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REVIEW ARTICLE

Chemotherapy in locoregionally advanced nasopharyngeal carcinoma-a review

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Summary

Locoregionally advanced nasopharyngeal carcinoma (NPC), when traditionally treated with radiotherapy (RT) alone, has been associated with low overall survival (OS). Efforts to improve the efficacy of treatment for locoregionally advanced NPC have led to the use of multimodality approach with combination of RT and chemotherapy (CT). Analyzing the historical progress of the incorporation of CT as an integral part of the management of advanced NPC, we reviewed 12 randomized controlled trials on induction, concurrent, and adjuvant therapy, or a combination of these approaches. Four meta-analyses on this subject have been also reviewed.

Evidence that concurrent chemoradiotherapy (CCRT) provides significant improvement in OS in patients with locoregionally advanced NPC is based on the results of 2 meta-analyses and several randomized studies on the administration of CT concomitantly with RT. The revealed survival benefits with CCRT compared with RT alone resulted in confirmation of CCRT as the currently recommended treatment for patients with advanced-stage NPC. The recognition of the development of distant metastatic disease as more frequent pattern of failure when concurrent CT is utilized has led to the assumption that the use of both induction chemotherapy (ICT) and CCRT in a sequential manner may provide improvement in overall treatment outcome in this patient category. The definition of the precise role of sequential CT in the management of patients with locally advanced NPC is to be revealed from the results of future phase III trials addressing this issue.

Key words: adjuvant chemotherapy, chemotherapy, concurrent chemoradiotherapy, induction chemotherapy, nasopharyngeal carcinoma

Introduction

NPC is uncommon in most countries, and the age-adjusted incidence is less than one per 100 000 population [1]. The endemic areas where the disease occurs with much greater frequency include Southern China, Southwest Asia, the Middle East, North Africa, Alaska and Greenland [1-3].

Because of the anatomic location, NPC has traditionally been treated with RT alone [4-6]. The results in patients with disease stages I and II are excellent, and RT has remained the initial treatment option for these patients [7]. However, despite the excellent initial tumor clearance with RT alone, high rates of both locoregional recurrence and distant metastases have been reported in patients with locally advanced NPC (stage III and IV) [7-9]. Isolated local and/or regional failures after definitive RT occur in 30-60% of these patients [8,10]. Local recurrences following RT and high propensity for distant metastasis represent two major causes of treatment failure resulting in 5-year OS rates from 32% to 52% [3,7,8].

NPC is both a radiosensitive and chemosensitive tumor [11,12]. To address the failure of primary RT to improve outcomes in patients with advanced NPC, CT has been incorporated into the standard treatment employing three different strategies: before (induction), during (concurrent), and after (adjuvant) RT. Each timing of CT has advantages and disadvantages and has been extensively investigated in the last 20 years. Although the results of the studies on the treatment of NPC by CCRT were not consistent, CCRT has

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proved its superiority to RT alone for the treatment of intermediate and advanced NPC [13]. A review of 12 randomized phase III trials and 4 meta-analyses has been made as an attempt to contribute to additional clarification of the investigations of CT as a treatment modality in advanced NPC.

Induction chemotherapy

The proposed advantages of ICT are the possibility of shrinkage of the macroscopic tumor, leading to reduction in irradiated volume, the possibility of assessment of clinical response to chemotherapy which predicts response to radiotherapy, as well as the possibility of delivering doses that are effective against occult systemic disease [14,15]. Regarding the possible disadvantages of ICT, there are theoretical concerns that this treatment option may be immunosuppressive reducing compliance to subsequent RT, which may induce accelerated repopulation, and also may allow for the emergence of radioresistant tumor cells clones [14,15].

There are 4 studies on ICT reported [16-19]. A multicenter, prospective, randomized phase III study comparing ICT with RT alone for patients with locoregionally advanced NPC was conducted by the Asian-Oceanian Clinical Oncology Association [16] (Table 1). No significant difference in relapse-free survival (RFS) and OS was observed between the two treatment arms (Table 2). There was also no significant difference in the distribution of failure sites between the two treatment arms.

In a phase III randomized VUMCA I trial [17] conducted by International Nasopharynx Cancer Study Group, 339 patients with locoregionally advanced undifferentiated NPC were randomized to receive either ICT plus RT or RT alone (Table 1). A comparable proportion of local and/or regional recurrences and distant metastases was seen in both arms. There was a significant difference in disease-free survival (DFS) favoring the CT arm ($p < 0.01$), but the OS was not statistically different between treatment modalities (Table 2).

