not be evaluated in this study due to short follow-up period.

Decreasing distant metastasis is one of the objects of IC. Budach et al. performed a meta-analysis and came to the conclusion that additional IC does not improve survival in patients with locally advanced cancer compared to definite CRT [15]. Our study is not a comparison of the treatment results with upfront CRT patients; however, the major cause of death was due to distant metastasis and the survival rate was not improved. The only benefit of single-cycle induction may be its use as a selection strategy. There are still multiple controversies surrounding the role of IC in the multidisciplinary treatment of HNSCC, including the regimen and cycles of IC. Although retrospective, our results suggest the potential of this sequential approach for treating patients with locally advanced, operable hypopharyngeal cancer.

Conclusions

This is the first report on treating patients with advanced hypopharyngeal cancer with a sequential strategy of

single-cycle IC (CDDP + and DOC) followed by CRT. We demonstrated that this strategy may be useful to identify patients who are suitable for receiving organ preservation treatment for advanced hypopharyngeal cancer patients. IC intended for organ preservation strategies should be of low toxicity. Although we recognize that there are limitations to our due to its retrospective design and small number of patients, we emphasize that patients with advanced hypopharyngeal cancer should be given the opportunities for both definitive CRT and surgery. Additional studies, including prospective studies, are necessary to verify our findings.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Forastiere AA, Weber RS, Trotti A (2015) Organ preservation for advanced larynx cancer: issues and outcomes. J Clin Oncol 33(29):3262–3268
2. Worden FP, Moyer J, Lee JS et al (2009) Chemoselection as a strategy for organ preservation in patients with T4 laryngeal squamous cell carcinoma with cartilage invasion. Laryngoscope 119(8):1510–1517
3. Urba S, Wolf G, Eisbruch A, et al (2006) Single-cycle induction chemotherapy selects patients with advanced laryngeal cancer for combined chemoradiation: a new treatment paradigm. J Clin Oncol 24(4):593–598
4. Nonoshita T, Shioyama Y, Nakamura K et al. (2011) Concurrent chemoradiotherapy with S-1 for T2N0 glottic squamous cell carcinoma. J Radiat Res (Tokyo) 52(1):47–53
5. NCCN Clinical Practice Guidelines (2016) In Oncology 2016 ver 2, Head and Neck Cancers, p 31
6. Forastiere AA, Zhang Q, Weber RS et al (2013) Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. J Clin Oncol 31(7):845–852
7. Lefebvre JL, Andry G, Chevalier D, Luboinski B, Collette L, Traissac L, de Raucourt D, Langendijk JA, EORTC Head and Neck Cancer Group (2012) Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891. Ann Oncol 23(10):2708–2714
8. Worden FP, Kumar B, Lee JS et al (2008) Chemoselection as a strategy for organ preservation in advanced oropharynx cancer: response and survival positively associated with HPV16 copy number. J Clin Oncol 26(19):3138–3146
9. Vermorken JB, Remenar E, van Herpen C, EORTC 24971/TAX 323 Study Group et al (2007) Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 357(17):1695–1704
10. Posner MR, Hershock DM, Blajman CR, TAX 324 Study Group et al (2007) Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 357(17):1705–1715
11. Pointreau Y, Garaud P, Chapet S et al (2009) Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst 101(7):498–506
12. Popovtzer A, Burnstein H, Stemmer S et al (2016) Phase II organ-preservation trial: concurrent cisplatin and radiotherapy for advanced laryngeal cancer after response to docetaxel, cisplatin, and 5-fluorouracil-based induction chemotherapy. Head Neck. doi: 10.1002/hed.24571
13. Céruse P, Cosmidis A, Belot A et al (2014) A pyriform sinus cancer organ preservation strategy comprising induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil, followed by potentiated radiotherapy: a multicenter, retrospective study. Anticancer Drugs 25(8):970–975
14. Matsuzuka T, Sato H, Suzuki R et al (2016) Chemoselection combined with alternating chemoradiotherapy or surgery for hypopharyngeal cancer. Laryngoscope 126(6):1349–1353
15. Budach W, Bölke E, Kammers K et al (2016) 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. Radiother Oncol 118(2):238–243