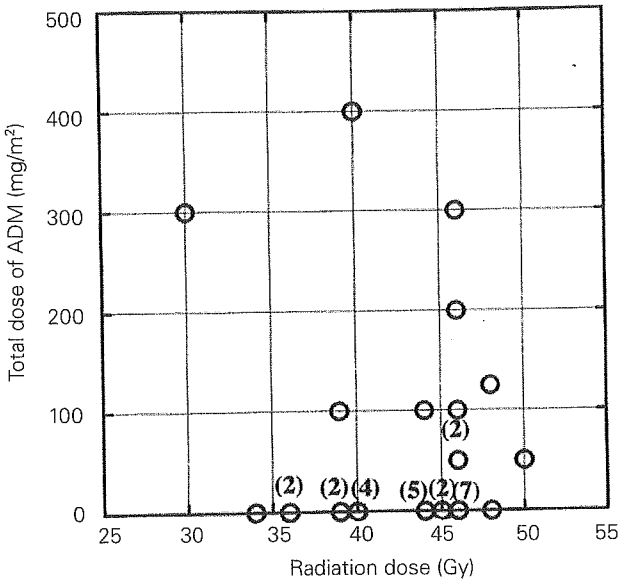

Figure 2. Relationship between local control, total dose of adriamycin (ADM), and total radiation dose in patients with MALT lymphoma. Number in parentheses indicates number of patients. The open circles indicate local control.

Abbildung 2. Zusammenhang zwischen lokaler Kontrolle, Adriamycin-Gesamtdosis (ADM), und Strahlungsgesamtdosis bei Patienten mit MALT-Lymphom. Zahlen in Klammern geben die Patientenzahl an. Die offenen Kreise stehen für lokale Kontrolle.

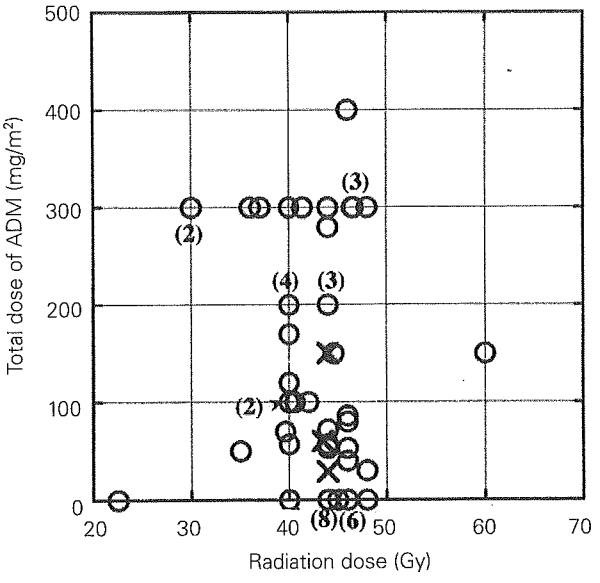

Figure 3. Relationship between local control, total dose of adriamycin (ADM), and total radiation dose in patients with diffuse large B-cell lymphoma. Number in parentheses indicates number of patients. The open circles indicate local control and the crosses local failure.

Abbildung 3. Zusammenhang zwischen lokaler Kontrolle, Adriamycin-Gesamtdosis (ADM), und Strahlungsgesamtdosis bei Patienten mit diffusem großzelligen B-Zell-Lymphom. Zahlen in Klammern geben die Patientenzahl an. Die offenen Kreise stehen für lokale Kontrolle.

survival rates than patients with follicular lymphoma ($p < 0.05$), DLBCL ($p < 0.01$), or peripheral T-cell lymphoma ($p < 0.05$). Patients with nasal NK/T-cell lymphoma showed significantly lower survival rates than patients with MALT lymphoma ($p < 0.01$), follicular lymphoma ($p < 0.05$), or DLBCL ($p < 0.05$). Figure 1b shows relapse-free survival rates of stage I and stage II patients according to histological classification. Patients with MALT lymphoma demonstrated higher relapse-free survival rates than patients with DLBCL ($p < 0.01$). Patients with nasal NK/T-cell lymphoma showed significantly lower survival rates than patients with MALT lymphoma ($p < 0.01$), or follicular lymphoma ($p < 0.05$). In patients with stage I or II, there were two relapses in MALT lymphoma, 23 relapses in DLBCL, and twelve relapses in T-cell lymphoma. In MALT lymphoma, both patients had relapses in distant sites. In DLBCL, three patients had relapses in radiation fields, one in regional lymph nodes, and 19 in distant sites. In T-cell lymphoma, two patients had relapses in radiation fields only, seven in radiation fields and distant sites, and one in distant site only.

Figure 2 demonstrates the in-field local control of MALT lymphoma according to intensity of chemotherapy and dose of radiotherapy. The intensity of chemotherapy was represented by doses of adriamycin. Most MALT lymphoma patients were early stage (Table 1). Eleven patients received radio- and chemotherapy and 24 patients radiotherapy alone. The radiation doses administered ranged from 30 to 50 Gy. No patients underwent in-field local recurrence even though there was a large variation in dose of radiotherapy and in the combinations of chemotherapy used in the treatment of MALT lymphomas.

Figure 3 demonstrates the in-field local control of DLBCL according to intensity of chemotherapy and dose of radiotherapy. There were only three recurrences in DLBCL. There were no recurrences in patients who received chemotherapy in which the doses of adriamycin were > 200 mg/m^2, nor in patients who were irradiated with > 45 Gy. All three patients with local recurrence had tumors < 6 cm in diameter.

Table 3 shows the effect of chemotherapy and tumor size on prevention of distant involvement. Chemotherapy was effective in preventing distant involvement for DLBCL patients whose tumor size was < 6 cm in diameter. However, the effect of chemotherapy in patients with a tumor size ≥ 6 cm was unclear.

