Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 1, pp. 47–56, 2006
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0360-3016/06/$–see front matter

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doi:10.1016/j.ijrobp.2005.06.037

CLINICAL INVESTIGATION **Head and Neck**

CHEMOTHERAPY IN LOCALLY ADVANCED NASOPHARYNGEAL CARCINOMA: AN INDIVIDUAL PATIENT DATA META-ANALYSIS OF EIGHT RANDOMIZED TRIALS AND 1753 PATIENTS

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Objectives: To study the effect of adding chemotherapy to radiotherapy (RT) on overall survival and event-free survival for patients with nasopharyngeal carcinoma.

Methods and Materials: This meta-analysis used updated individual patient data from randomized trials comparing chemotherapy plus RT with RT alone in locally advanced nasopharyngeal carcinoma. The log–rank test, stratified by trial, was used for comparisons, and the hazard ratios of death and failure were calculated.

Results: Eight trials with 1753 patients were included. One trial with a 2 × 2 design was counted twice in the analysis. The analysis included 11 comparisons using the data from 1975 patients. The median follow-up was 6 years. The pooled hazard ratio of death was 0.82 (95% confidence interval, 0.71–0.94; $p = 0.006$), corresponding to an absolute survival benefit of 6% at 5 years from the addition of chemotherapy (from 56% to 62%). The pooled hazard ratio of tumor failure or death was 0.76 (95% confidence interval, 0.67–0.86; $p < 0.0001$), corresponding to an absolute event-free survival benefit of 10% at 5 years from the addition of chemotherapy (from 42% to 52%). A significant interaction was observed between the timing of chemotherapy and overall survival ($p = 0.005$), explaining the heterogeneity observed in the treatment effect ($p = 0.03$), with the highest benefit resulting from concomitant chemotherapy.

Conclusion: Chemotherapy led to a small, but significant, benefit for overall survival and event-free survival. This benefit was essentially observed when chemotherapy was administered concomitantly with RT.
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Nasopharyngeal carcinoma, Randomized trial, Chemotherapy, Meta-analysis, Individual patient data.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is pathologically, epidemiologically, and clinically distinct from other head-and-neck cancers (1, 2). NPC is rare in the United States (except in Alaska) and Western Europe. Also, in these areas, the frequency of squamous cell carcinoma (World Health Organization [WHO] type 1) is about 25%, markedly greater than in the endemic areas. Areas of high incidence include Southern China, Southeast Asia, the Middle East, North Africa, Alaska, and Greenland. In these areas, the Epstein-Barr virus is strongly associated with NPC. Most patients have poorly or undifferentiated (WHO type 2 or 3) carcinoma and present with locally advanced disease. Nodal involvement and bilateral nodal disease are more frequently observed with NPC than with other head-and-neck cancers. NPC is commonly treated with radiotherapy (RT) and chemotherapy (2). RT at a dose of

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A complete list of the members of the MAC-NPC Collaborative Group is provided in the Appendix.

Supported by the Institut Gustave-Roussy, Aventis, Sanofi-Synthelabo, and Schering-Plough who had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The authors had full access to all the data and are fully responsible for the decision to submit the paper for publication.

Acknowledgments—We are grateful to Denise Avenell for secretariat support, Francine Courtial for trial search, Catherine Hill for her comments on the manuscript, and Lorna Saint Ange for editing.

Received May 20, 2005. Accepted for publication June 20, 2005.

65–75 Gy within 6–7 weeks is standard. The overall survival (OS) rate at 5 years ranges from 32% to 52% in large series of patients with locally advanced disease treated with RT alone (2). Chemotherapy has been proposed for locally advanced NPC to improve survival (1, 2). Despite 11 randomized trials comparing RT and RT plus chemotherapy in the English literature, the magnitude of the effect of chemotherapy on survival is not well-established. OS was the main endpoint in all these trials, except for one, but only two showed a beneficial effect on survival and four on relapse-free survival. Underpowered trials could account for the inconstancy of the benefit on survival, which was the case in the previously published Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) (3). The aim of the Meta-Analysis of Chemotherapy in Nasopharynx Carcinoma (MAC-NPC) was to assess the impact of adding chemotherapy to RT on OS.

METHODS AND MATERIALS

The methods of the meta-analysis are specified in a protocol published in the Cochrane library (4). The meta-analysis was based on individual patient data (5) and used a method similar to that used in the MACH-NC study (3) and the Prophylactic Cranial Irradiation Overview (6).

Eligibility criteria

Trials were eligible if RT plus chemotherapy had been compared with RT alone in previously untreated patients with nonmetastatic NPC (WHO Grade 1, 2, or 3). Each trial had to be randomized in a manner precluding prior knowledge of the treatment assignment. Trials were eligible if accrual had been completed before December 31, 2001 and if all patients had undergone potentially curative locoregional treatment.

Trial identification

Published and unpublished trials were included. Computerized searches of MEDLINE and EMBASE were supplemented with hand searches of meeting abstracts and references in review articles. Trial registers managed by the National Cancer Institute (PDQ, ClinProt) were consulted. Experts, pharmaceutical companies, and all trialists who took part in the meta-analysis were asked to identify potential trials. Hand searches of the Chinese medical literature were also performed (7).