In the single-center prospective randomized trial conducted by investigators in Guangzhou, China (the Guangzhou trial) [18], patients were randomized to either ICT consisting of cisplatin, bleomycin and 5-fluorouracil plus RT, or to RT alone (Table 1). The incidence of local failure was of borderline statistical significance in the investigational group. There was no difference in distant metastases between the two treatment groups. The difference in 5-year OS rate between the two groups was not statistically significant. The difference in 5-year RFS rates was of marginal statistical significance ($p=0.05$) (Table 2).

Japanese investigators designed and conducted a prospective, randomized phase III trial [19] to test the use of 2 cycles of CT consisting of cisplatin and 5-fluorouracil followed by RT compared with the use of RT alone (Table 1). A trend toward improved OS and DFS favoring the CT arm was observed although the difference was not significant (Table 2). There was no improvement in the locoregional RFS and distant metastasis free survival.

Concurrent chemoradiotherapy

The principle of improved efficacy by CCRT may be based on the up-regulated sensitivity to RT by che-

Table 1. Randomized studies comparing induction chemotherapy with radiotherapy alone in NPC

Study	*Patients n*	*Stage*	*RT*	*CT regimen*
Chua et al. [16], (AOCOA Trial), 1998	334	Ho's stage III/IV or any stage with node ≥ 3 cm	60-66 Gy + additional boost in case of residual neck nodes; the majority of patients treated with hypofractionated RT	2-3 cycles of cisplatin 60 mg/m^2 (day 1) + epirubicin 110 mg/m^2 (day 1)
VUMCA I Trial [17], 1996	339	1987 UICC any T, N ≥ 2	2.0 Gy/fx/d, 5 fx/wk, to 65-70 Gy	3 cycles of bleomycin 15 mg bolus + 12 mg/m^2/d (days 1-5 continuous infusion) + epirubicin 70 mg/m^2 (day 1) + cisplatin 100 mg/m^2 (day 1)
Ma et al. [18], (Guangzhou trial), 2001	456	1992 Chinese stage III-IV	2.0 Gy/fx/d, 5 fx /wk, to 68-72 Gy + additional boost to 80 Gy in case of residual disease	2-3 cycles of bleomycin 10 mg/m^2/d (days 1 and 5) + 5-fluorouracil 800 mg/m^2/d (days 1-5 continuous infusion) + cisplatin 100 mg/m^2 (day 1)
Hareyama et al. [19], 2002	80	1988 AJCC/ UICC all stages, M0	2.0-2.2 Gy/fx/d, 5 fx /wk, to 66-68 Gy	2 cycles of cisplatin 80 mg/m^2 (day 1) + 5-fluorouracil 800 mg/m^2/d (days 2-5 continuous infusion)

NPC: nasopharyngeal carcinoma, AOCOA: Asian-Oceanian Clinical Oncology Association, UICC: International Union Against Cancer, AJCC: American Joint Committee on Cancer, RT: radiotherapy, fx: fraction, d: day, wk: per week, CT: chemotherapy

Table 2. Summary of survival rates in randomized studies comparing combined chemoradiotherapy vs. radiotherapy alone in nasopharyngeal carcinoma

First author	*RFS*	*DFS*	*PFS*	*OS*
Chua [16]	48 vs. 42% (3-year), p=0.45	NR	NR	78 vs. 71% (3-year), p=0.57
VUMCA I Trial [17]	NR	52 vs. 32% (3-year), p <0.01	NR	60 vs. 54% (3-year), p=NS
Ma [18]	59 vs. 49% (5-year), p=0.05	NR	NR	63 vs. 56% (5-year), p=0.11
Hareyama [19]	NR	55 vs. 43% (5-year), p=NS		60 vs. 48% (5-year), p=NS
Al-Sarraf [22, 28]	NR	NR	58 vs. 29% (5-year), p<0.01	67 vs. 37% (5-year), p <0.01
Lin [23]	NR	NR	72 vs. 53% (5-year), p=0.0012	72 vs. 54% (5-year), p=0.002
Chan [24,32]	NR	NR	60 vs. 52% (5-year), p=0.16	70 vs. 59% (5-year), p=0.065
Kwong [25]	69 vs. 58% (3-year), p=0.14	NR	NR	87 vs. 77% (3-year), p=0.06
Lee [26]	72 vs. 62% (3-year), p=0.027	NR	NR	78 vs. 78% (3-year), p=0.97
Wee [27]	NR	72 vs. 53% (3-year), p=0.01	NR	80 vs. 65% (3-year), p=0.01
Rossi [33]	58 vs. 56% (4-year), p=0.45	NR	NR	67 vs. 59% (4-year), p=0.13
Chi [34]	54 vs. 50% (5-year), p=0.38	NR	NR	55 vs. 61% (5-year), p=0.5
Chan [35]	NR	72 vs. 68% (2-year), p=0.45	NR	81 vs. 80% (2-year), p=0.29

RFS: relapse-free survival, DFS: disease-free survival, PFS: progression-free survival, OS: overall survival, NR: not reported, NS: non significant

motherapy, the direct killing effect of CT to the tumor cells, and the reduction of the repair mechanisms of sublethally injured tumor cells [14,20]. CCRT has many potential advantages including no compromised blood supply, no time for development of cross-resistance or accelerated repopulation triggered by ICT, and no delay in primary treatment [14,21].

