BRIEF COMMUNICATIONS

Randomized Phase III Trial of Neoadjuvant Chemotherapy in Head and Neck Cancer: 10-Year Follow-Up

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In 1986, we initiated a multicenter, randomized trial to compare induction chemotherapy with cisplatin and 5-fluorouracil followed by locoregional treatment (surgery and radiotherapy or radiotherapy alone) with locoregional treatment alone in patients with head and neck squamous cell carcinoma. Here we report the long-term results of the trial. A total of 237 patients with nonmetastatic stage III or IV head and neck carcinoma were randomly assigned to receive four cycles of neoadjuvant chemotherapy followed by locoregional treatment (group A) or locoregional treatment alone (group B). Among all patients, overall survival at 5 and 10 years was 23% (95% confidence interval [CI] = 15.3% to 30.9%) and 19% (95% CI = 11.6% to 26.4%), respectively, for those in group A and 16% (95% CI = 9.6% to 23.4%) and 9% (95% CI = 3.5% to 14.7%), respectively, for those in group B (P = .13). Among operable patients, we observed no difference between group A and group B in overall survival at 5 and 10 years (group A, 31% [95% CI = 14.9% to 47.3%] and 22.7% [95% CI = 7.1% to 38.3%], respectively; group B, 43.3% [95% CI = 25.6% to 61.0%] and 14.2% [95% CI = 0.1% to 28.3%], respectively; P = .73). Among inoperable patients, overall survival at 5 and 10 years was 21% (95% CI = 12.3% to 30.1%) and 16% (95% CI = 7.7% to 23.9%), respectively, for group A and 8% (95% CI = 1.5% to 12.3%) and 6% (95% CI = 0.1% to 9.1%), respectively, for group B (log-rank P = .04). Four cycles of neoadjuvant chemotherapy is a promising approach for treating patients with inoperable advanced head and neck cancer but not for treating patients with operable disease. [J Natl Cancer Inst 2004;96:1714–7]

Head and neck squamous cell carcinoma (HNSCC) is a potentially curable malignancy when it is diagnosed at an early stage. However, 60% of HNSCC patients present with advanced inoperable locoregional disease and thus have a poor prognosis *(1).* Chemoradiotherapy is the standard treatment for locally advanced HNSCC; the standard treatment for patients with operable HNSCC is surgery followed by postoperative radiotherapy, with or without adjuvant chemotherapy *(2–6).* Although neoadjuvant chemotherapy has a proven role in organ preservation and statistically significantly reduces the incidence of distant metastases, especially in laryngeal and hypopharyngeal cancers, its efficacy in prolonging overall survival has not yet been demonstrated *(7–9).*

On the basis of results obtained in a phase II study *(10),* we initiated a phase III study to evaluate 2-year overall survival among HNSCC patients randomly assigned to receive four cycles of cisplatin and 5-fluorouracil followed by locoregional treatment (group A) or locoregional treatment alone (group B). In our first published analysis of the trial data *(11),* we found that when all patients were considered in the analysis, there was no statistically significant difference between the two treatment groups with respect to overall survival: 37% for group A versus 29% for group B at 2 years (P = .21). Among patients with operable cancer, there was also no difference between the treatment groups in 2-year overall survival: 56% for group A versus 59% for group B (P = .46). However, among patients with inoperable head and neck cancer, we found that compared with group B, those in group A had better 2-year overall survival (30% versus 19%; P = .04), disease-free survival (49% versus 28%; P = .06), and locoregional control (84% versus 72%; P = .05). We now present the updated results for overall survival after a minimum follow-up of 10 years.