Data

The data collected for each patient included age, gender, WHO performance status (or the equivalent), histologic type (WHO criteria), TNM stage, treatment allocated, date of randomization, cause of death, date of locoregional failure, date of distant failure, date and type of second primary, exclusion (yes/no) from trial analysis and the reason for exclusion, and at least one cycle of chemotherapy received (yes/no). Because different TNM classifications were used in the publications, those who used the Ho classification in their report were requested to provide, if possible, the equivalent American Joint Committee on Cancer/Internation Union Against Cancer (AJCC/UICC) stage. The last follow-up and survival status were updated, as far as possible, compared with the published analyses.

All data were checked for internal consistency and compared with the trial protocol and published reports. Ranges were checked, and any extremes were verified with the trialists. Each trial was reanalyzed, and the analyses were sent to the trialists for review.

Analysis

The main endpoint was OS, which was evaluated from the time of randomization until death, whatever the cause. Living patients were censored at the date of the last follow-up visit. The secondary endpoint was event-free survival (EFS), defined as the time from randomization until the first event, including locoregional/distant failure or death.

Early deaths (i.e., within 3 months) were also studied. All analyses were on an intent-to-treat basis; that is, all randomized patients were included in the analyses according to the allocated treatment, irrespective of whether they received the treatment or were excluded from the investigator's original analysis. The median follow-up was quantified using the potential follow-up method (8). Survival analyses were stratified by trial, and the log–rank The log-rank observed minus expected number of deaths (O–E) and its variance were used to calculate individual and overall pooled hazard ratios (HRs) with a fixed-effect model (9). The absolute differences in the 2- and 5-year survival rates were calculated using the pooled HR, and the assumption of proportional hazards was used to calculate the survival rates at 2 and 5 years using the control RT group (10). Nonstratified Kaplan-Meier survival curves are presented for the control and treatment groups. Chi-square heterogeneity tests were used to test for statistical heterogeneity among the trials (11). The percentage of variability in the estimates of the treatment effect due to heterogeneity between studies, rather than sampling errors, was estimated using I^2 statistics (11). A limited number of comparisons, planned in the meta-analysis protocol, were done among subsets of trials and subgroups of patients. Also, a test for interaction or a test for trend was performed to look for any significant variation in the treatment effect among these subgroups/subsets (12). All p values are two-sided.

The meta-analysis protocol specified that the covariates to be considered would be age in three categories, as in the MACH-NC study (3)—However, because the patient population was younger in this study, another distribution was used, corresponding to the tertiles ($\leq$40, 41–50, and $\geq$51 years)—gender, performance status (WHO Grade 0, 1, 2+), TNM stage, and histologic type. Tumor stage was divided into three categories according to the 1997 AJCC/UICC classification (T1, T2, and T3–T4) because five trials used the AJCC/UICC classifications before 1997, one trial used the Ho classification, and two used the 1997 AJCC/UICC classification, rendering the distinction between T3 and T4 patients impossible. The nodal stage was divided into three categories (N0, N1–N2, and N3) for the same reason. We could not use the data from the trial that used the Ho classification (13) for this covariate because nodes are classified topographically in that staging system. Histologic types were divided into two categories (WHO 1 vs. 2–3). We had to pool patients with WHO type 2 and 3 carcinoma because data were missing in one trial (only patients with WHO type 2 and 3 carcinoma were included). The trials were also grouped according to the timing of chemotherapy: induction (before RT), concomitant (chemotherapy given concomitantly with RT), and adjuvant (after RT). Trials combining induction and adjuvant chemotherapy or concomitant and ad-

Table 1. Meta-analysis of chemotherapy in nasopharyngeal carcinoma: description of eligible trials

Trial (reference)	Inclusion period	Stage (classification*)	Histologic type (WHO classification)	RT dose, duration	Chemotherapy		Patients randomized and analyzed (*n*)	Median follow-up (months)
					Timing	Dose × No. of cycles		
PWH-88 (13)	1988–91	III–IV (Ho)	3	T 66 Gy/6.5 wk, N− 58 Gy, N+ 65.5 Gy	Induction and adjuvant	Cisplatin 100 mg/m^2 × (2 + 4) 5-Fluorouracil 3000 mg/m^2 × (2 + 4), CI	77	35
AOCOA (18)	1989–93	II–IV (AJCC <1997)	2–3	T 66–74 Gy/6.5–7.5 wk; N− 60–66 Gy, N+ 66–76 Gy	Induction	Cisplatin 60 mg/m^2 × 2–3 Epirubicin 110 mg/m^2 × 2–3	334	65
VUMCA–89 (19)	1989–93	III–IV (AJCC <1997)	1–3	T 65–70 Gy/6.5–7.5 wk; N− 50 Gy, N+ 65 Gy	Induction	Bleomycin 15 mg/m^2 × 3 Bleomycin 60 mg/m^2 × 3, CI Epirubicin 70 mg/m^2 × 3 Cisplatin 100 mg/m^2 × 3	339	84
Japan-91 (20)	1991–98	I–IV (AJCC <1997)	1–3	T 66–68 Gy/6.5–7 wk, N− 50 Gy, N+ 66–68 Gy	Induction	Cisplatin 80 mg/m^2 × 2 5-Fluorouracil 3200 mg/m^2 × 2, CI	80	74
T-0099 (21)	1989–95	III–IV (AJCC <1997)	1–3	T 70 Gy/7 wk; N− 50 Gy, N+ 66–70 Gy	Concomitant and adjuvant	Cisplatin 100 mg/m^2 × 3 Cisplatin 80 mg/m^2 × 3 5-Fluorouracil 4000 mg/m^2 × 3, CI	193	110
PWHQEH-94 (22)	1994–99	II–IV (AJCC 1997)	1–3	T 66 Gy/6.5 wk; N− 58 Gy, N+ 65.5 Gy	Concomitant	Cisplatin 40 mg/m^2, weekly	350	67
QMH-95 (23)	1995–2000	II–IV (AJCC 1997)	1–3	T 62.5–68 Gy/7 wk N 62.5–66 Gy/7 wk ± boost 10 Gy	Concomitant Adjuvant	UFT 600 mg daily, p.o. Cisplatin 100 mg/m^2 × 3 5-Fluorouracil 3000 mg/m^2 × 3 Vincristine 2 mg × 3 Bleomycin 30 mg × 3 Methotrexate 150 mg/m^2 × 3	222	57
TCOG-94 (24)	1994–99	IV (AJCC <1997)	1–3	T 70–72 Gy/7–8 wk N− 50 Gy	Adjuvant	Cisplatin 20 mg/m^2 × 9 weekly, CI Fluorouracil 2200 mg/m^2 × 9 weekly, CI Leucovorin acid 120 mg/m^2 × 9 weekly, CI	158	72