In 69 patients with DLBCL (excluding brain lymphoma), 25 had bulky disease. Chemotherapy was performed in 40 patients before and in ten patients after radiotherapy. In patients who received chemotherapy before irradiation, 26 obtained complete remission (CR), eleven partial remission (PR), two no change (NC), and one progressive disease (PD) after chemotherapy.

Figure 4 shows the in-field local control of T-cell lymphoma (nasal NK/T-cell lymphoma, unclassified peripheral T-cell lym-

phomas, and anaplastic large-cell lymphoma) according to intensity of chemotherapy and dose of radiotherapy. Only nine of the 15 patients treated with ≤ 50 Gy and three of the five patients treated with > 50 Gy had local control. The dose of adriamycin had no influence on local control of T-cell lymphoma.

In T-cell lymphoma, the existence of bulky tumor was related to poor local control. Only two of eight patients with bulky tumor had local control, whereas seven of eleven patients without bulky tumor had local control. However, age, sex, or chemotherapy did not influence local control of T-cell lymphoma. Nasal NK/T-cell lymphoma tended to cause distant involvement more frequently, as compared with other histologies of T-cell lymphoma. In patients with stage I or II, eight of 15 patients with nasal NK/T-cell lymphoma developed distant involvement, whereas none of six patients with unclassified peripheral T-cell lymphomas and only one of four with anaplastic large-cell lymphoma did so. However, age, sex, or chemotherapy was not related to the frequency of distant involvement of T-cell lymphoma.

In follicular lymphoma, eight patients had stage I, four stage II, and two stage III disease. Four patients received radio- and chemotherapy and ten radiotherapy alone. No patient died of follicular lymphoma. Two patients died of stomach cancer. Three patients suffered distant relapse. None of the patients had local recurrence.

Discussion

It is necessary to identify the adverse prognostic factors in patients with localized aggressive NHL in order to select the patients who cannot be expected to be cured by the combined modality consisting of a short course of CHOP followed by radiotherapy. It is also important to select suitable radiation doses for the histological subtypes of NHL and to obtain local control. Most studies on the optimal radiotherapy dose required to achieve in-field disease control and prolonged relapse-free survival in NHL, including our previous report [26], utilized the Working Formulation [17, 23, 29]. Unfortunately, the Working Formulation is based on morphological features alone and its entities cannot be translated directly to those of the WHO classification. Thus, there is little information on the clinical characteristics of NHL from the perspective of the WHO classification.

In this series, about 20% of patients had T- and NK-cell lymphoma. This is a unusual distribution in terms of pathology of NHL patients in the USA and Europe [2, 9] and it reflects a difference in prevalence of NHL between Japan and western countries; T- and NK-cell lymphoma is relatively rare in the latter [16]. Nasal T/NK-cell lymphoma, which is characterized by progressive, unrelenting ulceration, and necrosis of the nasal cavity and midline facial tissues, is rare in the USA and Europe but more common in Asia. Therefore, little information is available on the optimal radiotherapy dose to achieve in-field disease control and prolonged relapse-free survival, especially in T/NK-cell lymphoma [7, 15].

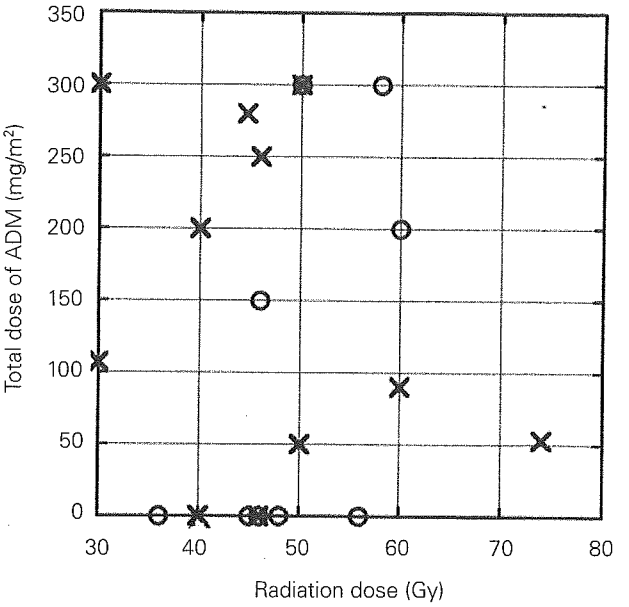

Figure 4. Relationship between local control, total dose of adriamycin (ADM), and total radiation dose in patients with T-cell and NK-cell lymphoma. Number in parentheses indicates number of patients. The open circles indicate local control and the crosses local failure.

Abbildung 4. Zusammenhang zwischen lokaler Kontrolle, Adriamycin-Gesamtdosis (ADM), und Strahlungsgesamtdosis bei Patienten mit T-Zell- und NK-Zell-Lymphom. Zahlen in Klammern geben die Patientenzahl an. Die offenen Kreise stehen für lokale Kontrolle.

The overall 5-year survival rate for patients with MALT lymphoma was 100% (Figure 1a). No patients underwent in-field local recurrence even though there were large variations in doses of radiotherapy and in the combinations of chemotherapy used in the treatment for MALT lymphoma (Figure 2). Chemotherapy is not necessarily required for treatment of MALT lymphoma, at least not in the case of stage I and II. Low-grade NHL of the gastrointestinal tract and other sites, such as salivary glands, the orbital regions, and thyroid, are grouped together as tumors arising in MALT. Lymphomas

Table 3. Incidence of distant involvement of diffuse large B-cell lymphoma (stage I, II) according to tumor size and adriamycin (ADM) dose.

Tabelle 3. Inzidenz entfernter Herde bei diffusem großzelligen B-Zell-Lymphom (Stadium I, II) in Abhängigkeit von Tumorgröße und Adriamycin-(ADM-)Dosis.

ADM dose (mg/m²)	Tumor size < 6.0 cm	≥ 6.0 cm
0	7/13	2/4
100	0/7	4/8
100–200	0/6	0/2
200–300	0/6	0/1
300–400	2/6	3/3

arising from MALT tend to remain localized until late in the course of the disease [14]. Therefore, patients with MALT lymphoma are good candidates for radiation therapy alone.

