Journal of BUON **7**: 311-317, 2002
© 2002 *Zerbinis Medical Publications. Printed in Greece.*

Squamous cell carcinoma of the head and neck



Jan B. Vermorken, MD, PhD
Professor of Oncology
University Hospital Antwerp
Edegem
Belgium

Dear Dr. Vermorken
How would you treat the following two patients?

Case #1

A 65-year-old man is diagnosed with stage IVA (T_2N_2b) cancer of the tongue. He is treated with hemiglossectomy and has multiple (> 4) unilateral involved regional lymph nodes, the largest measuring 4 cm. Histologic examination of the neck dissection specimen showed that there is extracapsular spread. He is to receive postoperative radiation therapy. ECOG performance status is 1. He has acceptable speech and normal swallowing function. The surgeon asks your opinion about other adjuvant therapy.

You would recommend:

1. Standard radiation therapy alone, no chemotherapy.
2. Cisplatin/5-fluorouracil (5-FU) followed by radiation therapy.
3. Cisplatin with concurrent radiation therapy.
4. Cisplatin/5-FU with concurrent radiation therapy.
5. Paclitaxel+platinum with concurrent radiation therapy.
6. Paclitaxel + 5FU+platinum with concurrent radiation therapy.
7. Docetaxel+platinum with concurrent radiation therapy.
8. Gemcitabine+platinum with concurrent radiation therapy.
9. Radiation therapy followed by chemotherapy.

Dr. Vermorken's answer:

The prognosis of this patient with stage IVA ($T_2N_2M_0$) is poor for the following reasons:

1) the presence of positive lymph nodes
2) the presence of extracapsular spread

Although no further data are given on other risk factors (see below) these two are considered of major importance.

High-risk factors for locoregional recurrence (LRR)

A retrospective analysis was done of 758 primary untreated patients with squamous cell carcinoma arising in the oral cavity seen and treated by the Head and Neck Service of the Memorial Sloan-Kettering Cancer Center in New York between 1960 and 1964 [1]. All patients had received what was called "adequate" initial treatment. LRRs were seen in 334 (44%) patients and 54 (7%) developed distant metastases, of whom 49 also had LRR. Both clinical factors and pathologic factors in the 370 patients without LRR and in the 334 with LRR were compared. Statistical analysis showed that **female patients** who had a higher **T status** and a higher **N status**, had more LRRs. Those patients whose primary tumors manifested **deep invasion** and those who had **positive margins** after surgical resection at the prima-

ry site had also a significantly higher incidence of LRR. Presence of **extracapsular spread (ECS)** of disease in cervical lymph nodes, **involvement of soft tissues** in the neck as well as the presence of **multiple lymph nodes** at multiple levels also put the patients in a high-risk category.

The impact of ECS was highlighted in a paper by Johnson et al. [2] describing the outcome of patients treated at the University Hospital of Pittsburgh in the period 1978 through 1982. All patients underwent radical neck dissection and patients frequently received radiotherapy. After two years only 13% of stage III patients with negative node had died, 25% of those with positive neck nodes without ECS did, while 61% with nodes plus ECS did. In stage IV disease these figures were 29%, 33% and 64%, respectively. Interestingly, ECS also had impact on the development of distant metastases: in stage III disease only 4% of those with uninvolved neck nodes or involved nodes without ECS developed distant metastases, while 18% of those with involved neck nodes plus ECS did. In patients with stage IV disease these figures were 9% and 19%, respectively.

High-risk factors for the development of distant metastases (DM)

Of a series of 331 patients who underwent 383 radical neck dissections between 1973 and 1983 at the Free University Hospital, in Amsterdam, 78 (23.5%) developed DM. Those with histologically positive nodes had a significantly greater likelihood of subsequent DM than those who had histologically negative neck specimens [3]. However, a further refinement in determining prognosis brought forward that the presence of ECS and the number of positive nodes were of most prognostic significance. Considering these two parameters it was found that patients with 4 or more positive nodes and ECS had a greater than 60% likelihood of developing DM. More than 80% of DM manifested within 2 years after radical neck dissection, a phenomenon that has also been reported by others [4].