Abbreviations: WHO = World Health Organization; RT = radiotherapy; PWH = Prince of Wales Hospital; AOCOA = Asian-Oceanian Clinical Oncology Association; VUMCA = International Nasopharynx Cancer Study Group; INT = United States intergroup; PWHQEH = Prince of Wales Hospital, Queen Elizabeth Hospital; QMH = Queen Mary Hospital; QMH-95conc = RT vs. RT + concomitant chemotherapy; QMH-95conc+ = RT + adjuvant chemotherapy vs. RT + adjuvant + concomitant chemotherapy; QMH-95Adj = RT vs. RT + adjuvant chemotherapy; QMH-95Adj+ = RT + concomitant chemotherapy vs. RT + concomitant + adjuvant chemotherapy; TCOG = Taiwan Cooperative Oncology Group; T = tumor; N− = negative neck lymph nodes; N+ = positive neck lymph nodes; AJCC = American Joint Committee on Cancer; CI = continuous infusion; UFT = Uracil + Tegafur.

PWH-88: 2 cycles of induction and 4 cycles of adjuvant chemotherapy; RT to nasopharynx, equivalent of 66 Gy with conventional fractionation + 20 Gy boost if parapharyngeal disease + 18–24 Gy using ^{192}Ir if residual disease 4 wk after RT; to neck, 58 Gy for lower neck, 66 Gy for upper neck. VUMCA-89: 110 patients treated with conventional RT and 176 patients with hypofractionated RT, 2.5 Gy × 3/wk followed by 3.5 Gy × 3/wk. INT-0099: 24% of histologic type 1, concomitant cisplatin every 3 wk, adjuvant cisplatin + 5-fluorouracil every 4 wk. PWHQEH-94: 10 or 20 Gy (depending on center), boost if parapharyngeal disease, 21–24 Gy using ^{192}Ir if residual local disease after RT, 7.5 Gy boost if residual nodal disease, radical neck dissection if proven residual neck nodes. QMH-95: 2 × 2 design, concomitant chemotherapy vs. none and adjuvant chemotherapy vs. none; for adjuvant chemotherapy, alternating cycles of cisplatin + 5-fluorouracil and vincristine + bleomycin + methotrexate. ±10 Gy additional boost in case of parapharyngeal space involvement and/or palpable residual nodes.

* Classification of data provided by authors that may be different from that used in the trial publication.

juvant chemotherapy were included in the induction group or concomitant group. respectively. Trials were also grouped according to the type of chemotherapy: cisplatin plus 5-fluorouracil–based chemotherapy vs. other chemotherapy.

RESULTS

Trial selection

Eleven trials, including 2,722 patients, were identified in the English literature. The data from one trial (229 patients) were lost at the institution (14). We received data from 10 trials. Two trials were excluded by the Steering Committee after blind review (740 patients) because they did not meet the eligibility criterion of unpredictable treatment assignment (15, 16).

We found 88 comparative trials in the Chinese literature (7) (list available on request). Twelve were selected according to criteria based on a quality score (7), size, and duration of follow-up (1,775 patients). We were able to contact nine teams. The data from three trials were lost. Five teams failed to respond despite numerous attempts. Only one database (300 patients) was obtained (17) but the trial was also excluded by the Steering Committee after blind review for the same reason as the other two trials.

The database thus included eight trials (13, 18–24) (Table 1). All were published as a full article.

Population

The eight trials included 1,753 patients. Overall, 728 deaths (42%) occurred. The median follow-up was 6 years (range, 3–9 years). Only two trials (299 patients) had a median follow-up of <5 years. On the intent-to-treat basis, 63 randomized patients who had been excluded from the published studies were included in the present analysis (4%). The patient characteristics are described in Table 2.

