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INDUCTION CHEMOTHERAPY IN SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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Summary

Chemotherapy represents an important component of multimodality treatment approach for locally and/or locoregionally advanced squamous cell carcinoma of the head and neck. There is now clear evidence that concurrent chemoradiotherapy provides statistically significant improvement in survival and locoregional control in patients with advanced head and neck cancer. Induction chemotherapy has been shown to permit organ preservation in operable patients and to reduce the risk of distant metastases. The renewed interest of re-integration of induction chemotherapy in the treatment of head and neck cancer is based upon the recognition that the development of distant metastatic disease has become more frequent pattern of failure when concurrent chemotherapy is utilized as standard of care for this patient category. Induction chemotherapy, being directed to decrease the incidence of distant metastases, is expected to improve overall treatment outcome. Recently documented improvement of response rates and survival outcome by the addition of a taxane to standard platinum plus 5-fluorouracil regimen has also indicated the possibility of a new role for induction chemotherapy. There are encouraging results of phase II trials investigating the sequential treatment approach of induction chemotherapy with three-drug regimens incorporating taxane followed by concurrent chemoradiotherapy. Phase III trials comparing taxane containing induction chemotherapy followed by chemoradiotherapy with chemoradiotherapy alone are currently underway. However, induction chemotherapy still remains an investigational treatment strategy in the management of advanced head and neck cancer.

KEY WORDS: *head and neck cancer, chemotherapy, concurrent chemoradiotherapy, induction chemotherapy*

INDUKCIJSKA KEMOTERAPIJA KARCINOMA PLOČASTIH STANICA GLAVE I VRATA

Sažetak

Kemoterapija je važan sastavni dio multimodalnog pristupa liječenju lokalnog i/ili lokoregionalno uznapredovanog karcinoma pločastih stanica glave i vrata. Sada postoje jasni dokazi da istodobna kemoradioterapija daje statistički znakovito bolje rezultate s obzirom na preživljenje i lokoregionalnu kontrolu bolesti u bolesnika s uznapredovalim rakom glave i vrata. Pokazalo se da indukcijska kemoterapija štiti organe kod operabilnih bolesnika te smanjuje rizik nastanka udaljenih metastaza. Ponovno zanimanje za uvođenjem indukcijske kemoterapije u liječenju raka glave i vrata temelji se na spoznaji da je udaljena metastatka bolest češća nakon neuspjele istodobne kemoterapije koja se primjenjuje kao standardni način liječenja te vrste bolesnika. Očekuje se da bi se indukcijskom kemoterapijom, kojoj je cilj smanjiti pojavnost udaljenih metastaza, mogli poboljšati sveukupni rezultati ishoda liječenja. Nedavno dokazano poboljšanje u stopama odgovora i preživljenju postignuto dodavanjem taksana standardnoj kemoterapijskoj shemi platina plus 5-fluorouracil također je uputilo na mogućnost da indukcijska kemoterapija preuzme novu ulogu. Rezultati ispitivanja faze II, u kojima se istražuje slijedni/sekvencijski pristup u liječenju primjenom indukcijske kemoterapije prema shemama s tri lijeka među kojima je i taksan nakon koje slijedi istodobna kemoteradioterapija, su obećavajući. U tijeku su i ispitivanja faze III u kojima se indukcijska kemoterapija koja sadrži taksan nakon koje slijedi kemoradioterapija uspoređuje s primjenom samo kemoteradioterapije. Međutim, primjena indukcijske kemoterapije u zbrinjavanju uznapredovalog raka glave i vrata još se ispituje.

KLJUČNE RIJEČI: *rak glave i vrata, kemoterapija, istodobna kemoradioterapija, indukcijska kemoterapija*

INTRODUCTION

Locally advanced squamous cell carcinomas of the head and neck are treated by multimodality treatment approaches involving the sequential or simultaneous use of surgery, radiotherapy and chemotherapy. The integration of chemotherapy as treatment option into combined modality approaches has been an effort to improve outcomes in this proportion of patients characterized with poor long-term disease-free and overall survival rates. Chemotherapy may be given as induction, delivered prior to definitive locoregional treatment (most commonly several cycles of cisplatin and infusional 5-fluorouracil), or as concurrent with radiotherapy (chemoradiotherapy).

