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CLINICAL INVESTIGATION **Head and Neck**

PATTERNS OF FAILURE IN PATIENTS WITH LOCALLY ADVANCED HEAD AND NECK CANCER TREATED POSTOPERATIVELY WITH IRRADIATION OR CONCOMITANT IRRADIATION WITH MITOMYCIN C AND BLEOMYCIN

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Purpose: The long term results and patterns of failure in patients with squamous cell head and neck carcinoma (SCHNC) treated in a prospective randomized trial in which concomitant postoperative radiochemotherapy with Mitomycin C and Bleomycin (CRT) was compared with radiotherapy only (RT), were analyzed.

Patients and Methods: Between March 1997 and December 2001, 114 eligible patients with Stage III or IV SCHNC were randomized. Primary surgical treatment was performed with curative intent in all patients. Patients in both groups were postoperatively irradiated to the total dose of 56–70 Gy. Chemotherapy included Mitomycin C 15 mg/m^2 after 10 Gy and 5 mg of Bleomycin twice weekly during irradiation. Median follow-up was 76 months (48–103 months).

Results: At 5 years in the RT and CRT arms, the locoregional control was 65% and 88% ($p = 0.026$), disease-free survival 33% and 53% ($p = 0.035$), and overall survival 37% and 55% ($p = 0.091$) respectively. Patients who benefited from chemotherapy were those with high-risk factors. The probability of distant metastases was 22% in RT and 20% in CRT arm ($p = 0.913$), of grade III or higher late toxicity 19% in RT and 26% in CRT arm ($p = 0.52$) and of thyroid dysfunction 36% in RT and 56% in CRT arm ($p = 0.24$). The probability to develop a second primary malignancy (SPM) was 34% in the RT and 8% in the CRT arm ($p = 0.023$). One third of deaths were due to infection, but there was no difference between the 2 groups.

Conclusion: With concomitant radiochemotherapy, locoregional control and disease free survival were significantly improved. Second primary malignancies in the CRT arm compared to RT arm were significantly less frequent. The high probability of post treatment hypothyroidism in both arms warrants regular laboratory evaluation.

Postoperative radiochemotherapy, Head-and-neck carcinoma.

INTRODUCTION

In the majority of patients with squamous-cell head and neck carcinoma the disease is diagnosed in an advanced stage (1), and despite aggressive locoregional treatment with surgery and postoperative irradiation, the treatment results are not satisfactory. Locoregional failure, extremely unpleasant for the patient and their families, occurs in a significant percentage of such patients. In randomized studies comparing postoperative irradiation with postoperative concomitant radiochemotherapy with cisplatin, locoregional control, disease free survival (2) and survival (3, 4) were significantly improved. Similar results were reported for postoperative concomitant radiochemotherapy with Mitomycin C (5, 6) or Mitomycin C and Bleomycin in our previously published experience (7). The inclusion criteria in all these studies were comparable.

When choosing which concomitant agent might be the best choice for the individual patient, efficacy must be considered as well as acute and late toxicity. So far, the differences in efficacy between the above mentioned concomitantly used drugs were not tested in randomized prospective trials. Therefore, long-term reports of prospectively conducted trials are helpful in making treatment plans.

In the present report, long-term results of a randomized trial (7) in which the treatment with concomitant postoperative radiochemotherapy with Mitomycin C and Bleomycin

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in patients with advanced head-and-neck carcinoma was tested, are presented. Late toxic effects and the frequency of distant metastases and second primary malignancies (SPMs) are analyzed.