One trial had a 2 × 2 design (23). The 222 patients in this trial were, therefore, counted twice, resulting in a total number of 11 comparisons using the data from 1975 patients. All trials used conventional RT. The doses delivered to the primary tumor site ranged between 65 and 74 Gy delivered within 6.5–8 weeks. Patients with N0 disease received 50–66 Gy. Patients with positive nodes received 60–76 Gy. The 76-Gy dose resulted from an additional boost delivered in the case of residual positive nodes after treatment completion in some of the patients in two trials (18, 23). Four comparisons (13, 18–20) (830 patients) investigated induction chemotherapy. In one (13) (77 patients), adjuvant chemotherapy was added to induction chemotherapy. Four comparisons (21–23) (765 patients) investigated concomitant chemotherapy. In one (21) (193 patients), adjuvant chemotherapy was added to concomitant chemotherapy. Three comparisons (23, 24) (380 patients) investigated adjuvant chemotherapy alone (including a comparison of concomitant chemotherapy vs. concomitant chemotherapy plus adjuvant chemotherapy). Three comparisons investigated monochemotherapy: uracil plus tegafur in 222 patients (23) and cisplatin in 350 patients (22). The eight other comparisons investigated cisplatin-based polychemotherapy: cisplatin plus 5-fluorouracil with or without other drugs in 730 patients (13, 21–24) and cisplatin plus epirubicin with or without bleomycin in 673 patients (18, 19). Of the patients in the RT plus chemotherapy group, 93% received at least one cycle of chemotherapy vs. 0.1% in the RT-alone group.

Table 2. Patient characteristics

Characteristic (n = 1975)	Treatment group (%) RT + chemotherapy (n = 990)	RT (n = 985)
Men	75	74
Age (y)		
<41	33	29
41–50	31	33
≥51	36	38
Performance status (n = 1468)*		
0	52	50
1	46	47
2	2	3
Tumor stage		
T1	46	47
T2	27	28
T3–T4	27	25
Nodal stage (n = 1898)†		
N0	10	9
N1–N2	65	68
N3	25	23
Histologic type (n = 1636)‡ (WHO)		
1	4	3
2	18	18
3	78	79

Abbreviations as in Table 1.
* Data missing from three trials.
† Data missing from one trial, using Ho's classification.
‡ Data missing mainly from one trial that did not distinguish between WHO histologic type 2 and 3 and did not include type 1.

Effect of chemotherapy on OS

A significant 18% reduction was found in the HR of death (p = 0.006) with the use of chemotherapy (HR, 0.82; 95% CI, 0.71–0.94; Fig. 1). This reduction corresponds to an absolute survival benefit of 4% at 2 years, from 77% to 81%, and of 6% at 5 years, from 56% to 62% (Fig. 2). Significant heterogeneity was found among the trials (p = 0.03; I^2 = 50%) largely owing to the timing of chemotherapy (p = 0.005). The concomitant trials showed a better treatment effect than induction trials or adjuvant trials (HR, 0.60; 95% CI, 0.48–0.76; vs. HR, 0.99; 95% CI, 0.80–1.21; and HR, 0.97; 95% CI, 0.69–1.38). The proportion of early deaths (i.e., within 3 months after randomization) was 1.6% in the RT plus chemotherapy group and 1.2% in the RT-alone group. The only excess treatment-related deaths were

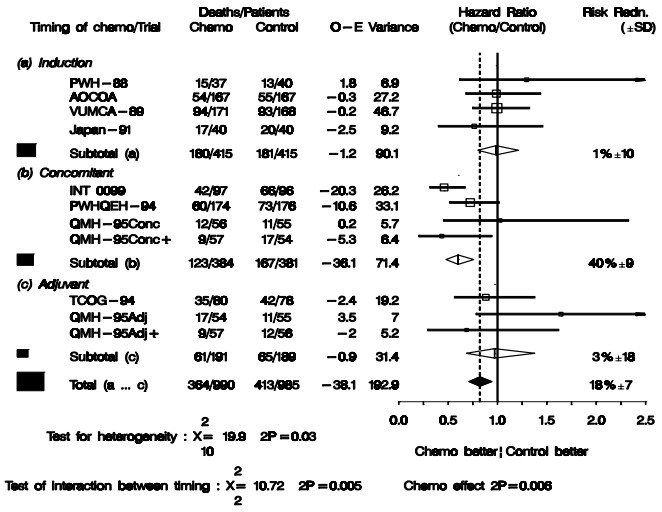

Fig. 1. Effect of chemotherapy on overall survival and hazard ratio (HR) of death by timing of chemotherapy. Center of each square is HR for individual trials; corresponding horizontal line is 95% confidence interval (CI); area of square is proportional to amount of information from trial. Broken line and center of black diamond indicate overall pooled HR and horizontal tip of diamond, 95% CI. Open diamonds indicate HRs for different chemotherapy timing. For each pooled HR, corresponding risk reduction (1 − HR) given with standard deviation. Queen Mary Hospital (QMH)-95 trial had 2 × 2 design and was counted twice in analysis PWH = Prince of Wales Hospital; AOCOA = Asian-Oceanian Clinical Oncology Association; VUMCA = International Nasopharynx Cancer Study Group; INT = Intergroup study; PWHQMH = Prince of Wales Hospital, Queen Mary Hospital; Conc = radiotherapy vs. radiotherapy plus concomitant chemotherapy; conc+ = radiotherapy plus adjuvant chemotherapy vs. radiotherapy plus adjuvant plus concomitant chemotherapy; TCOG = Taiwan Cooperative Oncology Group; Adj = radiotherapy vs. radiotherapy plus adjuvant chemotherapy; Adj+ = radiotherapy plus concomitant chemotherapy vs. radiotherapy plus concomitant plus adjuvant chemotherapy; 2P = two-sided *p* value.

observed in the RT plus chemotherapy group in the induction chemotherapy trials (19).