Six randomized controlled trials have reported on CCRT in the treatment of locoregionally advanced NPC [22-27]. In some of these trials adjuvant CT (AC) was added following RT [22,25-27].

The Intergroup Study 0099 (IGS 0099), coordinated by the Southwest Oncology Group (SWOG), was published by Al-Sarraf et al. in 1998 [22]. This randomized phase III trial evaluated CCRT with AC vs. RT alone in patients with NPC. Concurrent CT consisted of cisplatin 100 mg/m^2 on days 1, 22 and 43 during RT. AC consisted of cisplatin and 5-fluorouracil for 3 courses (Table 3). The 3-year progression-free survival (PFS) and 3-year OS were significantly better in the CCRT group (p <0.001 and p=0.005, respectively). An update of IGS 0099 in 2001 [28] reported the superiority of 5-year PFS and 5-year OS with CCRT vs. RT alone (Table 2).

The IGS 0099 [22] was the first randomized phase III trial demonstrating significant results with the use of CCRT in the management of advanced NPC. Hence, there were many criticisms concerning the extrapolation of the findings of this study to Asian countries, where NPC is endemic [29,30].

In a randomized phase III trial conducted in Taiwan [23], patients randomly assigned to CCRT received 2 cycles of CT during weeks 1 and 5 of RT (Table 3). There was significant improvement in the 5-year OS and PFS rates in the CCRT arm compared with the RT alone arm (Table 2). This was mainly attributable to the significant improvement of local control rates at 5 years in the CCRT arm.

In a phase III study by Chan et al. [24], patients were randomized to receive cisplatin 40 mg/m^2 weekly up to 8 weeks concurrently with RT or RT alone (Table 3). Although there was no statistically significant difference in PFS for the whole group, a highly significant improvement in PFS and time to first distant failure

Table 3. Randomized studies comparing concurrent chemoradiotherapy with radiotherapy alone in nasopharyngeal carcinoma

Study	*Patients n*	*Stage*	*RT*	*CT regimen*
Al-Sarraf et al. [22], IGS 0099, 1998	147	1988 AJCC/UICC stage III-IV	1.8-2.0 Gy/fx/d, 5 fx /wk, to 70 Gy	3 cycles of cisplatin 100 mg/m^2 on day 1, 22, and 43 of the RT course and 3 cycles of cisplatin 80 mg/m^2 (day 1) + 5-fluorouracil 1,000 mg/m^2/d (days 1-4 continuous infusion) after RT
Lin et al. [23], 2003	284	1992 AJCC stage III-IV	1.8-2.0 Gy/fx/d, 5 fx /wk, to 70-74 Gy	2 cycles of cisplatin 20 mg/m^2/d + 5-fluorouracil 400 mg/m^2/d (days 1-4 continuous infusion) during RT
Chan et al. [24], 2002	350	Ho's stage N2-3 or N1 with node ≥ 4 cm	2.0 Gy/fx/d, 5 fx /wk, to 66 Gy + additional boost in case of parapharyngeal extension, residual neck nodes, and/or residual nasopharyngeal disease (brachytherapy)	cisplatin 40 mg/m^2 weekly during RT
Kwong et al. [25], 2004	219	Ho's stage T3 or N2/N3 or N1 with node ≥ 4 cm	2.5 Gy/fx/d, 4-5 fx /wk, to 62.5-68 Gy + additional boost to 80 Gy in case of parapharyngeal extension or residual neck nodes	UFT 600 mg/d, 7 d/wk, p.o. during RT and cisplatin 100 mg/m^2 (day 1) + 5-fluorouracil 1,000 mg/m^2/d (days 1-3 continuous infusion) + vincristine 2 mg (day 1) + bleomycin 30 mg (day 1) + methotrexate 150 mg/m^2 (day 1) after RT every 3 weeks for 6 cycles
Lee et al. [26], 2005	348	1997 AJCC/UICC stage T1-4N2-3M0	2.0 Gy/fx/d, 5 fx /wk, to 66 Gy + additional boost up to 20 Gy to parapharyngeal space, the primary or nodal sites (when indicated)	3 cycles of cisplatin 100 mg/m^2 on days 1, 22, and 43 of the RT course and 3 cycles of cisplatin 80 mg/m^2 (day 1) + 5-fluorouracil 1,000 mg/m^2/d (days 1-4 continuous infusion) after RT
Wee et al. [27], 2005	221	1997 AJCC/UICC stage III-IVB	2.0 Gy/fx/d, 5 fx /wk, to 70 Gy	3 cycles of cisplatin 25 mg/m^2/d (days 1-4; 22-25, and 43-46) during RT and 3 cycles of cisplatin 20 mg/m^2/d for 4 days + 5-fluorouracil 1,000 mg/m^2/d for 4 days after RT