There were no in-field failures in patients with MALT lymphoma treated with doses of at least 30 Gy, suggesting that in our series the radiation doses used were adequate. Although most patients were treated with 40–46 Gy, our results indicate that a lower dose range is sufficient to obtain local control of MALT lymphoma. These results concur with those obtained in other studies [5, 27].

There were no recurrences in DLBCL patients who received chemotherapy in which the doses of adriamycin were > 200 mg/m^2 (Figure 3). When patients treated with adriamycin ≥ 200 mg/m^2 were compared with those treated with adriamycin < 200 mg/m^2, the difference in local control was not statistically significant, most likely because of the inadequate sample size. However, this result indicates that administration of chemotherapy of sufficient intensity may improve local control. 40 Gy may be enough to treat patients who have previously been treated with chemotherapy in which the doses of adriamycin are > 200 mg/m^2. However, ≥ 45 Gy might be required to treat patients who have received irradiation alone or chemotherapy in which the doses of adriamycin were < 100 mg/m^2.

The presence of tumor bulk has been suggested to influence treatment outcome [17, 23, 29], and recently, Oguchi et al. [23] introduced B-ALPS (tumor bulk, age, lactate dehydrogenase level, performance status, and stage), a new prognostic index for localized aggressive NHL, which included tumor bulk (< 6 cm vs. ≥ 6 cm) instead of the amount of extranodal involvement. In our series, chemotherapy was effective in preventing distant involvement in DLBCL patients whose tumor size was < 6 cm, whereas the effect of chemotherapy was unclear for patients whose tumor size was ≥ 6 cm (Table 3). These results may explain the poorer prognosis of DLBCL patients with bulky tumor.

Ott et al. reported that age was an independent prognostic factor of overall survival for patients with low-grade NHL [24]. In our study, age was not related to the overall survival (data not shown). Most patients in our study belonged to intermediate-grade NHL, which may explain this discrepancy of results.

Our study indicated that a minimum dose of 46 Gy was required to obtain local control of T-cell lymphoma and some radioresistant T-cell lymphomas could not be controlled even with ≥ 60 Gy (Figure 4). The prognosis for peripheral T/NK-cell lymphoma is poor even when treated by irradiation combined with multi-agent combination chemotherapy. Actually, the dose level of adriamycin had no influence on local control of T-cell lymphoma (Figure 4). Nasal NK/T-cell lymphoma in particular expressed P-glycoprotein [30], and it is therefore highly resistant to chemotherapy. Cheung et al. [1] recently reported that a combination of chemotherapy and involved-field radiotherapy demonstrated no therapeutic advantage over radiotherapy alone for localized nasal NK/T-cell lymphoma. According to these findings, radiation therapy is the key treatment method for this type of lymphoma to date. The control rate for T/NK-cell lymphomas was much poorer than for DLBCL. High total radiation doses of at least 50 Gy, and probably > 60 Gy, should be delivered to the lesions.

Although it is unclear whether there is a difference in responses to radio- and chemotherapy among subtypes of T/NK-cell lymphoma due to the small numbers of these lymphomas, our results indicate that the standard treatment strategy for NHL, i.e., a combined modality consisting of three cycles of CHOP and radiotherapy, is not sufficiently effective.

Kuhnt et al. reported a case of MALT lymphoma which relapsed outside of the treatment fields [18]. Frank et al. reported that in centroblastic-centrocytic NHL (stages I/II), most relapses were located outside the radiation portals, yet extended field radiotherapy was not superior to involved-field radiotherapy in terms of overall survival and relapse-free survival [8]. In our study, radiation therapy was usually delivered to the involved field. In patients receiving chemotherapy and subsequent radiotherapy, the radiation field was set for primary sizes of lesions. Most relapses were located outside the radiation portals. Prospective randomized trials are necessary to prove a potentially favorable effect of more extended radiotherapy portals (TLI or TNI [total nodal irradiation]) and to evaluate the optimal radiotherapy dose.

Conclusion

The WHO classification accurately indicated the prognosis of patients with NHL. Our analysis using the WHO classification indicates that patients with MALT lymphomas of stage I or II are good candidates for radiation therapy alone. The prognosis for peripheral T/NK-cell lymphoma is poor even when treated by irradiation combined with multi-agent combination chemotherapy. In reality, the dose level of adriamycin had no influence on local control of T-cell lymphoma.

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Three Cases of Diffuse Large B-cell Lymphoma of the Mandible Treated with Radiotherapy and Chemotherapy

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CASE REPORT

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Three Cases of Diffuse Large B-cell Lymphoma of the Mandible Treated with Radiotherapy and Chemotherapy

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Case Report: We report three cases of diffuse large B-cell lymphoma of the mandible and a review of the literature. All 3 of our patients had stage I AE disease and had complete remission for more than 2 years after 42-46 Gy of irradiation to the primary tumor with regional lymph nodes and 3 courses of chemotherapy consisting of cyclophosphamide, adriamycin, vincristine, and predonisolone (CHOP). Literature analysis, although biased toward published data, indicated that the 3-year disease-specific survival rates for non-Hodgkin's lymphoma (NHL) of the mandible were 90.5% and 47.6% for stages I and II, respectively. The treatment results for NHL of the mandible may be similar to general primary bone NHL and to other extranodal NHL's. ***Conclusion:*** Radiotherapy alone is not sufficient for tumor control for stage I-II, disease, and combination chemotherapy may be needed.

Key words: non-Hodgkin's lymphoma, bone, mandible, radiotherapy, chemotherapy, case report

Introduction

Primary lymphoma of the bone was first described by Parker and Jackson as primary reticulum cell sarcoma of bone.[1] Such lymphomas of the bone account for 3-5% of all primary bone tumors, and approximately 4% of all lymphomas.[2,3] The pelvic bones, long tubular bones, vertebrae, and ribs are common presentation sites. Coley *et al.*[4] described the criteria for primary malignant lymphoma of the bone as follows:

(1) Clinically a primary focus in a single bone on admission.
(2) Unequivocal histological proof from the bone lesion (not from metastasis).
(3) Metastases present on admission only if regional, or if the onset of symptoms of the primary tumor preceded the appearance of the metastases by at least six months.