Outcome of patients with resectable stages III/IV disease

Surgery is usually employed in patients with resectable stages III and IV disease. Most of these patients will also receive adjuvant radiation therapy, especially those with stage IV, nodal disease, or patients with positive surgical margin(s). However, the outcome of such patients is poor with more than 60% developing LRR, 20% DM, and 70% will have died in the first 5 years [5]. Recent advances in translational and clinical research into the management of head and neck squamous cell cancer have led to a multidisciplinary therapeutic approach. In this concept not only altered fractionation schedules are of importance, but also radio-chemotherapy combinations (whether given sequentially or concomitantly).

Radio-chemotherapy combinations

There are at least 4 basic mechanisms by which the combination of radiation therapy and chemotherapy may result in a therapeutic gain, i.e.: 1) spatial cooperation; 2) additivity; 3) enhanced radiation response; and 4) protection of normal tissues (doubtful in the clinical setting) [6]. More than 70 trials including over 12,000 patients have investigated combined locoregional treatment plus chemotherapy *versus* locoregional therapy alone and at least 5 formal meta-analyses have been published [7-11]. The individual patient-based meta-analysis of Pignon et al. [11] indicated that the overall absolute benefit at 5 years was of the order of 4% with the largest benefit (8%) for those receiving radiation therapy and chemotherapy concomitantly (chemoradiation). This benefit might be even greater when the more recent trials on chemoradiation, all employing cisplatin-based chemotherapy and concurrent radiation therapy and showing more impressive gains in locoregional control, disease-free survival, and overall survival, would have been included.

Adjuvant therapy after surgery for advanced resectable disease

Theoretically there are several possible options for this patient:

1. *Postoperative standard radiation therapy alone (recommendation 1)*

Standard postoperative radiation therapy would at present not be my treatment of choice, because, as indicated below, there are indications that a combined approach might be more beneficial. Phase III trials have demonstrated a major advantage of accelerated fractionation schedules of postoperative radiotherapy over standard fractionation schedules [12,13]. This concept is used *versus* conventional radiotherapy in an ongoing

randomized trial by the Medical Research Council in the UK.

2. *Postoperative chemotherapy followed by radiation therapy* *(recommendation 2)*

This concept was studied in an intergroup trial in the USA [14]. That trial was performed in patients categorized as having either "low-risk" or "high-risk" treatment volumes depending on whether the surgical margin was > 5 mm, there was ECS, and/or carcinoma-in-situ at the surgical margins. Eligible patients had completely resected tumors of the oral cavity, oropharynx, hypopharynx or larynx. A total of 442 analyzable patients were randomized to receive either 3 courses of cisplatin/infusional 5-FU (PF) followed by postoperative radiation therapy (CT/RT) or postoperative radiation therapy alone (RT). Radiation doses of 50-54 Gy were given to low-risk volumes and 60 Gy to high-risk volumes. At 4 years there was no difference in survival (44% for RT *versus* 48% for CT/RT), disease-free survival (38% *versus* 46%), or local failure rate (29% *versus* 26%). However, the overall incidence of DM was reduced (23% *versus* 15% ; p=0.03). The conclusion of the authors was that sequential chemotherapy should not be part of the standard treatment for patients with operable head and neck cancer.

3. *Postoperative chemoradiation* *(recommendations 3-8)*

The introduction of chemoradiation in the postoperative management of high-risk patients is a logic extrapolation of the experience with chemoradiation as a definitive treatment for squamous cell head and neck cancer [15-17]. Some investigators have suggested that combination chemotherapy plus definitive radiation therapy might lead more consistently to better outcome than single agent CRT [16]. However, a direct comparison of cisplatin-based combination chemotherapy plus RT *versus* cisplatin alone plus RT has not been made. Moreover, in the comprehensive meta-analysis by Browman et al. [10] no difference in the mortality odds ratios for single or multi-agents regimens came forward.

Conclusions that have been made from randomized studies of CRT *versus* RT as definitive treatment for locally advanced desease are: 1) chemoradiation is more efficacious than radiation therapy alone; 2) there is no consensus regarding the optimal radiation dose fractionation in chemoradiation trials; 3) chemoradiation may be more efficacious than maximally intensive radiation therapy alone; and 4) acute toxicity is increased with the use of concurrent treatment [17].