IGS: Intergroup Study, UFT: uracil and tegafur in 4:1 molar ratio. For other abbreviations see footnote of Table 1

was observed among patients with Ho's [31] T3 disease treated with CCRT. The results of the updated final report on OS [32] of the previously published progression-free analysis showed a borderline statistically significant difference in OS in favor of the concurrent arm (p=0.065) (Table 2). This analysis showed that there was no statistically significant difference between the two arms with respect to PFS (Table 2).

Kwong et al. [25] conducted a factorial study on the efficacy of CCRT and AC for advanced NPC. Patients were randomly assigned to have RT alone or CCRT with UFT (uracil and tegafur in 4:1 molar ratio) and to have AC or no AC after RT /CCRT (Table 3). An improvement in OS with CCRT was observed but without reaching statistical significance (Table 2). Distant metastases rate was significantly reduced with CCRT, whereas locoregional failure rates were similar for both treatment arms. The study reported no beneficial effect on OS with the use of AC.

Preliminary results of a randomized phase III trial conducted by the Hong Kong Nasopharyngeal Cancer Study Group [26] of concurrent CT with cisplatin followed by AC that incorporated cisplatin in addition to 5-fluorouracil (Table 3), showed an improvement in actuarial locoregional control at 3 years without any improvement in OS. The 3-year failure-free survival was significantly better in patients who received CCRT compared with patients who received RT alone (p=0.027) (Table 2).

Wee et al. [27] reported the results of a trial conducted by the National Cancer Center of Singapore, comparing the use of CCRT followed by AC vs. RT alone in 221 patients with locally advanced NPC of the endemic variety. Patients were randomized to receive RT alone or chemoradiotherapy consisting of concurrent cisplatin and adjuvant cisplatin and 5-fluorouracil for 3 cycles (Table 3). The 2-year cumulative incidence of distant relapse was 30% for the RT alone arm and 13% for the chemoradiotherapy arm, and this difference was statistically significant (p=0.029). The study reported a significant improvement in the 3-year DFS and 3-year OS in the chemoradiotherapy arm (Table 2), confirming the findings of the IGS 0099 [22] and demonstrating its applicability to endemic NPC.

Adjuvant chemotherapy with or without induction chemotherapy

AC is conducted after RT with the aim to eliminate the residual sub-clinical disease sites [20]. The major disadvantage is the reduced tolerance to CT due to the preceding RT [14].

In the past two decades 2 randomized studies have reported the results of the use of AC in the management of locoregionally advanced cases of NPC [33,34]. The first multicenter study performed by the Italian National Research Council was published by Rossi et al. in 1988 [33]. A total of 229 patients had been randomized either to no further therapy or to AC for 6 cycles (Table 4). The Milan study showed a similar pattern of failure in the two treatment arms. No significant effect on RFS or OS was demonstrated between the two treatment groups (Table 2).

In the trial conducted by the Taiwan Cooperative Oncology Group published by Chi et al. [34], patients were randomized either to a standard treatment protocol with RT alone, or to 9 weekly cycles of AC (Table 3). There was no significant statistical difference between the 5-year OS rate of 55% for the combined RT and AC group and the 5-year OS rate of 61% for the RT alone group (Table 2). Also no significant statistical difference was observed in RFS between the two treatment groups (Table 2).

In the randomized trial by Chan et al. [35], 2 courses of ICT and 4 courses of AC consisting of cisplatin and 5-fluorouracil were added to RT in the test group (Table 3). There was no statistically significant difference between the two arms in terms of DFS and OS (Table 2).

Meta-analyses

Considering the presence of controversy regarding the integration and the sequence of CT with RT in locoregionally advanced NPC, several meta-analyses have been conducted to provide a better understanding of the impact of combined treatment approach on the outcome of this patient category.

In an attempt to evaluate the long-term outcome in patients with NPC treated with ICT and RT vs. RT alone, the data from two phase III studies were updated and pooled together in the analysis by Chua et al. [36]. The authors merged and reanalyzed the data of AO-COA trial [16] and the Guangzhou trial [18] (Table 5). This pooled data analysis showed long-term benefits in terms of RFS and disease-specific survival. There was no statistically significant difference in the 5-year OS rates between the treatment groups.