The principal eligibility criteria were histologically proven squamous cell carcinoma of the hypopharynx, oropharynx, oral cavity, or paranasal sinus; stage III or IV disease without distant metastases, according to the staging system of the International Union Against Cancer *(12);* no previous treatment; age 70 years or younger at randomization; a performance score of 50 or more on the Karnofsky scale; and normal cardiac, hepatic, renal, and bone marrow functions. Patients were evaluated by a multidisciplinary team (i.e., a surgeon, a medical oncologist, and a radiotherapist). Stratification and evaluation of operability were performed before patients were assigned to a treatment group. A tumor was defined as inoperable if it was fixed to either a bone structure or lymph nodes or if it was too invasive to allow for its radical surgical removal. Patients were stratified by institution, initial tumor stage (III versus IV), Karnofsky performance score ($<$70 versus $\geq$70), and operability status. Patients provided oral consent prior to randomization, according to the guidelines of the Ethics Com-

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Locoregional treatment for patients with operable HNSCC was surgery (removal of primary tumor and total neck dissection) followed by adjuvant radiotherapy (45–50 Gy). Locoregional treatment for patients with inoperable HNSCC was radical radiotherapy (65–70 Gy) to involved areas and a dose of 45–50 Gy to the uninvolved neck. Radiotherapy interruptions were allowed for 2 weeks after a dose of 40 Gy if grade 3 or 4 World Health Organization mucositis occurred *(13).* Chemotherapy consisted of cisplatin given intravenously at a dose of 100 mg/m^2 on day 1 and 5-fluorouracil given at a dose of 1000 mg/m^2/day by continuous intravenous infusion on days 1–5, every 3 weeks for four cycles. A dose reduction of 50% for cisplatin was recommended when serum creatinine levels increased to at least 2.5 times the normal upper limit. The dose of 5-fluorouracil was reduced by 25% and 50% in cases of grade 2 and 3 stomatitis, respectively. For grade 4 stomatitis, chemotherapy was stopped.

Patients were evaluated after they completed locoregional treatment. When biopsy-confirmed complete remission of the primary tumor was found in inoperable patients, total neck dissection was performed in those patients with residual lymph node involvement. Patients were followed up every 2 months during the first year, every 3 months during the subsequent 2 years, and then twice a year thereafter. Patients were observed until 2001, providing a median follow-up of 12.5 years (range = 10.7–14.6 years). Approximately 16.6% of patients were not followed up according to this schedule after the first 5 years of follow-up.

The primary objective of the trial was to compare overall survival in group A with that in group B. Statistical analyses were performed on an intent-to-treat basis. Overall survival was defined as the time between treatment randomization and the date of the patient's last follow-up or death. The trial was designed to have an 80% power to detect improvements in 2-year overall survival of 25% for group B (i.e., the control group) and of 40% for group A (i.e., the experimental group) with a two-sided alpha of .05. Survival curves were estimated by the Kaplan–Meier method, and comparisons were made using the log-rank test. Cox proportional hazards regression analysis was used to evaluate the association between baseline factors and overall survival time (the data conformed to proportional hazards assumptions). Planned subgroup analyses were performed for operable and inoperable patients.

From March 3, 1986, to February 28, 1990, 237 patients with stage III or IV HNSCC were randomly assigned to receive four cycles of neoadjuvant chemotherapy with cisplatin–5-fluorouracil followed by locoregional treatment (group A) or locoregional treatment alone (group B). Patient characteristics were comparable for the two treatment groups *(11).* The proportions of patients with inoperable HNSCC were 71.2% in group A and 73.1% in group B.

Proportional hazards regression analysis applied to all randomly assigned patients gave hazard ratios of 1.25 (95% confidence interval [CI] = 0.82 to 1.90; $P = .29$) for site of disease (oropharynx versus oral cavity), 3.28 (95% CI = 1.56 to 6.90; $P = .002$) for stage T4 versus stage T1, 1.67 (95% CI = 1.03 to 2.69; $P = .04$) for lymph node status (N3 versus N0), and 0.92 (95% CI = 0.69 to 1.22; $P = .57$) for neoadjuvant chemotherapy with cisplatin–5-fluorouracil (group A versus group B) (Table 1). Among all patients, overall survival at 5 and 10 years was 23% (95% CI = 15.3% to 30.9%) and 19% (95% CI = 11.6% to 26.4%), respectively, for those in group A, and 16% (95% CI = 9.6% to 23.4%) and 9% (95% CI = 3.5% to 14.7%) respectively, for those in group B ($P = .13$) (Fig. 1). Among operable patients, we observed no difference in overall survival at 5 and 10 years between group A and group B (group A, 31% [95% CI = 14.9% to 47.3%] and 22.7% [95% CI = 7.1% to 38.3%], respectively; group B, 43.3% [95% CI = 25.6% to 61.0%] and 14.2% [95% CI = 0.1% to 28.3%], respectively; $P = .73$). By contrast, among inoperable patients, overall survival at 5 and 10 years was 21% (95% CI = 12.3% to 30.1%) and 16% (95% CI = 7.7% to 23.9%), respectively, for group A and 8% (95% CI = 1.5% to 12.3%) and 6% (95% CI = 0.1% to 9.1%), respectively, for group B (log-rank $P = .04$) (Fig. 1).