PATIENTS AND METHODS

Patients and treatments

Between March 1997 and December 2001, 114 patients with squamous cell carcinoma of the head and neck were randomly assigned to postoperative irradiation only (RT arm, 55 patients) or to irradiation with concomitant chemotherapy with Mitomycin C and Bleomycin (CRT arm, 59 patients). Patients in both groups were well balanced by sites, stage, and unfavorable prognostic factors. Primary surgical treatment was performed with curative intent in all patients. Patients in both groups were treated by 5 MV or Co^{60} supravoltage irradiation, mostly with conventional 3 field technique (2 parallel opposed fields, 1 low neck field) comprising tumor bed and postoperative scar. The daily dose was 2 Gy applied in 1 fraction, 5 times per week. The total dose was aimed to be 56–70 Gy. The total treatment dose and irradiated volume were tailored according to the presence or absence of high-risk prognostic factors. The conventional 2 stage reduced field technique was used in all patients. The dose to the spinal cord was limited to 40–46 Gy. The posterior neck lymph nodes were boosted to 50 Gy with electron beam. In case of no histopathologically confirmed residual disease (R0), the dose to the tumor bed was 56 Gy. If pathosytology microscopic residual disease (R1) or macroscopic residual disease (R2) was proved, the primary tumor bed was irradiated up to 66 Gy or 70 Gy respectively with further reduced fields. The neck regions where histopathologically extracapsular tumor or perineural spread, lymphatic and/or venous invasion were detected, received electron booster dose up to 64 Gy. The lower neck and supraclavicular regions were treated with 1 anterior field which abutted the primary upper neck fields at the skin surface with 50 Gy defined at a depth of 2 cm. Mitomycin C was applied at the dose of 15 mg/m^2 after 10 Gy of radiotherapy. On the day of Mitomycin C application, patients in the CRT arm were irradiated twice with interfraction interval of >6 hours. During irradiation, 5 mg of Bleomycin was given i.m. twice a week. Study design, entry criteria, detailed patient characteristics, treatment, and early results were reported elsewhere (7).

Follow-up

In the first year after treatment, the patients were followed once a month. Each year afterwards, the time interval between follow-up visits was prolonged by 1 month and after 5 years we followed them once yearly, looking for possible progression of the disease, and late adverse effects on the healthy tissues. Clinical examination, full blood count, electrolytes, liver, and renal tests were routinely performed at scheduled follow-up visits. Chest X-rays and thyroid hormones were checked twice a year. Toxicity was defined according to National Cancer Institute Common Toxicity Criteria (NCI CTC) (8).

Endpoints

The primary endpoint of our prospective randomized trial was loco regional control (LRC). Secondary endpoints were disease-free survival (DFS), overall survival (OS), acute and late toxicity, and the incidence of distant metastases and SPMs. For all these parameters, an intent-to-treat analysis is reported with updated data. Locoregional control was defined as the time from operation to the recurrence of primary tumor or to the development of cervical-node metastases. Disease free survival was defined as the time from operation to the appearance of local recurrence, regional recurrence, distant metastases, the appearance of SPM, or death from any cause. Overall survival was defined as time from operation to death from any cause.

All SPMs were histologically verified and the possibility that the new tumor represents metastasis from the index tumor was excluded (9).

Statistical methods

For all endpoints, Kaplan-Meier estimates were calculated and a logrank test was used to test the differences between curves. For LRC, DFS, and OS hazards ratios (HR) are reported with 95% confidence intervals (10, 11). Data were analyzed in such mode that values of HRs <1 favor treatment with chemoradiotherapy.

Median survival with 95% confidence intervals was calculated from the date of diagnosis of SPM.

RESULTS

The follow-up ranged from 48-103 months, median 76 months.

Survival

Five years after operation, in RT and CRT arms, LRC was 65% and 88% ($p = 0.026$, Fig. 1), DFS 33% and 53% ($p = 0.035$, Fig. 2), and OS 37% and 55% ($p = 0.091$, Fig. 3) respectively. Hazard ratios and their 95% confidence intervals were for LRC 0.38 (0.16–0.92), for DFS 0.61 (0.37–0.97), and for OS 0.66 (0.41–1.07). Locoregional control, DFS, and OS in RT ($n = 32$) and CRT ($n = 35$) arms for patients with high risk factors (extracapsular extension and/or R1 resection) were 42% and 84% ($p = 0.009$; HR 0.28; 95% CI, 0.1–0.8), 17% and 48% ($p = 0.054$; HR

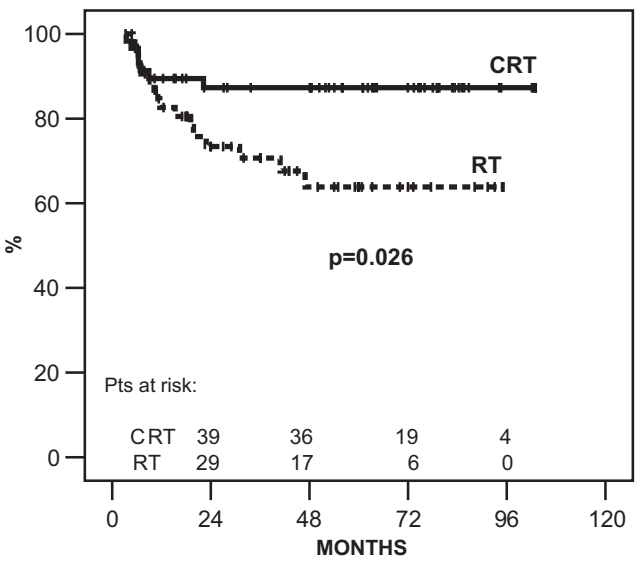

Fig. 1. Locoregional control. RT = postoperative radiotherapy, $n = 55$; CRT = postoperative chemoradiotherapy, $n = 59$.