The meta-analysis performed by the Marshfield Meta-Analysis Research Group [37] which evaluated

Table 4. Randomized studies comparing adjuvant chemotherapy with or without induction chemotherapy with radiotherapy alone in nasopharyngeal carcinoma

Study	*Patients n*	*Stage*	*RT*	*CT regimen*
Rossi et al. [33], 1988	229	1978 UICC stage II-IV, M0	1.8 Gy/fx/d, 5 fx /wk, to 60-70 Gy; a split-course adopted in most of the patients	6 cycles of vincristine 1.2 mg/m^2 (day 1) + cyclophosphamide 200 mg/m^2 (days 1-4) + doxorubicin 40 mg/m^2 (day 1)
Chi et al. [34], 2002	157	1992 AJCC/UICC stage IV	1.8-2.0 Gy/fx/d, 5 fx /wk, to 70-72 Gy	9 weekly cycles of 24-h infusion of cisplatin 20 mg/m^2 + 5-fluorouracil 2,200 mg/m^2 + leucovorin 120 mg/m^2
Chan et al. [35], 1995	82	Ho's stage N3 or any N ≥4 cm	66 Gy + additional boost in case of parapharyngeal extension, residual neck nodes, and/or residual nasopharyngeal disease	2 cycles of cisplatin 100 mg/m^2 (day 1) + 5-fluorouracil 1,000 mg/m^2 (days 2-4 continuous infusion) before RT and 4 cycles after RT (brachytherapy)

For abbreviations see footnote of Table 1

the data from 6 randomized trials [16,17,18,22,33,35], comparing CCRT with RT alone among patients with locoregionally advanced NPC, was published in 2002 (Table 5). Evaluating the data of more than 1500 patients, the authors reported an increase in 2-year DFS of 40% and increase in 4-year OS of 21% with the addition of CT to radical RT for locoregionally advanced NPC. Despite the revealed positive effect of the addition of CT to RT, the optimal strategy for integration of CT with RT and the most active CT regimen in this meta-analysis could not be determined.

However, the results of a subsequent meta-analysis performed by Langendijk et al. [38] and published in 2004 indicated that CCRT was probably the most effective sequence in the improvement of OS in patients with locally advanced NPC. In this meta-analysis based on the published literature, 10 randomized trials were included with a total of 2450 patients [16-19,22-24,33-35] (Table 5). The estimated increase in survival with CCRT in the subgroup analysis based only on the IGS 0099 [22] and the Taiwan trial [23] was 20% after 3 years. The meta-analysis failed to demonstrate any significant improvement in survival after ICT and/or AC. Regarding the impact of combined treatment approach on locoregional recurrence and distant metastases, a significant benefit in favor of the use of CCRT and ICT was found. The use of AC did not result in any significant positive effect on the incidence of locoregional recurrence or distant metastases.

The individual patient data meta-analysis of the Meta-Analysis of Chemotherapy in Nasopharyngeal carcinoma (MAC-NPC) Collaborative Group [39] included 8 trials with 1753 patients [16-19,22,24,25,34,35] (Table 5). Trials' grouping was done according to the sequence of CT and according to the type of CT. Trials combining CCRT and AC were included in the concurrent group. An absolute survival benefit of 4% at 2 years and 6% at 5 years was found with a significant interaction observed between the sequence of CT and OS (p=0.005), pointing out the highest beneficial effect from the use of concomitant CT. The analysis of the effect of CT on the event-free survival showed an absolute benefit of 9% at 2 years and 10% at 5 years. A significantly reduced risk of locoregional failure (p=0.003) and distant failure (p=0.001) was observed with the use of CT without significant interaction between the timing of CT and locoregional control, or between the timing of CT and distant control. Despite the confirmed significant beneficial effect on OS with CCRT, there was no substantial evidence indicating that the tumor effect of CCRT could be increased with the administration of particular chemotherapeutic agents, i.e. cisplatin and 5-fluorouracil.

Discussion and future directions

Randomized trials of ICT have not demonstrated any significant difference in OS, but these trials sug-