Also in the postoperative management of high-risk patients the optimal schedule remains to be clarified. Nevertheless, some data on the usefulness of chemoradiation is available from randomized trials in this setting. No experience with multiagent CRT is available from randomized trials, most likely because of the expected reduced tolerance of patients after surgery. The initial study of Bachaud et al. [18] using 50 mg of ciplatin weekly was positive, but in a limited number of patients, and needed to be confirmed (Table 1). Both the EORTC study [20] and the RTOG study [21] (Table 1) employed higher doses of cisplatin, i.e. 100 mg/m² on days 1, 22 and 43 of the treatment program.

No obvious explanation can be found so far for the differences in outcome of the EORTC trial and the RTOG trial and this needs further study. However, taking into account that also in the RTOG trial there was a significant difference in 2-year disease-free survival in favor of the chemoradiation arm (42% *versus* 54%, p= 0.049), the bulk of evidence suggests that postoperative chemoradiation with cisplatin is superior over conventional radiation therapy alone. Again, as in studies with definitive radiation therapy and concurrent chemotherapy, toxicity is generally enhanced in the combined arm, although to variable degree in the different studies.

In the 1980s and 1990s, the drugs of choice in chemoradiation studies were mitomcyin C, cisplatin and 5-fluorouracil, selected based on both *in vitro* and *in vivo*

Table 1. Randomized trials of postoperative chemoradiation

Reference	*Treatment arms*	*Patients n*	*Median FU*	*LR-CTR rate*	*Survival benefit*
Bachaud et al. [18] (1996)	RT / RT+CDDP	88	5 yrs	59% *versus* 77% (p=0.08)	13% *versus* 36% (p<0.05)
Haffty et al. [19] (1997)	RT / RT+MMC	203	138 mo	54% *versus* 76% (p=0.003)	42% *versus* 48% (NS)
Bernier et al. [20] (2001)	RT / RT+CDDP	334	34 mo	64% *versus* 83% (p=0.0014)	49% *versus* 65% (p=0.006)
Cooper et al. [21] (2002)	RT / RT+CDDP	459	26.6 mo	74% *versus* 79% (p=0.16)	57% *versus* 63% (p=0.51)

RT= radiotherapy; CDDP= cisplatin; MMC= mitomycin C; FUP= follow-up; LR-CTR= locoregional control

experiments. No randomized studies are available of new chemoradiation combinations, including taxanes, topo-I-inhibitors and nucleoside analogues (fludarabine and gemcitabine). However, in phase I-II trials these combinations induced high complete response rates, being higher than 60% in most studies. These promising results mostly coincide with an increase in local toxicity, in particular severe mucositis and dermatitis. Although early results of these newer radiochemotherapy combinations are very encouraging in terms of synergistic activity, future studies should address whether these new chemoradiation combinations are able to give an advantage, not only in terms of cure rate, but also of cost benefit ratio [22, 23].

4. *Postoperative radiation therapy followed by chemotherapy* *(recommendation 9)*

There are 4 randomized trials on the role of adjuvant chemotherapy in head and neck patients (excluding nasopharyngeal cancer). Two of these are studies on adjuvant chemotherapy *per se* [23,24] and 2 used both induction and adjuvant chemotherapy (Table 2) [26,27].

The problem with several of these studies is the acceptance of this maintenance therapy by the patients. This seems in particular to be the case in the studies in which both induction chemotherapy and maintenance therapy have been used. Of the 151 patients randomized to the maintenance arm in the Head and Neck Contract Program [26] only 13 (9%) completed all 6 cycles (poor tolerance). Sixty-seven (45%) never received any maintenance therapy (refusal 37%, recurrence 33%, death 16%). At the Dana Farber Institute only 46 of the original 73 patients eligible for randomization accepted this.

In conclusion, these studies have not shown a survival benefit and compliance to adjuvant chemotherapy after surgery and radiotherapy has been a difficult issue. Therefore, it can not be recommended at the present time.

Overall conclusion: based on the above mentioned data the recommended treatment for this patient is option # 3, i.e. cisplatin with concurrent radiation therapy.

Case #2

A 57-year-old man with a history of stage III ($T_2N_1M_0$) squamous cell carcinoma of the pyriform sinus treated with surgery and postoperative radiation therapy 4 years ago develops shorteness of breath and a persistent dry cough. Chest x-ray shows multiple bilateral pulmonary metastases. Chest CT scan confirms the multiple lesions but no dominant mass or mediastinal adenopathy is present. Bronchoscopy shows no evidence of endobronchial tumor and a transbronchial lung biopsy is positive for poorly differentiated squamous cell carcinoma. No other sites of metastatic disease are present on imaging studies. CBC and biochemical profile are normal. ECOG performance status is 1.