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Primary lymphoma of the mandible is rare. Ostrowski *et al.* reported that it accounted for 20/422 (4.7%) of all primary lymphomas of bone.[5] It commonly occurs between 20 and 50 years of age, and, like other primary lymphomas of bone, shows a male preponderance, with a male-to-female ratio of 3:2.[6] The main symptoms are swelling, pain, numbness, tooth mobility, and cervical lymphadenopathy.[3] It usually takes much time to make a diagnosis of non-Hodgkin's lymphoma (NHL), because these symptoms resemble dental caries, acute dental abscess, and osteomyelitis of the mandible in the first treatment.[7,8] In this paper, we report our experiences with three cases of diffuse large B-cell lymphoma of the mandible treated with radiotherapy and chemotherapy, and review the literature to elucidate optimal treatment of NHL of the mandible.

Case Reports

Case 1

In August 1997, a 46-year-old woman was referred to us with swelling of the jaw and gum, and numbness of the lower lip. At first, dental caries of her left molar tooth were treated and symptoms were relieved; however, swelling of the jaw remained. CT scan of the head and neck displayed a protruding tumor on the left side of the mandible and gingiva. Biopsy of the gingival

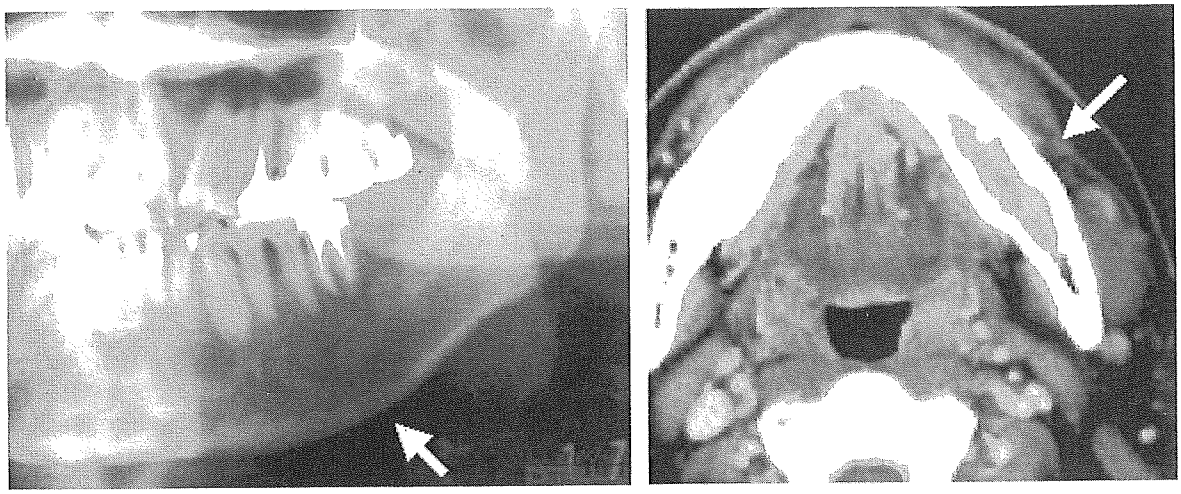

Fig. 1.
A: X-ray film shows radiolucency and alveolar bone destruction in the left ramus of the mandible.
B: CT scan of the neck displays tumor in the mandible (case 2).

A | B

tumor revealed diffuse large B-cell lymphoma (DLBCL) according to the WHO classification.[9] After staging of the disease, which consisted of physical examination, complete blood cell count, bone marrow biopsy, and CT scans of the head and neck, chest, and pelvic and abdominal regions, no other evidence of disease was found except the mandibular lesion.[10] She was diagnosed with stage I EA of primary DLBCL of the mandible. Her International Prognostic Index (IPI) score was 0.

Treatment was started with chemotherapy in November 1997. After administration of 80 mg of cisplatinum, the mandible was irradiated with 42 Gy in 21 fractions of radiotherapy. Consequently, 3 courses of systemic chemotherapy, which consisted of cyclophosphamide, adriamycin, vincristine, and predonisolone (CHOP), were performed after radiotherapy. The tumor disappeared, and we judged that she had complete remission (CR) according to the response criteria.[10] There was no evidence of recurrence at the 48-month follow-up.

Case 2

In August 1998, a 51-year-old man was referred to our hospital with pain in a lower left tooth. X-ray film and CT scan of the mandible showed radiolucency and alveolar bone destruction (Figs. 1A, 1B), and a gingival tumor was clearly visible. After extraction of his first lower left tooth, swelling of the gingival tumor appeared in the extraction site. In December 1998, biopsy of the gingival tumor was performed, revealing diffuse large B-cell lymphoma according to the WHO classification. The tumor was confirmed to be confined to the primary site by systemic examination, as in case 1, and was diagnosed as stage I EA DLBCL of the mandible. His IPI score was 0.

Three courses of CHOP were administered from January 1999. After chemotherapy, the whole neck and supraclavicular region were irradiated with 30 Gy in 20 fractions of radiotherapy, followed by 16 Gy in 8 fractions of radiotherapy to the mandible as a boost. The patient had CR according to the response criteria. There was no evidence of recurrence at the 28-month follow-up.

Case 3

In June 1999, a 54-year-old man was referred to us with swelling of the lower right gum and numbness of the right side of the lower lip. X-ray film of the mandible showed radiolucency and bone destruction on the right side of the mandibular body. A CT scan and magnetic resonance imaging (MRI) of the mandible displayed a destructive tumor in the right side of his mandible (Figs. 2A, 2B). In August 1999, biopsy of the gingival tumor revealed diffuse large B-cell lymphoma according to the WHO classification. The tumor was confirmed to be confined to the primary site by systemic examination, the same as in case 1, and was diagnosed as stage I EA of DLBCL of the mandible. His IPI score was 1.