Table 5. Randomized studies included in meta-analyses

Meta-analysis	*Studies according to sequence of chemotherapy (CT) in the experimental arm*		
	Induction CT	*Concurrent CT*	*Adjuvant CT*
Chua et al. [36], 2005	Chua et al. [16] (AOCOA Trial), 1998. Ma et al. [18] (Guangzhou trial), 2001.		
Huncharek and Kupelnick [37], 2002	Chua et al. [16] (AOCOA Trial), 1998. VUMCA I Trial [17] 1996. Ma et al. [18] (Guangzhou trial), 2001.	Al-Sarraf et al. [22], 1998 IGS 0099.	Rossi et al. [33], 1988. Chan et al. [35], 1995.
Langendijk et al. [38], 2004	Chua et al. [16] (AOCOA Trial), 1998. VUMCA I Trial [17], 1996. Ma et al. [18] (Guangzhou trial), 2001. Hareyama et al. [19], 2002.	Al-Sarraf et al. [22], 1998 IGS 0099. Chan et al. [24], 2002. Lin et al. [23], 2003.	Rossi et al. [33], 1988. Chi et al. [34], 2002. Chan et al. [35], 1995.
Baujat et al. [39], 2006	Chua et al. [16] (AOCOA Trial), 1998. VUMCA I Trial [17], 1996. Hareyama et al. [19], 2002. Chan et al. [35], 1995.	Al-Sarraf et al. [22], 1998 IGS 0099. Chan et al. [24], 2002. Kwong et al. [25], 2004.	Chi et al. [34], 2002.

gested that ICT may improve locoregional control [16-18]. According to Rischin et al. [4], the subgroup analysis in patients with bulky neck lymph nodes in the AOCOA trial [16] showed a significant difference in RFS that was attributable to improved local control in the ICT arm, without any difference in the incidence of distant metastases. A demonstrated improvement of local control in patients with regionally advanced NPC who received ICT compared to those treated with RT alone has been also reported in the large retrospective series from Hong Kong [40]. The significant difference in RFS observed in the Guangzhou trial [18] in favor of the CT treatment group could be also attributable to improved local control [4]. According to Hareyama et al. [19], the lack of efficiency of ICT in reducing distant metastasis in their randomized study and the comparable proportion of distant metastases shown in both arms in other neoadjuvant studies [16-18] could be explained by the assumption that 2 or 3 cycles of ICT were not sufficient to eradicate all the distant micrometastases.

Improvement of OS was reported in 4 of the concurrent studies [22,23,27,32], but the IGS 0099 [22] and the study from Taiwan [23] were the only 2 randomized trials to show an improvement in both PFS and OS. The trial of the Taiwan group was the only phase III trial to demonstrate a positive effect of CCRT without any adjuvant or neoadjuvant CT [23]. The report from Taiwan [23] has also lent support to the benefit of CCRT for patients with advanced NPC in endemic areas. Two of the concurrent studies showed an improvement of locoregional control rate [23,26] and in other 2 studies an improvement of distant metastasis control rate was observed [25,27].

The results of AC studies showed that AC administered as part of combined treatment approach in locoregionally advanced NPC did not convey a significant survival advantage and did not succeed to improve locoregional control [33-35]. A considerable compliance to this sequence of CT was noted in studies using AC following RT alone, as well as in studies using AC following CCRT [22,25,27,34,35].

The results of the extensive exploration of the effect of the addition of CT to RT for patients with advanced NPC during the last two decades revealed survival benefits with CCRT compared with RT alone in several randomized trials and 2 meta-analyses. On the basis of these findings, CCRT is the currently recommended treatment for patients with advanced-stage NPC.

Given that the major cause of treatment failure in the CCRT was distant metastases [41], sequential therapy (adding ICT to CCRT) could be considered in the future as recommendable treatment option for patients with advanced NPC, leading to improvement of systemic control. Supportive evidence to this approach is given by the results of studies on ICT followed by CCRT showing encouraging toxicity profiles and disease control [42-44]. The improvement in locoregional relapse-free survival, DFS and OS achieved by ICT followed by concurrent administration of chemotherapy during radiotherapy in patients with locally advanced NPC has been also confirmed by Atasoy et al. [45]. Reporting the results of their study, these authors emphasized that the toxicity induced by this combined treatment modality should be carefully considered. According to Al-Sarraf and Reddy [46], reversing the sequence of treatment by giving CT followed by CCRT, the 5-year survival of patients with advanced NPC may be improved to up to 90%. The definition of the precise role of sequential CT in the management of patients with locally advanced NPC is to be revealed from the results of future phase III trials addressing this issue. However, more accurate prognostication to stratify patient population that is expected to benefit from the sequential use of ICT and CCRT is warranted. Finally, it should be noted that the advancement of accurate tumor imaging and the improved techniques (such as intensity-modulated RT) also contribute to the enhancement of locoregional control in patients with NPC. Additional improvement of the outcome in this patient category may also result by further improvement in systemic control using novel combined therapies with newer agents as adjunct to CCRT.