Effect of chemotherapy on EFS

The number of events observed was 1,044. A significant 24% reduction occurred in the HR of tumor failure or death

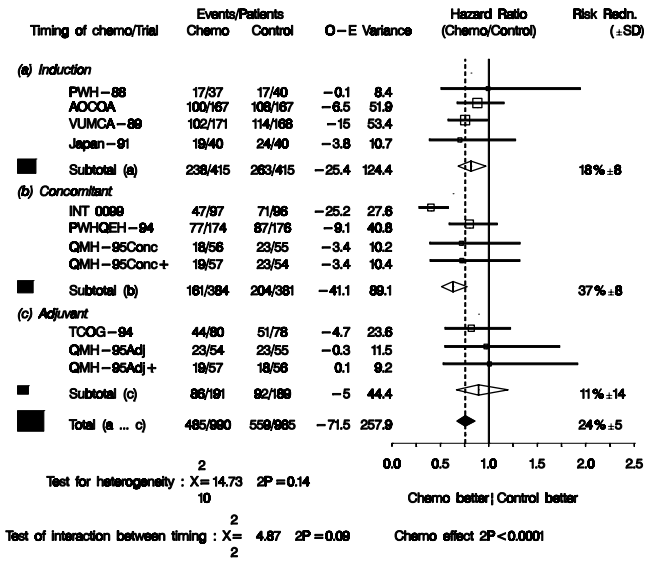

Fig. 3. Effect of chemotherapy on event-free survival, and hazard ratio (HR) of tumor failure, and death by timing of chemotherapy. Center of each square is HR for individual trials; corresponding horizontal line is 95% confidence interval (CI); area of square is proportional to amount of information from trial. Broken line and center of black diamond indicate overall pooled HR and horizontal tip of diamond, 95% CI. Open diamonds indicate HRs for different chemotherapy timing. For each pooled HR, corresponding risk reduction (1 − HR) given with standard deviation. Queen Mary Hospital (QMH)-95 trial had 2 × 2 design and was counted twice in analysis. PWH = Prince of Wales Hospital; AOCOA = Asian-Oceanian Clinical Oncology Association; VUMCA = International Nasopharynx Cancer Study Group; INT = Intergroup study; PWHQMH = Prince of Wales Hospital, Queen Mary Hospital; Conc = radiotherapy vs. radiotherapy plus concomitant chemotherapy; conc+ = radiotherapy plus adjuvant chemotherapy vs. radiotherapy plus adjuvant plus concomitant chemotherapy; TCOG = Taiwan Cooperative Oncology Group; Adj = radiotherapy vs. radiotherapy plus adjuvant chemotherapy; Adj+ = radiotherapy plus concomitant chemotherapy vs. radiotherapy plus concomitant plus adjuvant chemotherapy; 2P = two-sided *p* value.

($p < 0.0001$) for EFS with the use of chemotherapy (HR, 0.76; 95% CI, 0.67–0.86; Fig. 3). This reduction corresponds to an absolute EFS benefit of 9% at 2 years, from

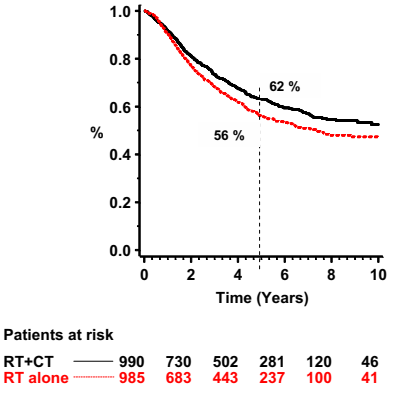

Fig. 2. Kaplan-Meier overall survival curves in radiotherapy (RT) and radiotherapy plus chemotherapy (RT+CT) groups.

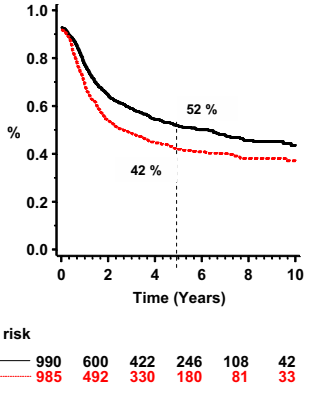

Fig. 4. Kaplan-Meier event-free survival curves in radiotherapy (RT) and radiotherapy plus chemotherapy (RT+CT) groups.