You would recommend:

1. 5FU + cisplatin
2. Docetaxel + cisplatin + 5FU
3. Paclitaxel + carboplatin
4. Docetaxel + cisplatin
5. Cisplatin
6. 5FU
7. Methotrexate
8. Other

Dr. Vermorken's answer:

This 57-year-old patient was treated 4 years ago for a stage III ($T_2N_1M_0$) pyriform sinus cancer with surgery and postoperative radiotherapy and presents now with symptoms which could go with pulmonary metastases.

The outlook of the patient 4 years ago was not good and is now extremely poor. In fact, pyriform sinus cancer is considered one of the most lethal head and neck cancers. Five-year disease-free survival figures range from 10% to 35% and this poor outcome has been accredited to the advanced stage of disease at presentation, the propensity of early dissemination and the advanced age of the patients at presentation [28]. Surgery followed by radiation therapy for long has been the standard approach.

Table 2. Randomized trials on adjuvant chemotherapy in squamous cell cancer of the head and neck

Reference	*Patient groups*	*Patients n*	*Chemotherapy*	*Outcome*
GETTEC [24]	N+, ECS+	287	PBM × 3*	DM ↑, OS ↓
UFT group [25]	Stages II-IV	424	UFT (1 yr)	DM ↓, OS =
H/N Contract [26]	Stages II-IV	443	CDDP × 6	DM ↓, OS =
Dana Farber [27]	Stages III-IV	46	PBM × 3	OS =

*followed by BM×5; PBM = cisplatin/bleomycin/methotrexate; CDDP = cisplatin; DM = distant metastases; OS = overall survival

These patients frequently require a total laryngectomy. Although recent organ preservation studies have shown that patients responding to induction chemotherapy might be treated by radiation therapy and by doing so save their larynx, surgery followed by postoperative radiation therapy remains the accepted reference [29].

The patient presented now with shortness of breath and a persistent dry cough. Chest X-ray showed multiple pulmonary metastases.Chest CT scan confirmed this, but in addition showed no dominant mass or mediastinal adenopathy while no endobronchial tumor was seen at bronchoscopy. A transbronchial lung biopsy was positive for poorly differentiated squamous cell carcinoma. This information is important and might suggest that we are dealing with metastases from the original head and neck squamous cell cancer and not with a second primary lung cancer. Second (mostly metachronous) primaries do occur frequently in head and neck cancer patients (at a rate of 1.2-4% per year), the majority of which occur within tobacco-exposed tissue, including the head and neck area itself, the lung, the esophagus, and remaining upper aerodigestive tract [30]. Several investigators found significant differences in the location of the second aerodigestive tract neoplasms in relation to the localization of the index tumor. In case of a hypopharynx tumor, the most frequent location seemed to be in the digestive axis (hypopharynx and esophagus) [30].

Kowalski and Carvalho have reported on the largest group of patients with untreated head and neck cancer (because of advanced tumor stage, poor performance status and/or patient refusal) [31]. These patients only received supportive care. Outcome was extremely variable: survival ranging from one day to 53.8 months and with a median of 3.82 months. Performance status proved to be the strongest predictor of survival [31]. The median survival of patients with locoregionally recurrent and/or systemic disease in most reported series in which treatment has been given is about 6 months, whith 20% of patients being alive at one year. Although one study suggested that platinum-based chemotherapy had an impact on the survival of these patients, it is generally accepted that chemotherapy hardly affect these statistics [32]. Nevertheless, chemotherapy at present is the only accepted treatment for patients with metastatic squamous cell carcinoma of the head and neck. Attempts in recent years to evaluate chemotherapy plus best supportive care *versus* best supportive care only have failed because both patients and doctors are not sufficiently motivated to study this. However, it still is of importance to be able to select those patients who might benefit most from chemotherapy in these circumstances. As pointed out by Al-Sarraf [33], some prognostic factors have indeed been identified by which patients might be selected. Apart from performance status, these include site and bulkyness of disease, and response to previous therapies. That is, patients with only local recurrence with or without regional lymph node involvement after definitive treatment have better responses to chemotherapy than do patients with systemic and visceral disease. Also a long disease-free interval between treatment of the primary tumor and the recurrence is a favorable factor. Patients with bulky disease, bone involvement with or without hypercalcemia, extensive skin involvement by lymphangitic spread, persistent disease after radiotherapy or failure to respond to induction (adjuvant) chemotherapy, respond poorly to chemotherapy [33]. Taking these factors into account, the present patient might have a reasonable chance to respond to chemotherapy (good performance status, only lung metastases, long disease-free interval).