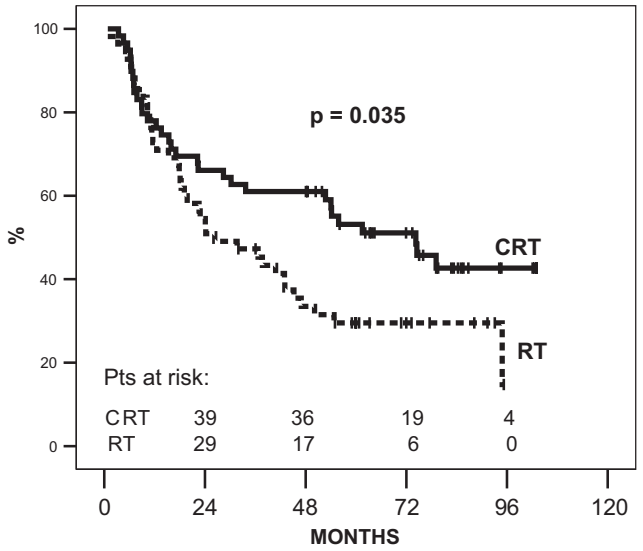

Fig. 2. Disease free survival. RT = postoperative radiotherapy, $n = 55$; CRT = postoperative chemoradiotherapy, $n = 59$.

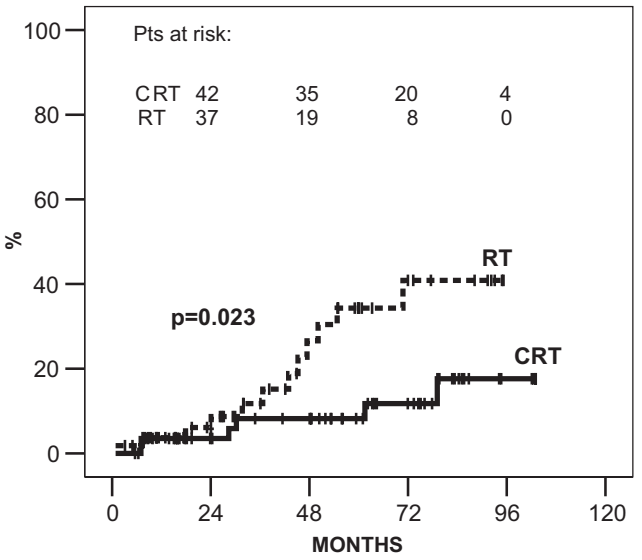

Fig. 4. Second primary malignancies. RT = postoperative radiotherapy (12/55), CRT = postoperative chemoradiotherapy (6/59).

0.57; 95% CI, 0.32–1.02), 26% and 48% ($p = 0.198$; HR 0.68; 95% CI, 0.37–1.23), respectively.

There was no significant difference in the probability of occurrence of distant metastases between treatment groups (at 5 years from operation, 22% in RT arm and 20% in CRT arm; $p = 0.913$). In all these cases distant metastases were also the causes of death.

Late adverse effects

There was no significant difference in the probability of developing grade III or higher late toxicity to the skin, s.c. tissue, muscles and bones in the irradiated field between treatment arms at 5 years from operation (19% in RT and 26% in CRT arm, $p = 0.52$) or to develop thyroid dysfunction—thyroid stimulating hormone (TSH) level above normal value (36% in RT and 56% in CRT arm, $p = 0.24$). All patients with elevated TSH levels received hormonal substitution and had normal TSH values thereafter with no clinical signs of thyroid dysfunction.