During the past 25 years, the extensive research of the influence of the addition of platinum-based chemotherapy to local treatment modalities of surgery and radiotherapy on overall survival resulted in confirmation that only concurrent chemoradiotherapy as definitive treatment for patients with locoregionally advanced head and neck cancer has succeeded to improve outcomes. The results of both numerous single-institution (1, 2, 3) and multi-institutional (4, 5, 6) randomized phase III trials comparing radiotherapy alone to chemoradiotherapy, as well as several meta-analyses (7, 8) seem to be quite sufficient to make evidence-based recommendations supporting radiotherapy and concurrent cisplatin-based chemoradiotherapy as a standard of care in patients with unresectable squamous cell head and neck tumors (9), nasopharyngeal cancer (10), laryngeal and oropharyngeal cancers with an intention to achieve vocal function and swallowing preservation (11, 12) and in the postoperative adjuvant setting for patients at high risk of recurrence (13, 14).

According to the largest meta-analysis performed by the Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) Collaborative Group which evaluated the data from 63 randomized trials, the estimated increase in survival with concurrent chemoradiotherapy was 8% ($p<0.0001$) (7). Intending to further confirm the results, MACH-NC performed an update of this analysis incorporating data from 24 additional trials. The update confirmed survival benefit of 8% at 5 years ($p<0.0001$) of concomitant chemotherapy with both definitive and postoperative radiotherapy (15).

INDUCTION CHEMOTHERAPY

Induction chemotherapy, the use of systemic chemotherapy before definitive surgery and/or radiotherapy has been a well-studied option in the management of squamous cell head and neck cancer for the last 25 years.

The proposed advantages of induction chemotherapy are the possibility of shrinkage of the macroscopic tumor leading to reduction in the irradiated volume, the possibility of assessment of clinical response to chemotherapy which predicts response to radiotherapy, as well as the possibility of delivering doses that are effective against occult systemic disease (16, 17). Regarding the possible disadvantages of induction chemotherapy there are theoretical concerns that this treatment option may be immunosuppressive reducing compliance to subsequent radiotherapy, which may induce accelerated repopulation, and also may allow for the emergence of radioresitant tumor cells clones (16, 17).

A high degree of responsiveness to induction chemotherapy was demonstrated with combination of cisplatin and 5-fluorouracil regimen with overall response rates of 60%-90% (18, 19) and complete responses in approximately 30% of previously untreated patients with head and neck cancer (20). These responses suggested that this treatment option might be attractive in permitting preservation of organ function and improving locoregional control and overall survival and might also demonstrate a substantial effectiveness in controlling distant metastatic disease.

In the 1980s, the demonstrated efficacy of induction chemotherapy in patients with head and neck cancer with regard to larynx preservation, suggesting that surgery could be omitted in responding patients without compromising survival (21, 22), led to three prospective randomized trials conducted by Department of Veterans' Affairs (DVA) (23), the European Organization for Research and Treatment of Cancer (EORTC) (24), and the Groupe d'Etudes des Tumeurs de La Tete et du Cou (GETTEC) (25). All of them were two-arm studies with the experimental arm consisted of two to three cycles of cisplatin 100 mg/m^2 on day 1 and 5-fluorouracil 1000 mg/m^2 by continuous infusion on days 1-5 and the control arm consisted of total laryngectomy and postoperative ra-

Table 1.

PHASE III TRIALS DEMONSTRATING IMPROVEMENT IN SURVIVAL RATES WITH INDUCTION CHEMOTHERAPY

Study and Patient characteristics	Study arm	Survival
Domenge et al. (28) GETTEC (n = 318) Stage III/IV disease Oropharynx	Experimental arm Induction chemotherapy (3 cycles with cisplatin and 5-fluorouracil) + locoregional treatment (surgery plus radiotherapy or radiotherapy alone) Control arm Same locoregional treatment without chemotherapy	Median survival of 5.1 years Overall survival significantly better (P = 0.03) Median survival of 3.3 years
Paccagnella et al. (29) Gruppo di Studio sui Tumori della Testa e del Collo (n = 237) Stage III/IV disease Oral cavity, oropharynx, hypopharynx, and paranasal sinuses	Experimental arm Induction chemotherapy (4 cycles cisplatin and 5-fluorouracil) followed by locoregional treatment (surgery plus radiotherapy or radiotherapy alone) Control arm Surgery with postoperative radiotherapy in operable patients and radiotherapy alone in inoperable patients	Overall survival in inoperable patients: at 2 years - 30%; at 3 years - 24%. Overall survival in inoperable patients: at 2 years - 19%; at 3 years - 10%. (P = 0.04)

diotherapy. Conventionally fractionated radiotherapy delivering a total dose of 70 Gy was preceded in responders to chemotherapy, while nonresponders were treated with total laryngectomy and postoperative radiotherapy. The results of combined chemotherapy and radiotherapy vs. primary surgery and postoperative radiotherapy in locally advanced carcinomas of the larynx and hypopharynx achieved in these three trials were investigated in a specific analysis as the third meta-analysis in the paper of Pignon et al. (7). There was a non-significant trend of a lower 6% survival in the group treated with induction chemotherapy followed with radiotherapy, while 58% of the surviving patients in this group had their larynx preserved.