Three courses of CHOP were given from September 1999. After chemotherapy, 30 Gy in 20 fractions of radiotherapy was administered to the whole mandible, followed by 14 Gy in 7 fractions of radiotherapy to the right side of the mandible as a boost. The tumor disappeared, and we judged that he had CR according to the response criteria. There was no evidence of recurrence at the 28-month follow-up.

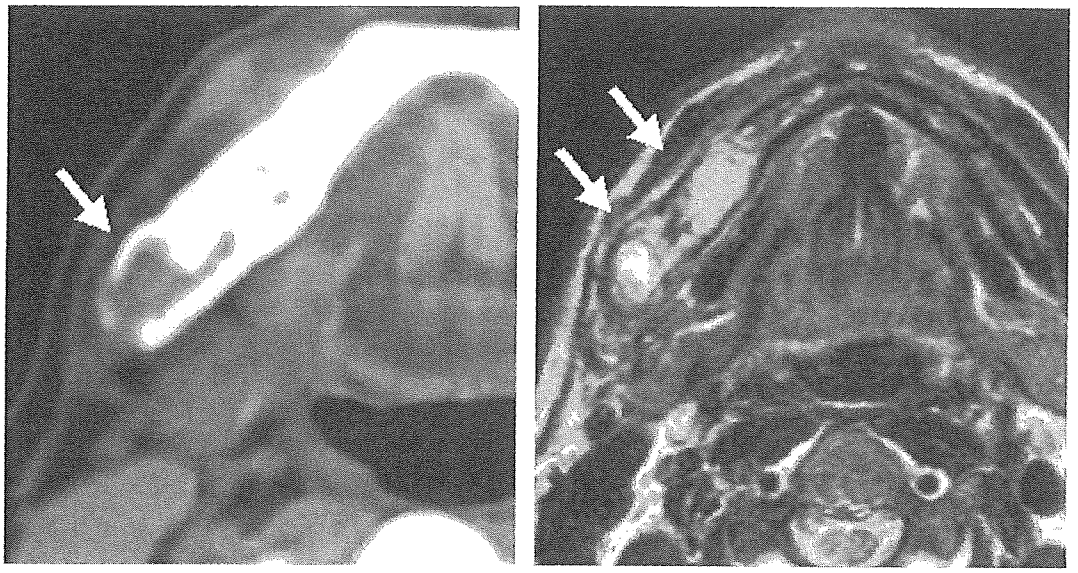

Fig. 2.
A: CT scan of the neck shows bone-destructive tumor in the left ramus of the mandible.
B: MRI of the neck displays high-intensity tumor in T2-weighted image (case 3).

A | B

Discussion

Literature analysis for NHL of the mandible

To clarify the treatment results for NHL of the mandible, we undertook a literature search for 'NHL of the mandible' covering the years 1970 through 2003. However, the majority of papers were not useful because of incomplete descriptions or lack of details on treatment and prognosis. Finally, 45 patients in 21 reports and the 3 patients from our experience were analyzed (Tables 1, 2).[3,6-8,11-27] Survival curves were calculated using the Kaplan-Meier method. Age at diagnosis ranged from 3 to 82 years (mean, 53.0); 30 patients (62.5%) were male and 18 patients (37.5%) were female. There were 37 patients (77.1%) with stage I E, and 11 patients (22.9%) with stage II E. Primary NHL of the mandible, for the most part, has intermediate and high-grade malignancy, but it tends to remain localized. Types of histology could not be analyzed, because different classification systems were used. Generally, diffuse large B-cell lymphoma was most frequently seen. Lewis *et al.* reported 28 cases of primary lymphoma of bone in a single institution.[28] In this series, 25 of 28 (89.3%) were diffuse large B-cell lymphoma. In our experience, all 3 patients also had diffuse large B-cell lymphoma. Analyses of disease-specific survival were performed (Fig. 3). For the 48 cases, 4-year disease-specific survival rates were 90.5% and 47.6% for stages I and II, respectively, and the 5-year disease-specific survival rate for stage I+II was 82.5%. However, these survival data were biased because we collected only published data.

Comparison of other sites of stage I+II NHL

For primary bone NHL (sites other than the mandible), Lewis *et al.* reported 63.8% and 40.0% 5-year overall survival for stages I E and II+IV, respectively, treated with chemotherapy combined with radiotherapy.[28] Zinzani *et al.* also described an 84% 8-year overall survival rate for patients treated with chemotherapy and radiotherapy.[29] These results indicated that the prognosis of stage I+II NHL of the mandible may be similar to that for other sites of bone.

For NHL of primary sites other than bone, Horning *et al.* reported 8 courses of CHOP plus involved-field radiotherapy for untreated bulky or extranodal stage I and stage II intermediate-grade NHL, and the 6-year overall survival rate was 79%.[30] Miller *et al.* described 3 courses of CHOP followed by involved-field radiotherapy for localized stage I and non-bulky stage II NHL in the Southwest Oncology Group phase III trial, and the 4-year overall survival rate was 87%.[31] These results indicate that the prognosis of stage I+II NHL of the mandible may be similar to that for other sites of NHL.