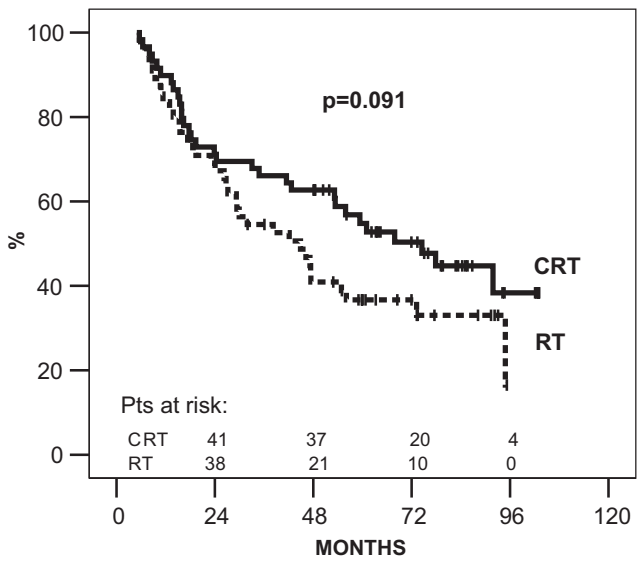

Fig. 3. Overall survival. RT = postoperative radiotherapy, $n = 55$; CRT = postoperative chemoradiotherapy, $n = 59$.

Second primary malignancies

Among SPMs there were no tumors within the anatomic vicinity of the primary tumor. The probability to develop an SPM was 8% in CRT arm and 34% in RT arm at 5 years from operation ($p = 0.023$, Fig. 4). Second primary malignancy by site and treatment are shown in Table 1. Of the 18 patients who developed an SPM, 3 are alive at the time of analysis; 12 died of the SPM, 2 of the index tumor and 1 of sepsis. From the date of diagnosis of the SPM, median

Table 1. Second primary malignancies by site, histologic subtype, and treatment

	Arm		
Site	RT	CRT	Total
Lung – SCC	4	3	7
Tongue - SCC	2	0	2
Colon - AC	1	0	1
Maxillary sinus - AC	1	1	2
Pleural mesothelioma	1	0	1
Renal pelvis - TCC	0	1	1
Prostate - AC	2	0	2
Stomach - AC	1	1	2
Total	12	6	18

Abbreviations: RT = radiotherapy; CRT = chemoradiotherapy; SCC = squamous cell carcinoma; AC = adenocarcinoma; TCC = transitional cell carcinoma.

survival of all patients was 6.5 months (95% CI, 4.5–8.3 months).

Causes of death

Out of 67 patients dying during the observation period, 33 (49%) died of primary disease, 12 (18%) of SPM, and 22 (33%) of other causes (pneumonia, tuberculosis, or sepsis). In the last group, there was no significant difference between treatment arms (11 patients dying in each arm).

DISCUSSION

In an updated analysis of our study, with a median follow-up of 76 months, we confirmed a significant improvement in LRC (Fig. 1), DFS (Fig. 2), and an improved OS (Fig. 3). The late toxic events did not differ significantly between treatment arms. A high but not significantly different incidence of laboratory thyroid dysfunction (elevated TSH) was present in both arms. A surprising outcome is a significantly decreased cumulative incidence of SPMs in the concomitant arm (Fig. 4).

Meta analysis of randomized trials comparing chemotherapy added to radiotherapy in patients with advanced head-and-neck squamous cell carcinoma (12) and nasopharyngeal carcinoma (13) demonstrated a significant benefit for concomitant treatment (14). The same principle was used in the postoperative setting by Haffty *et al.* with Mitomycin C reported already in 1993 (5), by Bachaud *et al.* with weekly cisplatin in 1996 (4) as well as in our trial reported by Smid *et al.* with Mitomycin C and Bleomycin in 2003 (7). As shown in Table 2, in all 3 trials a significant improvement in LRC and DFS was demonstrated for the concomitant arm, even though the statistical power was small, due to small number of patients in all of them. However, 2 large trials published by Bernier *et al.* (3) and Cooper *et al.* (2) in 2004 confirmed the efficacy of postoperative concomitant chemotherapy in high-risk patients with squamous cell head-and-neck carcinoma (Table 2). In our study, patients who benefited from chemotherapy were those with high-risk factors.

All studies (2, 3, 4, 7), except by Haffty *et al.* (5) reported a significant higher degree of acute toxicity (mucositis, dermatitis) in the concomitant arms. This is an expected outcome, because cytotoxic agents are not selective and damage tumor as well as surrounding healthy cells. Probably we can achieve some selectivity with Mytomycin C that is selectively activated in the hypoxic areas of the tumor and could, therefore, achieve a higher radiosensitizing effect than in the surrounding healthy tissues (15). In all studies, other acute toxicities such as neutropenia, thrombopenia, and in those using cisplatin, nausea/vomiting, and kidney toxicity were reported. These different acute toxic profiles have to be considered when planning treatment in everyday practice to choose the most appropriate regimen for the individual patient.