Despite the fact that approximately 70%-85% of patients treated with induction chemotherapy have a major response, this treatment option did not succeed to demonstrate major impact on locoregional control (26). Two randomized trials in patients with advanced resectable laryngeal cancer illustrated that induction chemotherapy did not improve locoregional control. One of these is the DVA trial (23). In this study, induction chemotherapy followed by radiotherapy achieved worse local control than total laryngectomy and postoperative radiotherapy. The other one is the RTOG 91-11 trial (11) the primary end-point of which was larynx preservation. Patients were randomly assigned to one of three treatments: induction chemotherapy (cisplatin plus 5-fluorouracil) followed by radiotherapy, radiotherapy with concurrent administration of cisplatin, or radiotherapy alone. Induction chemotherapy followed by radiotherapy achieved similar local control rate as did radiotherapy alone, but was associated with greater rate of high-grade toxic effects. The rate of locoregional control was significantly better with the concurrent chemoradiotherapy approach (78% vs. 61% with induction chemotherapy followed by radiotherapy and 56% with radiotherapy alone) (11). There were no significant differences in laryngectomy-free survival and overall survival between the three treatment arms which pointed out that despite the improvement in locoregional control, concurrent chemoradiotherapy had not provided an improvement in survival over induction chemotherapy or radiotherapy alone (11).

The results of the large number of phase III clinical trials thoroughly testing induction chemotherapy have consistently failed to demonstrate that this treatment approach leads to a survival benefit (26, 27). There were only two trials revealing the improvement in survival rates with induction approach (28, 29) (Table 1). Domenge at al. (28) reporting the results from the trial in oropharyngeal cancer conducted by GETTEC revealed that overall survival was significantly better (p=0.03) in the induction chemotherapy group than in the control group. This is the only trial showing an advantage in overall survival for induction chemotherapy over locoregional treatment alone for operable and inoperable patients

(P=0.03) (Table 1). The subset analysis of inoperable patients in the trial by Paccagnella et al. (29) conducted to evaluate the contribution of induction chemotherapy to the survival in patients with stages III and IV head and neck cancer suggested that this patients' category benefited from induction chemotherapy in term of overall survival (p=0.04). The updated results for overall survival after a minimum follow-up of 10 years were reported by Zorat et al. (30). The subset analysis showed that among inoperable patients, there was a statistically significant better survival observed in the induction chemotherapy group compared to patients who did not receive induction chemotherapy (5-year survival: 21% vs. 8%; 10-year survival 16% vs. 6%; P= 0.04).

Several meta-analyses have also failed to demonstrate any significant improvement in survival after induction chemotherapy followed by radiotherapy (7, 8, 31). The largest and most detailed of these, the MACH-NC, analyzed data from 31 trials of induction chemotherapy with more than 5,200 patients enrolled and reported 2% 5-year improvement in overall survival being statistically nonsignificant (HR=0.95, 95% CI= 0.88 to 1.01; P=0.38) (7). According to Posner (32), the modest benefit of induction chemotherapy on survival in these analyses could be partially attributed to the inclusion of suboptimal chemotherapy regimens with limited activity.

The effectiveness of induction chemotherapy in controlling distant disease has been also of a great interest. Induction chemotherapy appears to decrease the incidence of distant metastases. In the Paccagnella study, the analysis of time to distant metastases showed an advantage for induction chemotherapy group with 3-year estimate of distant metastases fell from 38% to 14% (P=0.002) (29). The impact on distant metastases has been also observed in DVA trial (23). There were significantly fewer distant metastases (P=0.016) in the chemotherapy group than in the surgery group.

In general, although there were conclusions that induction chemotherapy could modestly reduce the incidence of distant metastases, it's inability to improve locoregional control as well as to make an impact on survival demonstrated in most of the studies, had serious influence on continuous enthusiasm diminishment about this treatment approach (27).