Optimal treatment for stage I+II NHL of the mandible

Treatment characteristics of NHL of the mandible are summarized in Table 2, and Fig. 4 shows relapse-free survival according to the type of treatment. Twenty-five of the 50 patients were treated with radiotherapy alone; 17 patients had radiotherapy combined with chemotherapy, and 5 patients were treated with chemotherapy alone. Doses of radiotherapy to the primary tumor ranged from 24 to 60 Gy (mean, 42.5 Gy), and 33 of the 39

Table 1. Cases of NHL of the mandible in the literature

Author	Year	No. of patients	Age/gender	Histology	Stage	Treatment	Survival (months)
Mincey *et al.*	1974	1	32/F	Mix	I E	RT 40 Gy	Alive, 0
Campbell *et al.*	1975	1	52/M	RCS	I E	RT 28 Gy	Alive, 2
Cline *et al.*	1977	1	72/F	RCS	I E	RT 50 Gy+C	Alive, 42
Lian *et al.*	1980	2	40/M	RCS	II E	RT 30 Gy+C	DD, 16
			64/M	RCS	I E	RT 30 Gy+C	DD, 7
Van Sickels *et al.*	1980	1	77/M	Histiocytic	II E	Ope+C	DO, 2
Eisenbud *et al.*	1984	2	49/F	DL	I E	RT 50 Gy	DO, 60
			44/M	DL	I E	RT	Alive, 60
Robbins *et al.*	1986	8	(6M, 2F)				
			69	DL	I E	RT 40 Gy	R, 36
			74	DL	I E	RT 60 Gy	DO, 60
			60	DL	I E	RT 40 Gy	Alive, 24
			46	DL	I E	RT 45 Gy+C	Alive, 68
			67	DL	I E	Ope	Alive, 99
			36	DL	II E	Ope+RT 48 Gy	R, 2
			33	DU	II E	RT 50 Gy	R, 7
			3	DU	I E	RT 24 Gy+C	Alive, 108
Macintyre *et al.*	1986	1	52/M	Unclass	I E	RT 52.5 Gy	DD, 5
Murata *et al.*	1987	1	37/F	DL, Mix	II E	C+RT 40 Gy+C	Alive, 2
Yamamoto *et al.*	1987	1	42/M	Histiocytic	I E	C+Ope	Alive, 96
Wen *et al.*	1988	3	13/M	RCS	I E	RT 50.5 Gy	DD, 5
			56/M	RCS	I E	RT 45 Gy+Ope	DO, 180
			37/M	DL	II E	RT 41 Gy+C	Alive, 16
Pileri *et al.*	1990	13	65/F	B, Cb/Cc	II E	RT 44 Gy+C	Alive, 36
			65/F	B, Cbpol	I E	Ope+RT 50 Gy	Alive, 48
			58/M	B, Cbpol	II E	RT 36 Gy+C	DD, 12
			63/M	B, Cbpol	I E	RT 42 Gy	Alive, 12
			56/M	B, Cbpol	II E	RT 40 Gy	DD, 36
			64/F	B, Cbpol	I E	RT 46 Gy	Alive, 12
			49/M	B, Cbcyt	I E	RT 40 Gy	Alive, 72
			78/F	B, Cbcyt	I E	RT 46 Gy	Alive, 48
			42/F	B, Cbmul	I E	RT 42 Gy	Alive, 36
			51/M	B, Cbmul	I E	RT 41 Gy	Alive, 36
			77/F	B, Lb	I E	RT 42 Gy	FL, 0
			62/F	PTC	I E	RT 46 Gy	Alive, 60
			67/F	PTC	I E	RT 46 Gy	FL, 0
			53/M	DL	I E	Ope+C	Alive, 18
Gusenbauer *et al.*	1990	1	55/M	DM	II E	Ope+C	Alive, 24
Kida *et al.*	1993	1	29/M	NHL	I E	C+RT	Alive, 12
Ugar *et al.*	1995	1	48/F	L	I E	Ope+RT	Alive, 30
Sarda *et al.*	1995	1	68/M	B	I E	C+RT 40 Gy	Alive, 7
Kasuya *et al.*	1995	1	56/M	B, DL	II E	Ope+C+RT 40 Gy	Alive, 48
Rios-Martin *et al.*	1996	2	52/M	L	I E	Ope+C	Alive, 5
			82/F	B, DCb	I E	C+RT 30 Gy	Alive, 12
Piattelli *et al.*	1997	1	57/M	B, DL	I E	RT 40 Gy	Alive, 0
Parrington *et al.*	1999	1	48/M	B, DL	I E	RT 50 Gy+HC+PBSCT	Alive, 72
Kirita *et al.*	2000	1	46/F	B, DL	I E	RT 42 Gy+C	Alive, 48
Authors	2004	3	51/M	B, DL	I E	C+RT 46 Gy	Alive, 28
			54/M	B, DL	I E	C+RT 44 Gy	Alive, 28

B: B-cell type, Mix: mixed type, RCS: reticulum-cell sarcoma, DL: diffuse large-cell, DU: diffuse undifferentiated, Unclass: unclassified, L: large cell, Cb/Cc: centroblastic/centrocytic, Cbpol: centroblastic polymorphic, Cbcyt: centroblastic centrocytoid, Cbmul: centroblastic multilobulated, Lb: lymphoblastic, PTC: peripheral T-cell, DM: diffuse medium sized cell, RT: radiotherapy, C: chemotherapy, Ope: operation, HC: high-dose chemotherapy, PBSCT: peripheral blood stem cell transplantation, DD: died of disease, DO: died of other disease, R: relapse of disease, FL: lost to follow-up

Table 2. Treatment characteristics

Treatment	Stage	
	I E (n=37)	II E (n=11)
RT	22	3
RT+Chemo	11	6
Chemotherapy	3	2
Operation alone	1	0

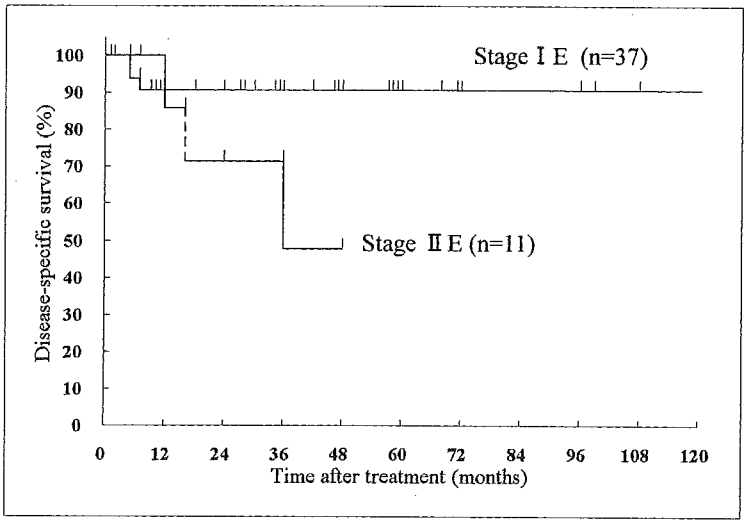

Fig. 3. Disease-specific survival of all patients reviewed in the literature.