References

1. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J (Eds). Cancer Incidence in Five Continents, vol 7. IARC 1997; 143: 814-815.
2. Vokes EE, Liebowitz DN, Weichselbaum RR. Nasopharyngeal carcinoma. Lancet 1997; 350: 1087-1091.
3. Ali H, Al-Sarraf M. Chemotherapy in advanced nasopharyngeal cancer. Oncology (Huntingt) 2000; 14: 1223-1230.
4. Rischin D, Corry J, Smith J, Stewart J, Hughes P, Peters L. Excellent disease control and survival in patients with advanced nasopharyngeal cancer treated with chemoradiation. J Clin Oncol 2002; 20: 1845-1852.
5. Wolden SL, Zelefsky MJ, Hunt MA et al. Failure of a 3D conformal boost to improve radiotherapy for nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2001; 49: 1229-1234.
6. Chow E, Payne D, O'Sullivan B et al. Radiotherapy alone in patients with advanced nasopharyngeal cancer: comparison with an intergroup study. Is combined modality treatment really necessary? Radiother Oncol 2002; 63: 269-274.
7. Mould RE, Tai TH. Nasopharyngeal carcinoma: treatments and outcomes in the 20th century. Br J Radiol 2002; 75: 307-339.

8. Lee AWM, Poon YF, Foo W et al. Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976-1985: overall survival and patterns of failure. Int J Radiat Oncol Biol Phys 1992; 23: 261-270.
9. Fu KK. Combined radiotherapy and chemotherapy in nasopharyngeal carcinoma. Semin Radiat Oncol 1998; 8: 247-253.
10. Johansen LV, Mestre M, Overgaard J. Carcinoma of the nasopharynx: analysis of treatment results in 167 consecutively admitted patients. Head Neck 1992; 14: 200-207.
11. Al-Kouraniy K, Crissman J, Ensley J et al. Excellent response to cisplatinum-based chemotherapy in patients with recurrent or previously untreated advanced nasopharyngeal carcinoma. Am J Clin Oncol 1988; 11: 427-430.
12. Dimery I, Legha S, Peters L et al. Effectiveness of combined induction chemotherapy and radiotherapy in advanced nasopharyngeal carcinoma. J Clin Oncol 1993; 11: 1919-1928.
13. Forastiere A, Koch W, Trotti A, Sidransky D. Head and neck cancer. N Engl J Med 2001; 345: 1890-1900.
14. Bernier J, Bentzen SM. Altered fractionation and combined radio-chemotherapy approaches: pioneering new opportunities in head and neck oncology. Eur J Cancer 2003; 39: 560-571.
15. Rudat V. Role of multimodal treatment in oropharynx, larynx and hypopharynx cancer. Semin Surg Oncol 2001; 20: 66-74.
16. Chua DTT, Sham JST, Choy D et al. Preliminary report of the Asian-Oceanian Clinical Oncology Association randomized trial comparing cisplatin and epirubicin followed by radiotherapy versus radiotherapy alone in the treatment of patients with locoregionally advanced nasopharyngeal carcinoma. Cancer 1998; 83: 2270-2283.
17. International Nasopharynx Cancer Study Group VUMCA I trial. Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs. radiotherapy alone in stage IV (≥N2, M0) undifferentiated nasopharyngeal carcinoma: a positive effect on progression free survival. Int J Radiat Oncol Biol Phys 1996; 35: 463-469.
18. Ma J, Mai HQ, Hong MH et al. Results of a prospective randomized trial comparing neoadjuvant chemotherapy plus radiotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. J Clin Oncol 2001; 19: 1350-1357.
19. Hareyama M, Sakata K, Shirato H et al. A prospective, randomized trial comparing neoadjuvant chemotherapy with radiotherapy alone in patients with advanced nasopharyngeal carcinoma. Cancer 2002; 94: 2217-2223.
20. Hu Q, Liu P, Wang L, Fu Z. Concurrent chemoradiotherapy followed by adjuvant chemotherapy for stage III-IVa nasopharyngeal carcinoma. J Cancer 2007; 26: 337-341.
21. Lin J, Liang W, Jan J, Jiang R, Lin AC. Another way to estimate outcome of advanced nasopharyngeal carcinoma- is concurrent chemoradiotherapy adequate? Int J Radiat Oncol Biol Phys 2004; 60: 156-164.
22. Al-Sarraf M, LeBlanc M, Giri PGS et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup Study 0099. J Clin Oncol 1998; 16:1310-1317.
23. Lin J, Jan J, Hsu C, Liang W, Jiang R, Wang W. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. J Clin Oncol 2003; 21: 631-637.
24. Chan ATC, Teo PML, Ngan RK et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. J Clin Oncol 2002; 20: 2038-2044.
25. Kwong DLW, Sham JST, Au GKH et al. Concurrent and adjuvant chemotherapy for nasopharyngeal carcinoma: a factorial study. J Clin Oncol 2004; 22: 2643-2653.
26. Lee AWM, Lau WH, Tung SY et al. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 trial by the Hong Kong Nasopharyngeal Cancer Study Group. J Clin Oncol 2005; 23: 6966-6975.
27. Wee J, Tan EH, Tai BC et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/ International Union Against Cancer stage III and IV nasopharyngeal cancer of the endemic variety. J Clin Oncol 2005; 23: 6730-6738.
28. Al-Sarraf M, LeBlanc M, Giri PGS et al. Superiority of five year survival with chemo-radiotherapy (CT-RT) vs. RT alone in patients (Pts) with locally advanced nasopharyngeal cancer (NPC). Intergroup (0099) (SWOG 8892, RTOG 8817, ECOG 2388) phase III study: final report. Proc Am Soc Clin Oncol 2001; 20: 227a (abstr).
29. Isobe K, Kawakami H, Uno T et al. Concurrent chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma: is Intergroup Study 0099 feasible in Japanese patients? Jpn J Clin Oncol 2003; 33: 497-500.
30. Wei WI, Sham JS. Nasopharyngeal carcinoma. Lancet 2005; 365: 2041-2054.
31. Ho JHC. An epidemiologic and clinical study of nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 1978; 4: 183-198.
32. Chan ATC, Leung SF, Ngan RKC et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. J Natl Cancer Inst 2005; 97: 536-539.
33. Rossi A, Molinari M, Boracchi P et al. Adjuvant chemotherapy with vincristine, cyclophosphamide, and doxorubicin after radiotherapy in local-regional nasopharyngeal cancer: results of a 4-year multicenter randomized study. J Clin Oncol 1988; 6: 1401-1410.
34. Chi KH, Chang YC, Guo WY al. A phase III study of adjuvant chemotherapy in advanced nasopharyngeal carcinoma patients. Int J Radiat Oncol Biol Phys 2002; 52: 1238-1244.
35. Chan ATC, Teo PML, Leung TW et al. A prospective randomized study of chemotherapy adjunctive to definitive radiotherapy in advanced nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 1995; 33: 569-577.
36. Chua DTT, Ma J, Sham JST et al. Long-term survival after cisplatin-based induction chemotherapy and radiotherapy for nasopharyngeal carcinoma: a pooled data analysis of two phase III trials. J Clin Oncol 2005; 23: 1118-1124.
37. Huncharek M, Kupelnick B. Combined chemoradiation versus radiation therapy alone in locally advanced nasopharyngeal carcinoma: results of a meta-analysis of 1,528 patients from six randomized trials. Am J Clin Oncol 2002; 25: 219-223.
38. Langendijk JA, Leemans ChR, Buter J, Berkhof J, Slotman