Table 1. Multivariate analyses*

Variable	HR (95% CI)	P†
Site of primary tumor		
Oral cavity	1.00 (referent)	
Hypopharynx	1.13 (0.72 to 1.80)	.59
Oropharynx	1.25 (0.82 to 1.90)	.29
Tumor stage‡		
T1	1.00 (referent)	
T2	1.23 (0.56 to 2.54)	.58
T3	2.18 (1.10 to 4.35)	.03
T4	3.28 (1.56 to 6.90)	.002
Lymph node status‡		
N0	1.00 (referent)	
N1	1.48 (0.90 to 2.42)	.11
N2	1.69 (0.96 to 3.00)	.07
N3	1.67 (1.03 to 2.69)	.04
Treatment arm		
No chemotherapy (group B)	1.00 (referent)	
Chemotherapy (group A)	0.92 (0.69 to 1.22)	.57

*HR = hazard ratio; CI = confidence interval.
†Two-sided Wald test.
‡*(12).*

Although chemotherapy in HNSCC has a proven role in organ preservation *(7–9),* the value of neoadjuvant chemotherapy is still controversial because survival data from individual studies are not concordant *(7,9,11,14–17).* Data from meta-analyses performed by the Meta-Analysis of Chemotherapy in Head and Neck Cancer Collaborative Group showed that patients treated with a cisplatin–5-fluorouracil combination as neoadjuvant chemotherapy had a small but statistically significant advantage in overall survival ($P = .05$) compared with patients treated with radiotherapy alone *(3).*

Current data do not support the use of neoadjuvant chemotherapy for HNSCC. However, neoadjuvant chemotherapy continues to be a common clinical practice for HNSCC in many centers. Thus far, results of at least seven other phase III trials that had study designs similar to that of our study, including the use of a cisplatin–5-fluorouracil combination, and with adequate numbers of patients, have been published *(7–9,14–17).* For three of those trials *(7–9),* the primary objective was organ preservation among patients with laryngeal and hypopharyngeal cancers; the other four trials were designed to verify the impact of chemotherapy on overall survival in operable and inoperable patients. Only the Groupe d'Etude des Tumeurs de la Tete et du Cou (GETTEC) trial *(16)* showed an advantage in overall survival for neoadjuvant chemotherapy over locoregional treatment alone for operable and inoperable patients (median sur-