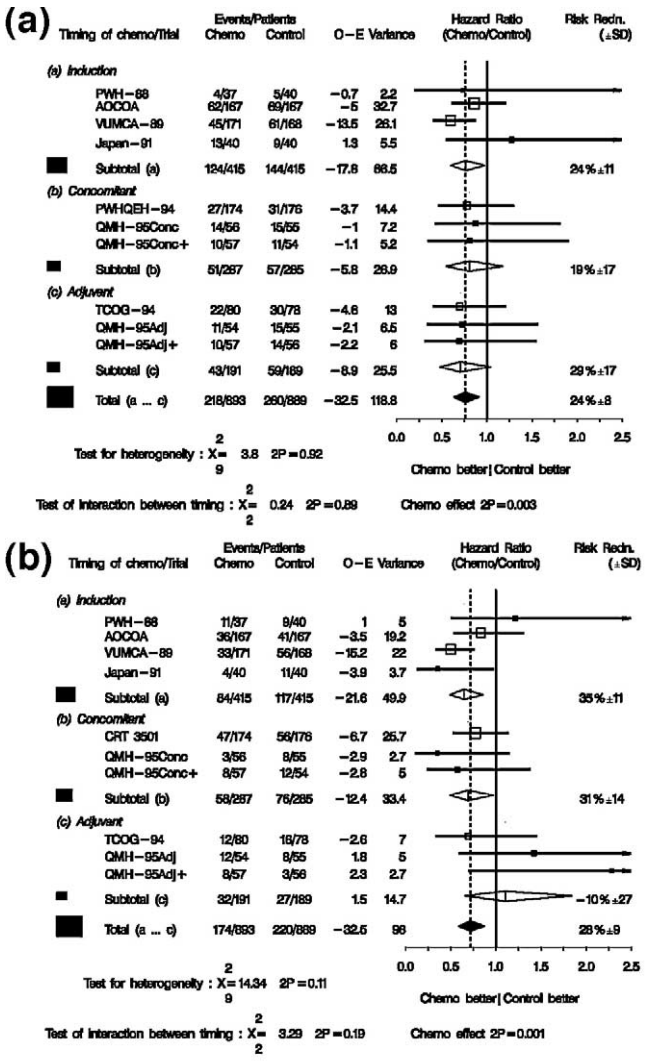

Fig. 5. (a) Effect of chemotherapy on locoregional control and hazard ratio (HR) of locoregional failure by timing of chemotherapy. (b) Effect of chemotherapy on distant control and HR of distant failure by timing of chemotherapy. Center of each square is HR for individual trials; corresponding horizontal line is 95% confidence interval (CI); area of square is proportional to amount of information from trial. Broken line and center of black diamond indicate overall pooled HR and horizontal tip of diamond, 95% CI. Open diamonds indicate HRs for different chemotherapy timing. For each pooled HR, corresponding risk reduction (1 − HR) given with standard deviation. Queen Mary Hospital (QMH)-95 trial had 2 × 2 design and was counted twice in analysis. PWH = Prince of Wales Hospital; AOCOA = Asian-Oceanian Clinical Oncology Association; VUMCA = International Nasopharynx Cancer Study Group; INT = Intergroup study; PWHQMH = Prince of Wales Hospital, Queen Mary Hospital; Conc = radiotherapy vs. radiotherapy plus concomitant chemotherapy; conc+ = radiotherapy plus adjuvant chemotherapy vs. radiotherapy plus adjuvant plus concomitant chemotherapy; TCOG = Taiwan Cooperative Oncology Group; Adj = radiotherapy vs. radiotherapy plus adjuvant chemotherapy; Adj+ = radiotherapy plus concomitant chemotherapy vs. radiotherapy plus concomitant plus adjuvant chemotherapy; 2P = two-sided p value.

54% to 63%, and 10% at 5 years, from 42% to 52% (Fig. 4). No significant heterogeneity was found among the trials ($p = 0.14$; $I^2 = 32\%$), and no significant interaction was observed in the timing of chemotherapy ($p = 0.09$).

The events recorded were locoregional failure (46%), distant failure (38%), both locoregional and distant failure (5%), and death without failure (11%). Data on the type of failure were missing for one trial (21). Chemotherapy lowered the risk of locoregional failure ($p = 0.003$; HR, 0.76; 95% CI, 0.64–0.91; Fig. 5a) and distant failure ($p = 0.001$; HR, 0.72; 95% CI, 0.59–0.87; Fig. 5b). No significant interaction was observed between the timing of chemotherapy and locoregional control ($p = 0.89$), nor between the timing of chemotherapy and distant control ($p = 0.19$).

Interactions between treatment effect and trial characteristics

A significant beneficial effect of chemotherapy was observed for EFS and OS in the subset of six trials (730 patients; two induction, one concomitant plus adjuvant, and three adjuvant trials) using cisplatin plus 5-fluorouracil, with a HR of tumor failure or death of 0.69 (95% CI, 0.56–0.85) and HR of death of 0.74 (95% CI, 0.59–0.93). A significant benefit was observed for EFS, but not for OS, in the other subset of five trials (1,245 patients; two induction and three concomitant trials), with a HR of tumor failure or death of 0.80 (95% CI, 0.69–0.93) and HR of death of 0.87 (95% CI, 0.73–1.04). However, the difference between these treatment effects was not significant for either EFS ($p = 0.25$) or OS ($p = 0.28$).