What options with respect to chemotherapy do we have?

Basically there are two options: single agent chemotherapy or combination chemotherapy. The question is, what is most appropriate for this patient. The fact that this patient has favorable factors and has symptomatic disease, which in case of deterioration might lead to invalidating disease, does favor the use of chemotherapy inducing the highest response rate. No doubt cisplatin-based combinations lead to superior response rates. However, survival (median and at 1-year) does not seem to be any better than observed with what otherwise is considered standard palliative chemotherapy for recurrent disease, i.e. weekly methotrexate (given at a dose of 40-60 mg/m^2) [32]. The most extensive experience has been obtained with the Wayne State University PF (cisplatin and infusional 5-FU) regimen. In the recurrent disease setting PF needs to be given in a schedule with 4 days of 5-FU, while in untreated patients PF with a 5-day 5-FU infusion is preferred. Taking all nonrandomized PF trials together (frequently including the patients in a better condition) the average response rate in patients with recurrent and metastatic disease is 50% (and complete response rate 16%) [34]. It is also the response rate that can be expected for the present patient. The 50% response rate is clearly higher than the 15-30% response rate reported in pooled series of nonrandomized studies with the traditional single agents. Response rates with PF in

the more recent randomized trials are only 31-32%, while the single agents comparators (cisplatin, 5-FU or methotrexate) induce responses in only 10-17% of cases. These response and survival results with the PF regimen observed in the randomized trials serve as a benchmark for comparison of regimens incorporating new agents [32]. Platinum/5-FU combinations in which carboplatin is used instead of cisplatin seem clearly less active [35].

Of the newer agents, the taxanes have been studied most extensively [32,36,37]. In nonrandomized studies 2-drug combinations of paclitaxel with cisplatin or carboplatin induced response rates in the range of 32-39%, while 2-drug combinations of docetaxel with cisplatin induced a response rate of 33% in one study and 52% in another study. Three-drug combinations of paclitaxel or docetaxel with cisplatin and 5-FU induced responses in 38 to 44%, i.e. without much difference. There are no data from randomized trials available in this disease setting suggesting that such 3-drug regimens are in any way superior to a 2-drug taxane/cisplatin combination. Exceptionally good data have been obtained in phase II trials with two 3-drug regimens studied at the M.D. Anderson Hospital in Houston, i.e. TIP (paclitaxel/ ifosfamide/cisplatin) and TIC (paclitaxel/ifosfamide/carboplatin). These regimens induced in particular a high overall response rate (58% and 59%, respectively), a complete response rate of 17% (for both) and acceptable survival data (median survival 8.8 and 9.1 months, respectively and 42.1% 1-year survival with TIP). However, TIP induced grade 3 or 4 neutropenia in 90% of the patients and neutropenic fever in 27% of the patients. Moreover, TIP was associated with significant renal, neurologic, otic and emetic side effects. Also TIC induced neutropenic fever in a high percentage (30% of the patients), but grade 3 nonhematologic toxicity occurred significantly less than with TIP [37]. Further studies with TIP or TIC seem warranted in a larger multicenter setting. Clearly, a balance of efficacy and toxicity is warranted in patients with recurrent and metastatic disease in whom chemotherapy is merely given for palliation. In that sense the early data of the ECOG/SWOG study, comparing cisplatin plus 5-FU (PF) with paclitaxel plus cisplatin (TP) seem quite promising [38]. So far, efficacy data were reported as being comparable (response rate 22% *versus* 28%, median survival 8 *versus* 9 months, 1-year survival 41% *versus* 30%) but both grade 3-5 hematologic and grade 3-5 nonhematologic toxicity were less with TP. Further follow-up data are to be awaited.