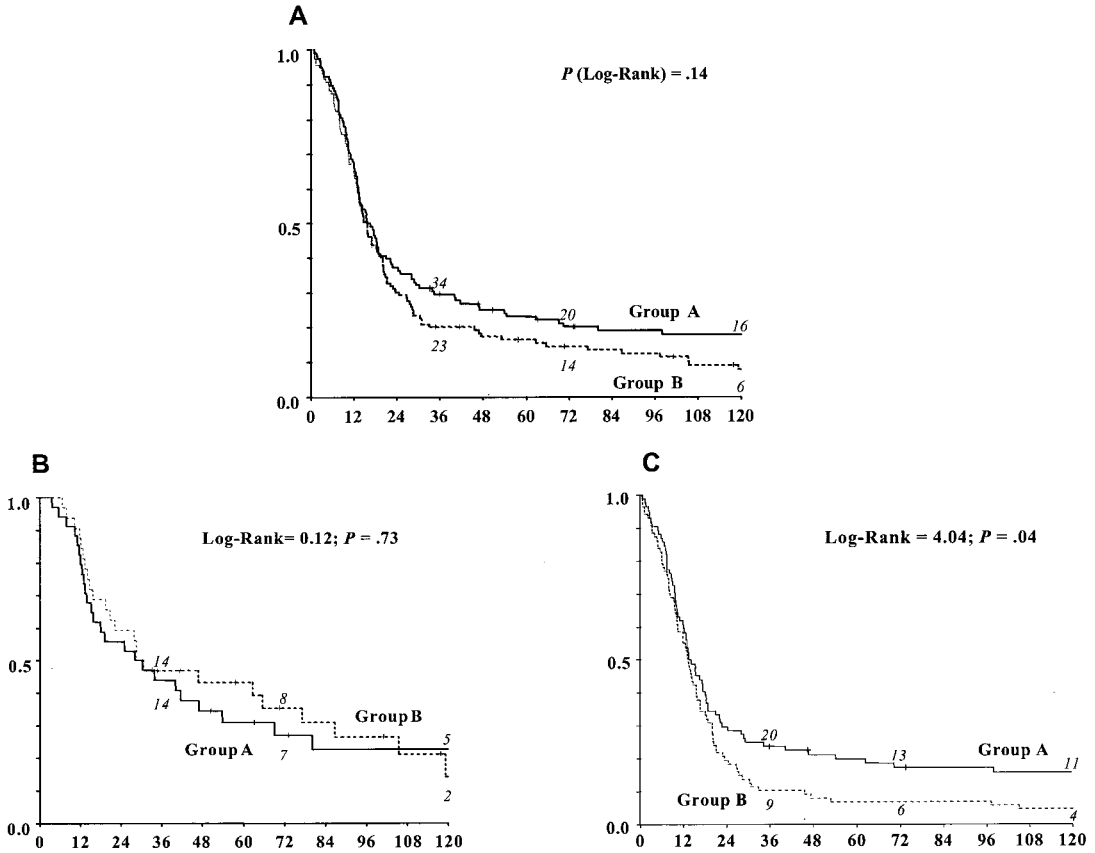

Fig. 1. Overall survival by treatment arm for all patients (**A**), operable patients (**B**), and inoperable patients (**C**). *Y*-axes show overall survival; *X*-axes show months from randomization. Numbers in italics correspond to the number of patients at risk. Group A = patients randomly assigned to receive four cycles of cisplatin and 5-fluorouracil followed by locoregional treatment; group B = patients randomly assigned to receive locoregional treatment alone.

vival: 5.1 years versus 3.3 years in favor of neoadjuvant chemotherapy; $P = .03$).

A potential limitation of our study is our use of locoregional treatment as the reference arm for inoperable patients. We used this reference group because radiotherapy alone was the accepted standard treatment for inoperable HNSCC when this trial was designed. Trials initiated after this study have demonstrated the superiority of concomitant chemotherapy and radiotherapy in locally advanced disease *(18–21)* over radiotherapy alone.

The value of the addition of neoadjuvant chemotherapy before concomitant chemotherapy and radiotherapy for patients with inoperable HNSCC has not yet been investigated. Our results provide a strong rationale for studies investigating this issue. The advent of new active drugs, such as taxanes, makes questions about the utility of neoadjuvant chemotherapy more interesting. Results of recent phase II and III trials that incorporated taxanes as neoadjuvant chemotherapy in cisplatin–5-fluorouracil combination have shown high partial and complete response rates in previously untreated patients *(22–28);* results of a retrospective analysis *(29)* comparing the efficacy of neoadjuvant cisplatin–5-fluorouracil and docetaxel, cisplatin, and 5-fluorouracil seems to support these promising data. These retrospective results have been recently confirmed in a prospective European Organisation for Research and Treatment of Cancer (EORTC) randomized study showing the superiority of docetaxel, cisplatin, and 5-fluorouracil over cisplatin and 5-fluorouracil in terms of response rate, progression-free survival, and overall survival, thus establishing a new reference regimen for neoadjuvant chemotherapy *(30).*