Interactions between treatment effect and patient characteristics

Table 3 summarizes the statistical analyses exploring the interactions between patient characteristics and the treatment effect. No significant interaction was found between the treatment effect and age, gender, performance status, T stage, or N stage. No significant interaction was found between T stage or N stage and the treatment effect within each subset of trials grouped according to the timing of chemotherapy. The only significant interaction was between the WHO histologic type and the effect of chemotherapy: chemotherapy was more efficient against WHO type 1 disease than against WHO type 2 or 3 disease ($p = 0.003$ for OS and $p < 0.0001$ for EFS).

Sensitivity analyses

Sensitivity analyses were performed to check the robustness of the results (Table 4). After exclusion of patients with WHO type 1 disease, the overall result remained significantly in favor of chemotherapy ($p = 0.03$), and this exclusion diminished the heterogeneity between trials, which was no longer significant ($p = 0.09$). Because 49 of 55 patients with WHO type 1 disease were from the Intergroup (INT)-0099 trial (21), analyses were also performed after exclusion of this trial. The overall benefit of chemotherapy remained significant for EFS ($p = 0.002$), but not for OS ($p =$

Table 3. Treatment effect on overall and event-free survival according to patient characteristics

Characteristic	Patients receiving RT+CT/RT (*n*)	Hazard ratio of death (95% CI)	*p* (*t* for test for trend)	Hazard ratio of tumor failure or death (95% CI)	*p* (*t* for test for trend)
Gender					
Male	742/727	0.81 (0.69–0.95)		0.76 (0.66–0.87)	
Female	248/258	0.85 (0.62–1.16)	0.81	0.74 (0.58–0.96)	0.89
Age (y)					
≤40	326/285	0.85 (0.63–1.14)		0.67 (0.52–0.85)	
41–50	308/327	0.77 (0.59–1.01)		0.80 (0.64–1.00)	
>50	356/373	0.86 (0.70–1.05)	0.85 (t)	0.79 (0.66–0.95)	0.31 (t)
Performance status*					
0	380/368	0.89 (0.71–1.11)		0.78 (0.64–0.94)	
1	342/340	0.71 (0.55–0.92)		0.66 (0.53–0.83)	
2	17/21	1.55 (0.65–3.69)	0.73 (t)	1.40 (0.65–3.02)	0.92 (t)
T stage (AJCC 1997)					
T1	267/272	0.68 (0.51–0.90)		0.69 (0.54–0.87)	
T2	350/363	0.83 (0.64–1.07)		0.82 (0.66–1.02)	
T3–T4	373/350	0.90 (0.73–1.12)	0.12 (t)	0.73 (0.60–0.88)	0.80 (t)
N stage (AJCC 1997)†					
N0	91/83	1.02 (0.61–1.69)		0.65 (0.42–1.00)	
N1–N2	620/643	0.82 (0.68–0.99)		0.79 (0.68–0.93)	
N3	242/219	0.68 (0.52–0.88)	0.24 (t)	0.64 (0.51–0.81)	0.47 (t)
WHO histologic type‡					
1	29/26	0.30 (0.15–0.59)		0.18 (0.09–0.36)	
2–3	958/959	0.85 (0.73–0.98)	0.003	0.78 (0.69–0.89)	<0.0001
Total	990/985	0.82 (0.71–0.94)	0.006	0.76 (0.67–0.86)	<0.0001

Abbreviations: CT = chemotherapy; CI = confidence interval; other abbreviations as in Table 1.
* Data missing from 3 trials.
† Data missing from one trial, using Ho's classification.
‡ Data missing for 3 patients in one trial.

0.17). However, the treatment effect remained significant for the concomitant subset, even though the HR increased from 0.60 (95% CI, 0.48–0.76) to 0.71 (95% CI, 0.53–0.94). Excluding a small trial, two trials with <5 years of follow-up, and the two comparisons that used a control group that received chemotherapy did not significantly modify the overall results (Table 4).

DISCUSSION

Despite numerous trials investigating the effect of chemotherapy on NPC, to date, no consensus has been reached about the magnitude of its benefit and the optimal protocol. An individual patient data meta-analysis was therefore justified. The exhaustiveness principle of meta-analysis was impossible to reach because of the difficulties encountered when trying to include the Chinese trials. Thus, the term "pooled analysis" could also be applied to the present study. The quality of the missing data remains unknown, and the quality of our data has been thoroughly checked. Very few data are missing from the trials included, which comply with long-term follow-up. The data from 11 trials and 2,793 patients were collected. The quality of the trials, especially concerning randomization, was verified. Three trials, totaling 1,040 patients, were excluded because they did not fulfil the eligibility criterion of unpredictable treatment assignment (14–16). Our meta-analysis demonstrated a small, but significant, treatment effect in terms of OS and EFS. These results seem to be robust, as confirmed by our sensitivity analyses. Chemotherapy also seemed to be active in terms of locoregional control (HR, 0.76) and distant control (HR, 0.72). A second meta-analysis based on published results was recently reported (25). Its results included two of the three trials we had excluded (15, 16), but it did not include the results of the Queen Mary Hospital-95 trial (23) nor the OS data from the Prince of Wales Hospital and Queen Mary Hospital-94 trial (22). The individual patient data from an old trial (14) included in their meta-analysis were lost and, therefore, were not included in our results. Literature-based meta-analyses tend to have limitations: no quality control of data, analyses not based on the intent-to-treat principle in all trials, analyses of the interaction between prognostic factors and treatment effects not possible, and trials not necessarily updated. These differences may explain why the effect of chemotherapy observed in our individual patient data–based meta-analysis in the concomitant group of trials was smaller than the effect observed in their meta-analysis. However, in that study, the observed effect of chemotherapy on OS was close to our findings.