BJ. The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: a meta-analysis of the published literature. J Clin Oncol 2004; 22: 4604-4612.
39. Baujat B, Audry H, Bourhis J et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. Int J Radiat Oncol Biol Phys 2006; 64: 47-56.
40. Teo PM, Chan AT, Lee WY, Leung TW, Johnson PJ. Enhancement of local control in locally advanced node-positive nasopharyngeal carcinoma by adjunctive chemotherapy. Int J Radiat Oncol Biol Phys 1999; 43: 261-271.
41. Cheng SH, Jian JJM, Tsai SYC et al. Prognostic features and treatment outcome in locoregionally advanced nasopharyngeal carcinoma following concurrent chemotherapy and radiotherapy. Int J Radiat Oncol Biol Phys 1998; 41: 755-762.
42. Oh JL, Vokes EE, Kies MS et al. Induction chemotherapy followed by concomitant chemoradiotherapy in the treatment of locoregionally advanced nasopharyngeal cancer. Ann Oncol 2003; 14: 564-569.
43. Chan AT, Ma BB, Lo YM et al. Phase II study of neoadjuvant carboplatin and paclitaxel followed by radiotherapy and concurrent cisplatin in patients with locoregionally advanced nasopharyngeal carcinoma: therapeutic monitoring with plasma Epstein-Barr virus DNA. J Clin Oncol 2004; 22: 3053-3060.
44. Akman F, Sen M, Erdag T, Cetinayak O, Eyiler F. Accelerated radiotherapy in locally advanced head-neck carcinomas: are concomitant boost and chemotherapy feasible in the routine outpatient-based radiotherapy clinic? J BUON 2002; 7: 221-228.
45. Atasoy BM, Dane F, Yumuk PF et al. Toxicity and feasibility analysis for cisplatin-based concomitant chemoradiotherapy in locally advanced nasopharyngeal carcinoma. J BUON 2008; 13: 43-50.
46. Al-Sarraf M, Reddy MS. Nasopharyngeal carcinoma. Curr Treat Options Oncol 2002; 3: 21-32.