There are no published data from phase III trials comparing neoadjuvant chemotherapy followed by concomitant chemotherapy and radiotherapy with the standard treatment of concomitant chemotherapy and radiotherapy alone. We have completed a phase II study to test the feasibility of neoadjuvant chemotherapy with docetaxel, cisplatin, and 5-fluorouracil followed by concomitant polychemotherapy with cisplatin–5-fluorouracil during radiation treatment for patients with HNSCC *(31).* On the basis of our feasibility data, an Italian multicenter phase III trial has been initiated that is testing the efficacy of concomitant chemotherapy and radiotherapy (i.e., two cycles of polychemotherapy with cisplatin–5-fluorouracil during radiotherapy) with or without three cycles of neoadjuvant chemotherapy with docetaxel, cisplatin, and 5-fluorouracil.

REFERENCES

(1) Million RR. Cancer of the head and neck. In: De Vita VT Jr, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 4th ed. Philadelphia (PA): JB Lippincott; 1992. p. 396–420.

(2) Munrow AJ. A systematic review of chemotherapy trials in head and neck cancer [abstract]. Eur J Cancer 1999;35(Suppl 4/9): 602a.

(3) Pignon JP, Bourhris J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 2000;355: 949–55.

(4) Bernier J, Domenge C, Ozsahin, M, Matuszewska K, Lefebvre JL,Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945–52.

(5) Cooper SJ, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937–44.

(6) Adelstein DJ, Li Y, Adams GL, Wagner H Jr, Kish JA, Ensley JF, 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 2003;21:92–8.

(7) Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. N Engl J Med 1991;324:1685–90.

(8) Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349:2091–8.

(9) Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst 1996;88:890–9.

(10) Paccagnella A, Pappagallo GL, Segati R, Zorat P, Cavaniglia G, Fosser VP, et al. Response and toxicity of cisplatin and 120-h 5-fluorouracil infusion in pretreated and untreated patients with advanced epidermoid cancer of the head and neck. Am J Clin Oncol 1990;13:194–8.

(11) Paccagnella A, Orlando A, Marchiori C, Zorat PL, Cavaniglia G, Sileni VC, et al. Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: a study by the Gruppo di Studio sui Tumori della testa e del Collo. J Natl Cancer Inst 1994;86:265–72.

(12) International Union Against Cancer (UICC). TNM classification of malignant tumors. 3rd ed. Geneva (Switzerland): UICC; 1978.

(13) World Health Organization (WHO). Handbook for reporting results of cancer treatment. No. 48. Geneva (Switzerland): WHO; 1979.

(14) Dalley D, Beller E, Aroney R, Dewar J, Page J, Philip R, et al. The value of chemotherapy prior to definitive local therapy in patients with locally advanced squamous cell carcinoma of the head and neck [abstract 856]. Proc ASCO 1995;44:297.

(15) Lewin F, Damber L, Jonsson H, Andersson T, Berthelsen A, Biorklund A, et al. Neoadjuvant chemotherapy with cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the head and neck: a randomized phase III study. Radiother Oncol 1997;43:23–8.

(16) Domenge C, Hill C, Lefebvre JL, De Raucourt D, Rhein B, Wibault P, et al. Randomized trial of neoadjuvant chemotherapy in oropharyngeal carcinoma. French Groupe d'Etude des Tumeurs de la Tete et du Cou (GETTEC). Br J Cancer 2000;83:1594–8.

(17) Licitra L, Grandi C, Guzzo M, Mariani L, Lo Vullo S, Valvo F, et al. Primary chemotherapy in resectable oral cavity squamous cell cancer: a randomized controlled trial. J Clin Oncol 2003,21:327–33.

(18) Calais G, Alfonsi M, Bardet E, Sire C, Germain T, Bergerot P, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. J Natl Cancer Inst 1999;91:2081–6.