There were no significant differences between the treatment arms in grade III or higher late toxicities in all 5 studies. In our study, a high proportion of thyroid dysfunction was registered in later post-treatment period in patients from both treatment arms. This finding should be taken into account in the follow-up of these patients. It was not possible to find the correlation between the dose to the thyroid tissue and the incidence of toxicity, probably because the dose to the thyroid gland was not uniform. In cases when the thyroid was adjacent to the area that needed boost, this part of the thyroid (the volume of which we mostly could not assess precisely) received a higher dose.

Table 2. Prospective randomized trials with postoperative radiochemotherapy

	Haffty *et al.* (1993)	Bachaud *et al.* (1996)	Cooper *et al.* (2004)	Bernier *et al.* (2004)	Present report
Number of patients	113	83	459	334	114
Concomitant treatment	Mitomycin	Cisplatin	Cisplatin	Cisplatin	Mitomycin + bleomycin
Follow-up (years)	5	5	3	5	5
LRC					
RT arm	67%	55%	67%	69%	65%
CRT arm	87%	70%	78%	82%	88%
p	0.015	0.05	0.01	0.007	0.026
DFS					
RT arm	44%	23%	36%	36%	33%
CRT arm	67%	45%	47%	47%	53%
p	<0.03	<0.02	0.04	0.04	0.035
OS					
RT arm	41%	13%	47%	40%	37%
CRT arm	56%	36%	56%	53%	55%
p	NS	<0.01	0.09	0.02	0.09
Remarks	All stages	Stage III&IV with extracapsular spread	N2+ and/or ECE and/or R1	Locally advanced	Stage III&IV

Abbreviations: RT = radiotherapy; CRT = concomitant chemoradiotherapy; LRC = locoregional control; DFS = disease-free survival; OS = overall survival; NS = non significant; N2+ = two or more lymphnodes involved with tumor; ECE = extracapsular spread; R1 = microscopically involved surgical margins.

Furthermore, there was no statistical significant difference in the incidence of distant metastases and the percentages of distant metastases reported were from 20–25% at 3–5 years. This could be explained by the fact that the dose of the drugs applied during irradiation only was sufficient to enhance the effect of irradiation, but did not have a sufficient systemic effect.

Second primary malignancies are frequent events in head-and-neck cancer patients. The incidence of SPMs reported in large retrospective studies was 4–6% per year and 5 year survival rates after the diagnosis of SPMs are 26–28%, significantly worse than in those without an SPM (16–20). Radiotherapy to the index tumor was not associated with an increased risk of developing an SPM (18). The cumulative incidence at 5 years of SPMs reported by Bernier *et al.* (3) and Haffty *et al.* (6), were similar in the RT and in the CRT arm. In the study by Bonner *et al.*, comparing cetuximab concomitantly with irradiation alone in inoperable patients, even a higher percentage of SPMs was reported in the arm with cetuximab (8% vs. 5%) (21). In our study, the overall incidence of SMP was comparable to other reports, *i.e.,* 18%. An unexpected finding of our study was a significantly smaller probability to develop an SPM in the CRT arm (8%) compared to RT arm 34% ($p = 0.023$) (Fig. 4). The reason for this remains unclear. There is a possibility that *in situ* SPMs were cured or delayed in development with our chemotherapy or, on the other hand, it could be a type I statistical error.

An unexpected finding is that previously reported significant difference in overall survival between treatment arms (7), despite more deaths due to SPM in the RT arm, disappeared with longer follow-up (Fig 3). Bernier *et al.* observed a similar phenomenon and stated that the shape of the progression free survival curve (a similar shape has also their overall survival curve) suggests that the effect of chemoradiotherapy decreases over time (3). From data of our study, in the second half of the observation period after 5 years from operation, the number of patients at risk was almost double in the CRT arm compared to RT arm (Fig 3). Five years from operation and thereafter, in RT arm 3 patients died (2 of SPM, 1 of other causes) and in CRT arm 6 (1 of SPM and 5 of other causes), that is proportionally similar. We further analyzed the main reason and time when our patients died of other causes. Six out of 22 patients (11 in each arm) who died of other causes, died in the hospital: 3 of pneumonia, 2 of sepsis and 1 of lung tuberculosis. The other patients died at home, the reported cause of death being respiratory infection, but detailed data were not available. All these patients were disease free at last follow-up visit. A high number of deaths due to respiratory infections in our patients might be due to local effects of changed anatomy after operation and additional radiotherapy or chemotherapy interfering with the protective respiratory mechanisms. Although the risk of dying from other causes, mainly respiratory infections, was not statistically different between treatment arms, the incidence of deaths was somewhat delayed in the CRT arm. This caused the banana shape of the survival curves and a nonsignificant log-rank *p* for OS in the present report.