Overall conclusion: Based on these data my preference for this patient would the combination of cisplatin 100 mg/m^2 and 5-FU 1000 mg/m^2/day for 96 hours, whereby response can be evaluated by chest X-ray (and if necessary chest CT scan). At least 2 cycles of chemotherapy should be given unless this is clearly not in the best interest of the patient (e.g. in case of early disease progression or unexpected unacceptable toxicity) in order to evaluate response.

References

1. Shah JP, Cendon RA, Farr HW, Strong EW. Carcinoma of the oral cavity. Factors afffecting treatment failure at the primary site and neck. Am J Surg 1976; 132: 504-507.
2. Johnson JT, Myers EN, Bedetti CD et al. Cervical lymph node metastases. Incidence and implications of extracapsular carcinoma. Arch Otolaryngol 1985; 111: 534-537.
3. Snow GB, Balm AJM, Arendsen JW et al. Prognostic factors in neck node metastasis. In: Larson DL, Ballantyne AJ, Guillamondequi OM (eds): Cancer in the neck. New York: Macmillan, 1986: pp 53-63.
4. Vermorken JB. Adjuvant chemotherapy for advanced squamous cell carcinoma of the head and neck. In: Snow GB, Clark JR (eds): Multimodality therapy for head and neck cancer. New York: Georg Thieme Verlag, 1992: pp 112-126.
5. Al-Sarraf M, Hussein M. Head and neck cancer: present status and future prospects of adjuvant chemotherapy. Cancer Investig 1995; 13: 41-53.
6. Steel GG, Peckham MJ. Exploitable mechanisms in combined radiotherapy-chemotherapy: the concept of additivity. Int J Radiat Oncol Biol Phys 1979; 5: 85-91.
7. Stell PM, Rawson NS. Adjuvant chemotherapy in head and neck cancer. Br J Cancer 1990; 61: 779-787.
8. Munro AJ. An overview of randomised controlled trials of adjuvant chemotherapy in head and neck cnacer. Br J Cancer 1995; 71: 83-91.
9. El Sayed S, Nelson N. Adjuvant and adjunctive chemotherapy in the management of squamous cell carcinoma of the head and neck region. A meta-analysis of prospective and randomized trials. J Clin Oncol 1996; 14: 838-847.
10. Browman GP, Hodson DI, Mackenzie RJ et al. Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer. A systemic review of the published literature with subgroup analysis. Head Neck 2001; 23: 579-589.
11. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck cancer 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: 949-955.
12. Ang KK, Trotti A, Brown BW et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001; 51: 571-578.
13. Awwad HK, Lotayef M, Shouman T et al. Accelerated hyperfractionation (AHF) compared to conventional fractionation (CF) in the postoperative radiotherapy of locally advanced head and neck cancer: influence of proliferation. Br J Cancer 2002; 86: 517-523.
14. Laramore GE, Scott CB, Al-Sarraf M et al. Adjuvant chemotherapy for resectable squamous cell carcinomas of the head