(19) Wendt TG, Grabenbauer GG, Rodel CM, Thiel HJ, Aydin H, Rohloff R, et al. Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: a randomized multicenter study. J Clin Oncol 1998;16:1318–24.

(20) Brizel DM, Albers ME, Fisher SR, Scher RL, Richtsmeier WJ, Hars V, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. N Engl J Med 1998;338:1798–804.

(21) Jeremic B, Shibamoto Y, Milicic B, Nikolic N, Dagovic A, Aleksandrovic J, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. J Clin Oncol 2000;18:1458–64.

(22) Colevas AD, Busse PM, Norris CM, Fried M, Tishler RB, Poulin M, et al. Induction chemotherapy with docetaxel, cisplatin, fluorouracil and leucovorin for squamous cell carcinoma of the head and neck: a phase I/II trial. J Clin Oncol 1998;16;1331–9.

(23) Colevas AD, Norris CM, Tishler RB, Fried MP, Gomolin HI, Amrein P, et al. Phase II trial of docetaxel, cisplatin, fluorouracil, and leucovorin as induction for squamous cell carcinoma of the head and neck. J Clin Oncol 1999;17:3503–11.

(24) Colevas AD, Norris CM, Tishler RB, Lamb CC, Fried MP, Goguen LA, et al. Phase I/II trial of outpatient docetaxel, cisplatin, 5-fluorouracil, leucovorin (op TPFL) as induction for squamous cell carcinoma of the head and neck (SCCHN). Am J Clin Oncol 2002;25:153–9.

(25) Schrijvers D, Van Herpen C, Kerger J, Joosens E, Le Bouder C, Castelijns JA, et al. Phase I-II study with docetaxel, cisplatin and 5 fluorouracil in patients with locally advanced inoperable squamous cell carcinoma of the head and neck [abstract 1524]. Proc ASCO 1999;18.

(26) Janinis J, Papadakou M, Panagos G, Panousaki A, Georgoulias V, Hatzidaki D, et al. Sequential chemoradiotherapy with docetaxel, cisplatin and 5-fluorouracil in patients with locally advanced head and neck cancer. Am J Clin Oncol 2001;24;227–31.

(27) Posner MR, Glisson B, Frenette G, Al-Sarraf M, Colevas AD, Norris CM, et al. Multicenter phase I-II trial of docetaxel, cisplatin, and fluoruracil induction chemotherapy for patients with locally advanced squamous cell cancer of the head and neck. J Clin Oncol 2001;19:1096–104.

(28) Hitt R, Lopez-Pousa A, Rodriguez M, Martinez-Trufero J, Cervantes A, Carles J, et al. Phase III study comparing cisplatin and 5 fluorouracil versus cisplatin + 5-fluorouracil and paclitaxel as induction therapy in locally advanced head and neck cancer [abstract 1997]. Proc ASCO 2003;22.

(29) Pignon JP, Syz N, Posner M, Olivares R, Le Lann L, Yver A, et al. Adjusting for patient selection suggests the addition of docetaxel to 5-fluorouracil-cisplatin induction therapy may offer survival benefit in squamous cell cancer of the head and neck. Anticancer Drugs 2004;15:331–40.

(30) Vermorken J, Remenar E, Van Herpen C, Germa Lluch J, Stewart S, Gorlia T, et al. Standard cisplatin/infusional 5-fluorouracil (PF) vs docetaxel + PF (TPF) as neoadjuvant chemotherapy for non resectable locally advanced squamous cell carcinoma of the head and neck: a phase III trial of the EORTC Head and Neck Cancer Group [abstract 5508]. J Clin Oncol 2004;22(14S):490S.

(31) Ghi MG, Paccagnella A, D'Amanzo P, Mione CA, Fasan S, Paro S, et al. Neoadjuvant docetaxel, cisplatin, 5-fluorouracil before concurrent chemoradiotherapy in locally advanced squamous cell carcinoma of the head and neck versus concomitant chemoradiotherapy: a phase II feasibility study. Int J Radiat Oncol Biol Phys 2004;59:481–7.

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