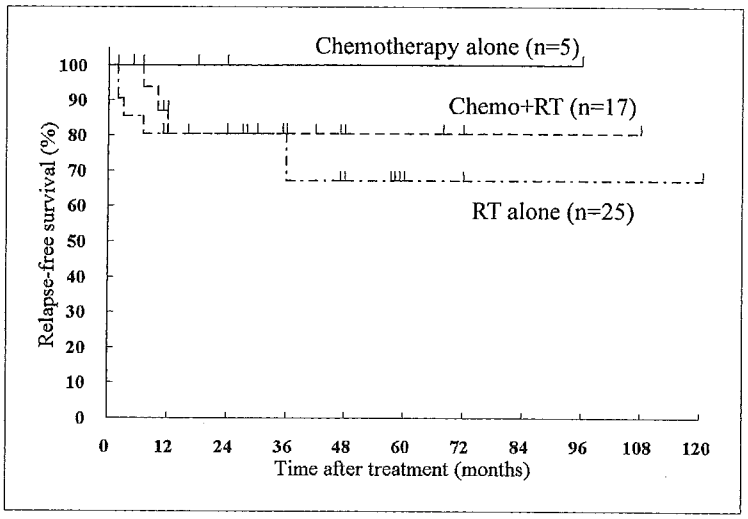

Fig. 4. Disease-specific survival of stage I+II patients according to the type of treatment.

patients (84.6%) were irradiated with 40 Gy or more; however, most papers did not mention details of the radiation field.

In the radiotherapy-alone group, 5 of the 25 patients (20.0%) had recurrent disease. Of these, one had loco-regional recurrence, 3 had distant involvement outside of the radiation field, and the other died of disease with an unreported recurrent site. We cannot conclude the optimal radiation dose for NHL of the mandible because there was only one in-field recurrence. In the group with combined chemotherapy and radiotherapy, 3 of the 16 had recurrent disease. Of these, 2 were treated with

chemotherapy not including adriamycin and had recurrent disease outside the radiation field, whereas the other had received CHOP chemotherapy but died of disease with a recurrent site not detailed. In the chemotherapy-alone group, no patient had recurrent disease.

Based on this analysis, radiotherapy alone would not be sufficient for treatment of NHL of the mandible for stage I+II disease, and combination with chemotherapy, especially including adriamycin, may be required. No patient had recurrent disease in the chemotherapy-alone group; however, it is uncertain that chemotherapy alone is sufficient for tumor control, because the number of cases was too small and the chemotherapy regimens differed.

Zinzani *et al.* reported 52 patients with primary bone NHL in sites other than the mandible treated with chemotherapy and/or radiotherapy.[29] Chemotherapy plus radiotherapy had a better complete response rate than radiotherapy alone (85% vs. 64%, p=0.01), and relapse-free survival was also significantly higher with chemotherapy plus radiotherapy than with radiotherapy alone (p=0.01). These results suggest that a combination of chemotherapy and radiotherapy is required not only for most patients with bone NHL, but also for NHL of the mandible.

Surgery ranged from tumorectomy to hemimandibulectomy; however, radical surgery was not the first modality of treatment if the histology of NHL was confirmed, because chemotherapy combined with radiotherapy was effective for local control of NHL of the mandible.

In summary, we have reported 3 cases of NHL of the mandible and a review of the literature. All 3 of our patients had stage I AE disease and had complete remission for more than 2 years with 42-46 Gy of irradiation to the primary with regional lymph nodes and 3 courses of CHOP.

Literature analysis estimated that 3-year disease-specific survival rates for NHL of the mandible were 90.5% and 47.6% for stages I and II, respectively. However, literature analysis had some limitations because of the bias that we collected only published data. The treatment results for NHL of the mandible may be similar to primary bone NHL in general and to other extranodal NHLs. Radiotherapy alone appears not to be sufficient for tumor control for stage I+II disease, and combination with chemotherapy may be needed.

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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.

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.

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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

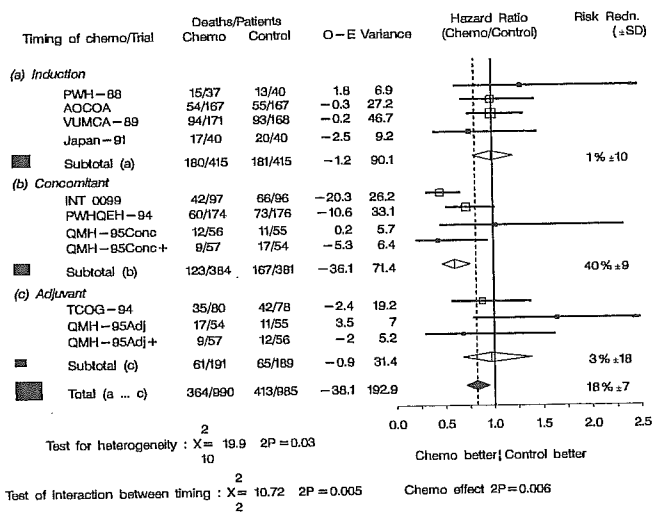

Fig. 1. Effect of chemotherapy on overall survival and hazard ratio (HR) of death by timing of chemotherapy. Center of each square is HR for individual trials; corresponding horizontal line is 95% confidence interval (CI); area of square is proportional to amount of information from trial. Broken line 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

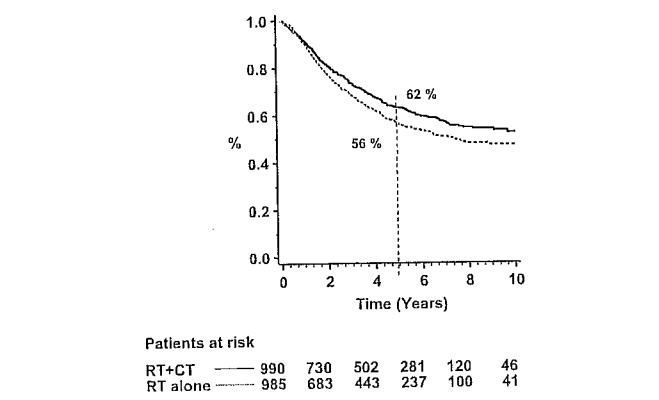

Fig. 2. Kaplan-Meier overall survival curves in radiotherapy (RT) and radiotherapy plus chemotherapy (RT+CT) groups.