RENEWED INTEREST IN INDUCTION CHEMOTHERAPY

However, treatment failure due to the development of distant metastases in 1 of 5 patients with stage III-IV disease treated with new multimodality approaches including concurrent chemoradiotherapy should not be underestimated (16). The adoption of concurrent chemoradiotherapy as a standard of care for these patients increased locoregional treatment intensity leading to an increased risk of distant metastatic disease. This lack of impact on distant metastases after concurrent chemoradiotherapy, despite an improvement in survival, has been reported from many of the major phase III trials that have tested this approach (1, 2, 4). Consequently, the pattern of treatment failure may be shifting from locoregional recurrence to distant metastatic disease (33, 34).

The renewed interest in re-exploration of induction chemotherapy is predominantly based upon the fact that it consistently demonstrates a systemic effect to suppress the development of distant metastases as well as upon the recognition that improvement in locoregional control with aggressive concurrent treatment approaches results in a relative risk of distant metastases. The recognition that response to induction chemotherapy is predictive of a response to subsequent radiotherapy is another observation resulting in enhanced interest in the use of this treatment approach. The chemotherapy responsiveness might identify those patients most appropriately treated with definitive radiotherapy instead of surgery (23). Another striking observation leading to necessity of future investigation of induction chemotherapy incorporated in the multimodality treatment of advanced head and neck cancer is the recognition of preliminary reports suggesting that there are combination chemotherapy regimens more efficacious than cisplatin and 5-fluorouracil (35, 36). Several phase I/II studies have indicated that adding a taxane improves responsiveness to cisplatin plus 5-fluorouracil based induction chemotherapy. High response rates with docetaxel, cisplatin and 5-fluorouracil induction chemotherapy were seen in several studies which reported overall response rates of 71%-100% (36, 37, 38, 39, 40) (Table 2). The addition of paclitaxel to cisplatin plus 5-fluorouracil based induction chemotherapy has been eva-

Table 2.

PHASE I/II TRIALS OF TAXANE AND CISPLATIN PLUS 5-FLUOROURACIL INDUCTION CHEMOTHERAPY

Study	Regimen	Overall response rate	Overall survival
Posner et al. (36) (n=43)	Docetaxel 75 mg/m^2, day 1; cisplatin 75-100 mg/m^2, days 1; 5-fluorouracil 1000 mg/m^2, days 1-4;	93%	Not reported
Colevas et al. (37) (n = 23)	Docetaxel 25-60 mg/m^2, day 1; cisplatin 25 mg/m^2, days 1-5; 5-fluorouracil 700-800 mg/m^2, days 1-5; leucovorin 500 mg/m^2, days 1-5	100%	100% at 1 year; 83% at 2 years; 78% at 3 years
Colevas et al. (38) (n = 30)	Docetaxel 60 mg/m^2, day 1; cisplatin 25 mg/m^2, days 1-4; 5-fluorouracil 700 mg/m^2, days 1-4; leucovorin 500 mg/m^2, days 1-4	93%	83% at 1 year; 80% at 2 years; 77% at 3 years
Schrijvers et al. (39) (n = 48)	Docetaxel 75 mg/m^2, day 1; cisplatin 75-100 mg/m^2, day 1; 5-fluorouracil 750 mg/m^2, days 1-5	71%	69% at 1 year; 41% at 2 years
Tsukuda et al. (40) (n = 18)	Docetaxel 60-70 mg/m^2, day 1; cisplatin 60-70 mg/m^2, day 4; 5-fluorouracil 600-750 mg/m^2, days 1-5	94%	Not reported
Hitt et al. (35) (n = 70)	Paclitaxel 175 mg/m^2, day 1; cisplatin 100 mg/m^2, day 2; 5-fluorouracil 500-750 mg/m^2, days 2-6	88%	44% at 5 years
Hitt et al. (41) (n = 35)	Paclitaxel 175 mg/m^2, day 1; cisplatin 35 mg/m^2, days 1-2; 5-fluorouracil 1,000 mg/m^2, days 1-2; leucovorin 200 mg/m^2, day 1; leucovorin 500 mg/m^2, days 1-4	86%	Median, 18 months

Table 3.