and neck: report on intergroup study 0034. Int J Radiat Oncol Biol Phys 1992; 23: 705-713.
15. Adelstein DJ. Recent randomized studies of chemoradiation in the management of locally advanced head and neck cancer. Curr Opin Oncol 1998; 10: 213-218.
16. Adelstein DJ. Oropharynx cancer: the role of the medical oncologist in organ-function conservation. ASCO Educational Book 1999, pp 544-550.
17. Brizel DM. Management of advanced head and neck cancer with radiotherapy and concurrent chemotherapy: improvements in efficacy and toxicity management strategies. ASCO Educational Book 2000, pp 219-225.
18. Bachaud JM, Cohen JE, Alzieu C et al. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. Int J Radiat Oncol Biol Phys 1996; 36: 999-1004.
19. Haffty BG, Son YH, Papac R et al. Chemotherapy as an adjunct to radiation in the treatment of squamous cell carcinoma of the head and neck: results of the Yale mitomycin randomized trials. J Clin Oncol 1997; 15: 268-276.
20. Bernier J, Domenge C, Eschwege F. Chemo-radiotherapy, as compared to radiotherapy alone, significantly increases disease-free and overall survival in head and neck cancer patients after surgery: results of EORTC phase III trial 22931. Int J Radiat Oncol Biol Phys 2001; 51 (Suppl 1): 1 (abstr).
21. Cooper JS, Pajak TF, Forastiere AA et al. Postoperative concurrent radiochemotherapy in high-risk SCCA of the head and neck: initial report of RTOG 9501/intergroup phase III trial. Proc Am Soc Clin Oncol 2002; 21: 225a (abstr).
22. Busto G, Corvo R, Ricci I et al. New chemoradiotherapy combinations in head and neck cancer. Expert Rev Anticancer Ther 2001; 1: 111-115.
23. Feher O, Valadares AD, Nicolau UR et al. Paclitaxel and cisplatin concurrent with radiotherapy for larynx preservation in advanced resectable laryngeal and hypopharyngeal squamous cell carcinomas: preliminary results of a phase II study. Proc Am Soc Clin Oncol 2002; 21: 240a (abstr).
24. Domenge C, Marandas P, Vignoud J et al. Post-surgical adjuvant chemotherapy in extracapsular spread invaded lymph node (N+R+) of epidermoid carcinoma of the head and neck. A randomized mutlicentric trial. Second Intern Conf Head Neck Cancer, Boston, 1988. Am Soc Head Neck Surg 1988; 74 (abstr).
25. Tsukuda M, Ogasawara H, Kaneko S et al. A prospective randomized trial of adjuvant chemotherapy with UFT for head and neck carcinoma. Head and Neck UFT study group. Gan To Kagaku Ryoho 1994; 21: 1169.
26. Adjuvant chemotherapy for advanced head and neck squamous carcinoma: final report of the Head and Neck Contract Program. Cancer 1987; 60: 301-311.
27. Ervin TJ, Clark JR, Weichselbaum RR et al. An analysis of induction and adjuvant chemotherapy in multidisciplinary treatment of squamous cell carcinoma of the head and neck. J Clin Oncol 1987; 5: 10-20.
28. Marks SC, Lolachi CM, Shamsa F et al. Outcome of pyriform sinus cancer: a retrospective institutional review. Laryngoscope 1996; 106: 27-31.
29. Sarini J, Bocciolini C, Fournier C et al. Induction chemotherapy and larynx preservation: is such practice useful ? Bull Cancer 2002; 89: 411-417.
30. Leon X, Quer M, Orus C, Prado Venegas M. Can cure be achieved in patients with head and neck carcinomas? The problem of second neoplasm. Expert Rev Anticancer Ther 2001; 1: 125-133.
31. Kowalski LP, Carvalho AL. Natural history of untreated head and neck cancer. Eur J Cancer 2000; 36: 1032-1037.
32. Schantz SP, Harrison LB, Forastiere AA. Tumors of the nasal cavity and paranasal sinuses, nasopharynx, oral cavity, and oropharynx. In: DeVita CT, Hellman S, Rosenberg SA (eds). Cancer: Principles & Practice of Oncology, Lippincott-Raven Publishers, Philadelphia (6th edn), 2001, pp 797-860.
33. Al-Sarraf M. Head and neck cancer: chemotherapy concepts. Semin Oncol 1988; 15: 70-85.
34. Urba SG, Forastiere AA. Systemic therapy of head and neck cancer: most effective agents, areas of promise. Oncology 1989; 3: 79-88.
35. Forastiere AA, Metch B, Schuller DE et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil *versus* methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. J Clin Oncol 1992; 10: 1245-1251.
36. Schrijvers D, Vermorken JB. Role of taxoids in head and neck cancer. The Oncologist 2000; 5: 199-208.
37. Kim KB, Khuri FR, Shin DM. Recent advances in the management of squamous cell carcinoma of the head and neck. Exper Rev Anticancer Ther 2001; 1: 99-110.
38. Murphy B, Li Y, Cella D et al. Phase III study comparing cisplatin & 5-fluorouracil *versus* cisplatin and paclitaxel in metastatic/recurrent head & neck cancer. Proc Am Soc Clin Oncol 2001; 20: 224a (abstr #894).

Correspondence to:

Jan B. Vermorken, MD, PhD
Professor of Oncology
University Hospital Antwerp
Wilrijkstraat 10
B-2650 Edegem
Belgium
Tel: +32 3 8213375
Fax: +32 3 8250564
E-mail: Jan.B.Vermorken@uza.be