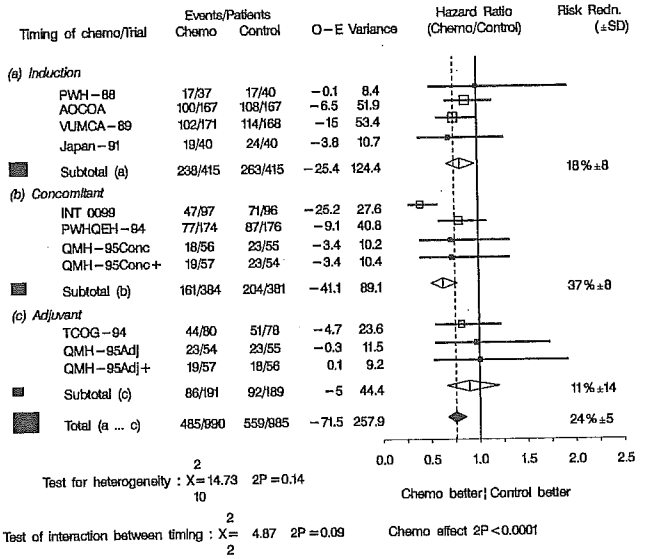

Fig. 3. Effect of chemotherapy on event-free survival, and hazard ratio (HR) of tumor failure, and death by timing of chemotherapy. Center of each square is HR for individual trials; corresponding horizontal line is 95% confidence interval (CI); area of square is proportional to amount of information 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

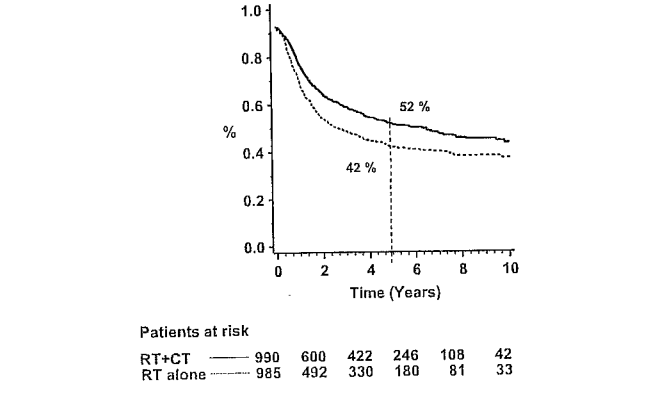

Fig. 4. Kaplan-Meier event-free survival curves in radiotherapy (RT) and radiotherapy plus chemotherapy (RT+CT) groups.

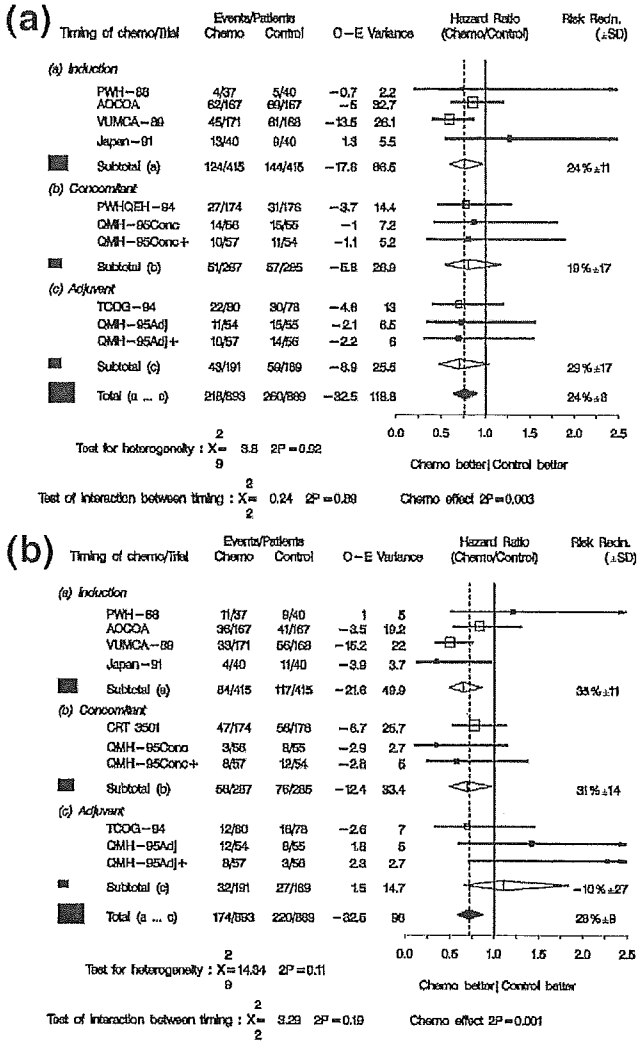

Fig. 5. (a) Effect of chemotherapy on locoregional control and hazard ratio (HR) of locoregional failure by timing of chemotherapy. (b) Effect of chemotherapy on distant control and HR of distant failure by timing of chemotherapy. Center of each square is HR for individual trials; corresponding horizontal 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			
				Heterogeneity				Heterogeneity	
		Hazard ratio (95% CI)	*p*	I^2 (%)	*p*	Hazard ratio (95% CI)	*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.