CONCLUSION

With postoperative radiochemotherapy, locoregional failure, the main pattern of failure in patients operated on for carcinoma in the head-and-neck region in the past is now to be expected only in up to 20% of patients. A significant smaller probability to develop an SPM in the CRT arm compared to RT arm was found. Despite meticulous follow-up, the major causes of death in these patients are infections and distant failures. Most probably, prolongation of systemic treatments incorporating chemotherapy and biologic agents might reduce distant failures. Infections and SPMs will continue to remain a difficult problem to confront. The high probability of post treatment hypothyroidism warrants twice yearly laboratory evaluation in these patients.

REFERENCES

1. Cancer Registry of Slovenia Cancer Incidence in Slovenia 1998. Institute of Oncology Ljubljana, Slovenia; 2005.
2. Cooper JS, Pajak TF, Forastiere AA, *et al.* Radiation Therapy Oncology Group 9501/Intergroup. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med* 2004;350: 1937–1944.
3. Bernier J, Domenge C, Ozsahin M, *et al.* Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004;350: 1945–1952.
4. Bachaud JM, Cohen-Jonathan E, Alzieu C, *et al.* Combined postoperative radiotherapy and weekly Cisplatin infusion for locally advanced head and neck carcinoma: Final report on a randomized trial. *Int J Radiat Oncol Biol Phys* 1996;6:999–1004.
5. Haffty BG, Son YH, Sasaki CT, *et al.* Mitomycin C as an adjunct to postoperative radiation therapy in squamous cell carcinoma of the head and neck: Results from two randomized clinical trials. *Int J Radiat Oncol Biol Phys* 1993;27:241–250.
6. 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.
7. Smid L, Budihna M, Zakotnik B, *et al.* Postoperative concomitant irradiation and chemotherapy with mitomycin C and bleomycin for advanced head-and-neck carcinoma. *Int J Radiat Oncol Biol Phys* 2003;56:1055–1062.
8. Available at: http://ctep.cancer.gov/forms/CTCv20_4–30–992.pdf. Accessed on September 9, 2006.
9. Lin K, Patel SG, Chu PY, *et al.* Second primary malignancy of the aerodigestive tract in patients treated for cancer of the oral cavity and larynx. *Head Neck* 2005;27:1042–1048.
10. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *JASA* 1958;53:457–481.
11. Armitage P. Statistical methods in medical research. Oxford: Blackwell Scientific Publications; 1971.
12. Pignon JP, Bourhis J, Domenge C, *et al.* On behalf of the MACH-NC Collaborative group. Chemotherapy added to lo-

coregional treatment for head and neck squamous-cell carcinoma: Three meta-analyses of updated individual data. *The Lancet* 2000;355:949–955.
13. Baujat B, Audry H, Bourhis J, *et al.* Chemotherapy in locally advanced nasopharyngeal carcinoma: An individual patient data meta-analysis of eight randomized trials and 1,753 patients. *Int J Radiat Oncol Biol Phys* 2006;64:47–56.
14. Pignon JP, Baujat B, Bourhis J. Individual patient data meta-analyses in head and neck carcinoma: What have we learnt? *Cancer Radiother*. 2005;9:31–36.
15. Sartorelli AC. Therapeutic attack of hypoxic cells of solid tumors. *Cancer Res* 1988;48:775–778.
16. Leon X, Quer M, Diez S, *et al.* Second neoplasm in patients with head and neck cancer. *Head Neck* 1999;21:204–210.
17. Jones AS, Morar P, Phillips DE, *et al.* Second primary tumors in patients with head and neck squamous cell carcinoma. *Cancer* 1995;75:1343–1353.
18. Vikram B, Strong EW, Shah JP, *et al.* Second malignant neoplasms in patients successfully treated with multimodality treatment for advanced head and neck cancer. *Head Neck Surg* 1984;6:734–737.
19. Di Martino E, Sellhaus B, Hausmann R, *et al.* Survival in second primary malignancies of patients with head and neck cancer. *J Laryngol Otol* 2002;116:831–838.
20. Vaamonde P, Martin C, del Rio M, *et al.* Second primary malignancies in patients with cancer of the head and neck. *Otolaryngol Head Neck Surg* 2003;129:65–70.
21. Bonner JA, Harari PM, Giralt J, *et al.* Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 20069;354:567–578.