PHASE III TRIALS EVALUATING ADDITION OF TAXANE TO CISPLATIN BASED INDUCTION CHEMOTHERAPY

Study	Regimen	Overall survival
Remenar et al. (42) EORTC 24971 (n = 358)	Experimental arm: docetaxel 75 mg/m^2, cisplatin 75 mg/m^2, day 1; 5-fluorouracil 750 mg/m^2, days 1-5. Control arm: cisplatin 100 mg/m^2, day 1; 5-fluorouracil 1,000 mg/m^2, days 1-5.	37% at 3 years Median, 18.6 months 24% at 3 years Median, 14.2 months (P = 0.0052)
Gibson et al. (43) E1395 Intergroup trial of ECOG (n = 204)	Experimental arm: cisplatin 75 mg/m^2, day 1; paclitaxel 175 mg/m^2, day 1. Control arm: cisplatin 100 mg/m^2, day 1; 5-fluorouracil 1,000 mg/m^2, days 1-4.	41% at 1 year 32% at 1 year (P = 0.49)

luated in phase II trials in patients with advanced head and neck cancer, also producing high overall response rates (35, 41) (Table 2). There was a survival benefit demonstrated for docetaxel, cisplatin and 5-fluorouracil over cisplatin and 5-fluorouracil induction chemotherapy in a randomized phase III trial conducted by EORTC (P=0.0052) (42) (Table 3). In contrast, in a phase III randomized, multicenter trial of the Eastern Cooperative Oncology Group (ECOG), no statistically significant difference in survival was seen between patients treated with cisplatin plus 5-fluorouracil and those treated with cisplatin plus paclitaxel induction chemotherapy (43) (Table 3).

SEQUENTIAL THERAPY

While concomitant chemotherapy is conceptually supported by the natural history of head and neck cancer, which indicates a primary need to improve locoregionally therapy and only a secondary need to improve systemic therapy, the utilization of induction chemotherapy which has been shown to demonstrate activity against systemic micrometastatic disease, is expected to improve the effectiveness of systemic therapy (27, 33). The use of both induction chemotherapy and concurrent chemoradiotherapy in a sequential approach may provide optimal benefit for patients

with locoregionally advanced head and neck cancer since the intervention with induction chemotherapy is directed at improving distant control which might be important in improving overall treatment outcome (44). According to Brockstein et al. (45) whose analysis showed that 5-year distant relapses had become more frequent in chemoradiotherapy group compared with the group treated with induction chemotherapy followed by chemoradiotherapy, randomized clinical trials of induction chemotherapy are warranted to determine if a decrease in distant metastases can lead to increase in survival in the setting of effective chemoradiotherapy for locoregional control.

A number of phase II randomized comparative trials exploring sequential therapy approaches have been conducted. Hainsworth et al. (46) reported the results of a multicenter, community based phase II study enrolling 123 patients with locally advanced squamous cell carcinoma of the head and neck. Induction chemotherapy included paclitaxel, carboplatin and 5-fluorouracil while concurrent chemotherapy consisted of six weekly doses of paclitaxel and carboplatin. Clinical complete response to treatment was achieved in 60% of patients.

The results of a University of Pennsylvania phase II trial using induction chemotherapy with high-dose paclitaxel and carboplatin for two cycles followed by weekly chemoradiotherapy with low-dose paclitaxel in patients with resectable oropharyngeal tumors showed complete response rate of 90% and actuarial 3-year survival rate estimated to be 70% (47).

In a trial conduced at the University of Chicago there were high response activity and possibility of decrease of distant failure rates observed by administration of carboplatin and paclitaxel as a brief course of induction chemotherapy before concurrent chemoradiotherapy of paclitaxel, infusional 5-fluorouracil, hydroxiurea and twice-daily radiation therapy (TFHX) regimen (48).

The results of phase II study conducted by investigators at Yale University of induction chemotherapy consisted of two courses of cisplatin, 5-fluorouracil and leucovorin followed by concurrent chemoradiotherapy consisting of cisplatin 100 mg/m2 on days 1 and 22 and 70 Gy of radiotherapy, showed complete response rate of 67% and 5-year overall survival rate of 52% after cisplatin chemoradiotherapy (49).

In the Southwest Oncology Group designed phase II trial for patients with base of tongue or hypopharyngeal cancer, two courses of cisplatin and 5-fluorouracil induction chemotherapy was administered to select patients for organ preservation (50). Patients who had greater response than 50% received concurrent cisplatin and radiotherapy. Histological complete response was achieved in 54% of the patients.