The treatment effect could be dependent on the timing of chemotherapy. No evidence of an OS benefit was observed with induction and adjuvant chemotherapy, unlike that evidenced with concomitant chemotherapy. A benefit for EFS was, however, demonstrated in the subset of trials using in-

Table 4. Sensitivity analyses

Trials included in analysis	Patients receiving RT+CT/RT (*n*)	Overall survival				Event-free survival			
		Hazard ratio (95% CI)	*p*	Heterogeneity		Hazard ratio (95% CI)	*p*	Heterogeneity	
				I^2 (%)	*p*			I^2 (%)	*p*
All trials	990/985	0.82 (0.71–0.94)	0.006	50	0.03	0.76 (0.67–0.86)	<0.0001	32	0.14
Without INT0099	893/889	0.90 (0.77–1.05)	0.17	0	0.37	0.82 (0.72–0.93)	0.002	0	0.99
Without patients with WHO type 1 cancer	958/959	0.85 (0.73–0.98)	0.03	38	0.09	0.78 (0.69–0.89)	0.0001	0	0.58
Without one small trial (PWH-88)	953/945	0.81 (0.70–0.93)	0.003	51	0.03	0.75 (0.66–0.85)	<0.0001	36	0.12
Without QMH-95 combined arms (QMH-95Conc+, QMH-95Adj+)	876/875	0.84 (0.73–0.98)	0.02	53	0.03	0.75 (0.66–0.85)	<0.0001	43	0.08
Without PWH88, QMH95: follow-up ≤ 5 y	729/725	0.80 (0.68–0.93)	0.004	58	0.04	0.73 (0.64–0.84)	<0.0001	32	0.03

Abbreviations as in Tables 1 and 3.

duction chemotherapy. The observed effect in the subset of trials with adjuvant chemotherapy could be attributed to the absence of an effect on distant control. However, the power of our study may have been insufficient to demonstrate this hypothesis. The INT-0099 trial (21), in which adjuvant chemotherapy was added to concomitant chemotherapy, was included in the concomitant chemotherapy group. However, the affect of adjuvant chemotherapy in this trial remained unclear, because compliance with adjuvant chemotherapy was poor, which was also the case in the Prince of Wales Hospital-88 trial (13) (adjuvant after induction chemotherapy). Only 55% of patients in these trials completed the adjuvant chemotherapy protocol. In addition, when adjuvant chemotherapy was used alone, the trials failed to demonstrate a positive impact on OS or EFS. In the present meta-analysis, the INT-0099 trial was the only trial to demonstrate a significant OS benefit imputable to chemotherapy. Some controversy arose about the relevance of this trial because 49 of the 193 patients had WHO type 1 carcinoma, and survival in the control group was lower than usual (26). Furthermore, trial accrual was stopped early owing to the highly significant survival benefit evidenced at first planned interim analysis. Stopping the trial early may have artificially led to an overestimation of the treatment effect. Two ongoing trials should clarify this point: the SQNP01 trial conducted by the Nasopharynx Cancer Work Group in Singapore (27), and the NPC 99-01 trial conducted by the Hong Kong Nasopharyngeal Cancer Study group and the Princess Margaret Hospital in Canada (28). The preliminary results of the first trial seem to confirm the findings of the INT-0099 trial, but the second study does not seem to be demonstrating any effect of this protocol on OS. Longer follow-up is needed for both trials. However, the result of our meta-analysis could not be simply attributable to the INT-0099 trial, because the EFS benefit for the whole group of trials and the OS benefit in the concomitant group afforded by chemotherapy remained significant after exclusion of the INT-0099 trial. In our meta-analysis, only 55 patients had WHO type 1 carcinoma, and they account for part of the heterogeneity of the treatment effects. This heterogeneity may have stemmed from a significantly more pronounced treatment effect of chemotherapy in this subgroup of patients. Because most of these patients were from the INT-0099 trial, in which a strong treatment effect was observed, a bias may have been introduced. However, this was probably not the case, because the treatment effect in this trial was also more pronounced among patients with WHO type 1 carcinoma. However, the difference in the treatment effect between patients with WHO type 1 carcinoma and those with WHO type 2 and 3 carcinoma was not significantly different. No other significant interaction between the effect of chemotherapy and patient characteristics could be found. A slight trend was noted in favor of better efficiency of cisplatin plus 5-fluorouracil–based protocols, but this could partly be attributable to the highly significant result from the INT-0099 trial alone. A further update of this meta-analysis will allow us to increase its power and probably clarify these hypotheses.

CONCLUSION

The addition of chemotherapy to standard RT provides a small, but significant, survival benefit in patients with NPC. This benefit is essentially observed when chemotherapy is administered concomitantly with RT. The role of induction chemotherapy and adjuvant chemotherapy given alone or added to concomitant chemotherapy is more questionable.

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APPENDIX

A complete list of the MAC-NPC collaborative group follows.

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