Anticipating that induction chemotherapy decreases the risk of distant metastases, the best way to answer the question about the contribution that re-introduction of induction chemotherapy will make to overall survival would be the study design with utilization of platinum-based concurrent chemoradiotherapy regimen in both control and experimental treatment arm preceded by three-drug induction regimen utilizing taxane, cisplatin or carboplatin and 5-fluorouracil. Two randomized phase III studies evaluated the benefits of the addition of taxane to platinum plus 5-fluorouracil based induction chemotherapy. The TAX 324 study evaluated induction cisplatin and 5-fluorouracil with or without docetaxel followed by concurrent chemoradiotherapy with weekly carboplatin and surgical resection in patients with locally advanced squamous cell head and neck cancer (51). The overall response rate after induction chemotherapy trended toward an improvement with the addition of docetaxel (72% vs. 64%, $P = 0.07$). There was also a highly significant 3-year survival advantage demonstrated in cisplatin/5-fluorouracil/docetaxel arm (62% vs. 48%, $P=0.01$). In the study conducted by the investigators in Madrid (52), induction chemotherapy treatment of paclitaxel, cisplatin, and 5-fluorouracil was compared with standard cisplatin and 5-fluoruracil induction therapy, both followed by concurrent chemoradiotherapy with cisplatin. The addition of paclitaxel to standard induction chemotherapy resulted in significantly higher complete response rate ($P<0.001$) as well as in a trend to a longer overall survival ($P=0.06$).

The best way to answer the question whether sequential treatment approach utilizing both induction chemotherapy and concurrent chemoradiotherapy might provide better results than concurrent chemoradiotherapy alone should be the comparison of these two treatment modalities in phase III trials. Considering the fact that addition of induction chemotherapy to concurrent chemo-

radiotherapy is a complicated treatment schedule leading to a considerable toxicity, it has to be investigated in prospective randomized trials of patients with advanced regional nodal disease and/or large primary tumors because these advanced stages of disease are associated with an increased risk of distant dissemination. The appropriate phase III study should be a comparison of a three-drug induction regimen followed by concurrent chemoradiotherapy, with concurrent chemoradiotherapy alone. It is of great importance to best select the patients at high risk of developing distant disease based on stage-related prognostic indicators (27). In the retrospective study carried out in 1244 patients with head and neck cancer who achieved locoregional control, Leon et al. (53) indicated nodal stage, tumor stage, and the location of the tumor at the hypopharynx and supraglottis as factors that significantly increase the risk of distant metastases. In a retrospective review with long-term follow-up reported from the Cleveland Clinic Foundation studying concurrent chemoradiotherapy, both hypopharyngeal primary site and poorly differentiated histology were independent predictors for the development of distant metastases while distant disease control did not correlate with tumor stage and nodal stage (1).

In North America, three trials testing induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil followed by concurrent chemoradiotherapy, compared with chemoradiotherapy alone in a high-risk patient population, are currently open (27, 32). The University of Chicago trial with an eligibility restricted to patients with N2-3 disease applies hyperfractionated radiotherapy, where as the trial jointly conducted by Southwest Oncology Group (SWOG) and the Eastern Cooperative Oncology Group (ECOG) recruiting patients with resectable stage III and IV oropharyngeal carcinoma uses conventionally fractionated radiotherapy. The third trial conducted at Dana-Faber Cancer Institute stipulating the enrolment of 300 patients is planned to use an accelerated fractionation/concomitant boost radiotherapy schedule (27).

CONCLUSION

According to the fact that the research into radiobiological predictive assays has so far failed to develop a clinically useful assay for identifying patients with minimal systemic disease at the time of diagnosis, the stratification of patient population that is at high risk for development of distant metastases and is expected to benefit from sequential use of induction chemotherapy and concurrent chemoradiotherapy, should be done by identification of prognostic factors for distant relapse.

There are also no published data so far from phase III trials comparing induction chemotherapy followed by concurrent chemoradiotherapy with the standard treatment of concurrent chemoradiotherapy alone.

Trials initiated in North America addressing the role of addition of induction chemotherapy to concurrent chemoradiotherapy in advanced disease with primary end-point being overall survival, have the potential to define the role of induction chemotherapy in the management of patients with locally advanced head and neck cancer. Expecting the results of phase III studies comparing induction chemotherapy followed by concurrent chemoradiotherapy with concurrent chemoradiotherapy alone, we consider that induction chemotherapy remains only an investigational treatment option in the multimodality treatment of squamous cell carcinoma of the head and neck.

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