Locally advanced nasopharyngeal carcinoma: Current and emerging treatment strategies

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Abstract
Although nasopharyngeal carcinoma (NPC) is a widespread malignant tumor, it is particularly frequent in Southeast Asia. Although T1 tumors can be effectively controlled with exclusive radiotherapy, this treatment modality is insufficient for most NPC patients, who present with locally advanced disease at diagnosis. In fact, for stages ranging from T2b N0 to T4 N3, definitive scientific evidence supports the use of concurrent platinum-based chemotherapy with standard external beam radiotherapy. This treatment approach has shown a statistically significant advantage in terms of overall survival, with respect to radiotherapy alone. Several trials have also investigated the use of neoadjuvant and adjuvant chemotherapy in combination with radiotherapy or chemo-radiotherapy. Platinum compounds, anthracyclines and taxanes are among the chemotherapy agents employed. This review focuses on the clinical results obtained in the field of adjuvant/concurrent/neoadjuvant chemotherapy for locally advanced NPC, for which exclusive concurrent chemo-radiotherapy currently represents the standard treatment approach.

INTRODUCTION
Nasopharyngeal carcinoma (NPC), a malignant tumor originating from the epithelium of the nasopharynx, is particularly frequent in Southeast Asia and can be divided into three different histological types, that is, non-keratinizing squamous cell carcinoma, keratinizing squamous cell carcinoma and undifferentiated carcinoma[1]. At diagnosis, most NPC patients have locally advanced disease, which includes stages ranging from T2b N0 to T4 N3 (Table 1).

Radiotherapy (RT) can control early stage NPC effectively, yielding an excellent 90%-95% 5-year local control rate in clinical trials. However, radiotherapy alone is not the optimal treatment for patients with locally advanced disease, which is the most frequent clinical presentation at diagnosis, since it yields an unsatisfactory 5-year survival rate of about 50%[2]. For this reason, concurrent platinum-based chemotherapy and radiotherapy has become the standard treatment for locally advanced NPC. While in early stage NPC (T1-2a N0), the addition of chemotherapy to standard radiotherapy has not provided
a survival advantage in clinical trials\(^3\), a clear superiority has emerged for concurrent chemoradiotherapy when compared to RT alone in patients with locally advanced disease\(^4,5\).

In locally advanced NPC patients, there are presently few data regarding the use of neoadjuvant/adjuvant chemotherapy, as an alternative to concurrent chemoradiotherapy. The role of neoadjuvant chemotherapy before RT or concurrent chemoradiotherapy is a matter of great interest. In fact, induction chemotherapy is an effective way to control subclinical metastatic foci, especially in patients with lymph node metastasis. Moreover, in some patients with large tumors infiltrating the brain stem, it is often difficult to deliver the total required dose to the clinical target volume (CTV) with preservation of critical tissues. Neoadjuvant chemotherapy is often able to provide objective responses in tumor lesions, which offers the possibility to shrink the CTV and reduce toxicity\(^6\).

Retrospective studies that used RT alone for NPC indicated that local control was closely linked to the radiation dose delivered to target tissues\(^7,8\). Intensity modulated RT (IMRT) is a special type of conformal RT that creates a high dose volume that is precisely shaped around the target volume in order to minimize the radiation dose delivered to surrounding healthy tissues. Investigators compared dosimetric plans of IMRT with conventional RT techniques and concluded that IMRT provided improved tumor coverage and preservation of normal tissues. The proximity of the nasopharynx to critical normal tissues, such as the brainstem and optic structures, makes it challenging for radiotherapists to deliver the optimal radiation dose to the tumor using conventional conformal RT, and underdosing of affected areas is often necessary to preserve healthy tissues. IMRT for locally advanced NPC spares critical portions of the brain stem and of the parotid glands, avoiding neurologic toxicity and permanent xerostomia, respectively. While IMRT has completely replaced conventional conformal RT and has become the standard practice for early stage NPC, its role in the locally advanced setting is not yet well defined\(^9\).

Intracavitary brachytherapy may be used in patients with residual mass after exclusive upfront radiotherapy, especially in the case of a T2b tumor (parapharyngeal infiltration) at initial diagnosis\(^10\). The combination of external beam RT followed by endocavitary brachytherapy may play an important role in patients with T2b disease. In this review, the treatment of patients with locally advanced NPC is reviewed and discussed, with a special focus on novel experimental therapeutic options.

### Table 1  Standard approach to nasopharyngeal carcinoma

| Stage | Denomination | Gold standard therapy |
|-------|--------------|-----------------------|
| T1-2a N0 M0 | Early stage | - IMRT alone |
| From T2b N0 M0 to T4b N3 M0 also every N2/3 M0 | Locally advanced | - Neoadjuvant platinum-based CT followed by IMRT or CCRT (platinum-based) |
| Every T every N MI | Metastatic | - Concurrent cDDP and RT |

RT: Radiotherapy; IMRT: Intensity modulated RT; CCRT: Concurrent chemoradiotherapy; CT: Computed tomography.

### ROLE OF EXCLUSIVE CONCURRENT CHEMORADIOThERAPY

In several phase III trials, radiotherapy with concurrent platinum-based chemotherapy has been compared to standard external beam radiotherapy alone in patients with locally advanced NPC. Concurrent chemo-radiotherapy has shown a statistically significant advantage in terms of survival and response rate when compared with radiotherapy alone, but at the expense of more severe toxicity, mainly mucositis and bone marrow suppression\(^4,5,11\). Results of a large meta-analysis carried out by Zhang et al\(^12\) which included 1608 patients enrolled in seven studies confirmed the superiority of concurrent chemo-radiotherapy with respect to RT alone. Of note, this meta-analysis was the first to include studies conducted in endemic areas only.

Another meta-analysis included 18 trials enrolling a total of 1993 patients from China. A comparison between concurrent chemo-radiotherapy and RT alone showed that concurrent chemo-radiotherapy was able to obtain a 3-year overall survival rate of 68.5%, compared with 56.4% in the RT alone arm\(^13\).

More recently, the association of cisplatin and paclitaxel given concurrently with standard radiotherapy was evaluated in a phase II trial. Thirty-one patients with locally advanced NPC received three-weekly 120 mg/m\(^2\) of paclitaxel and 75 mg/m\(^2\) of cisplatin concurrently with standard 70 Gy external beam radiotherapy. Three-year overall survival rate was 83.9% and the main grade 3/4 toxicity was neutropenia, reported in 12.9% of patients\(^14\). Another way of improving the effectiveness of standard concurrent chemo-radiotherapy may be to modify the radiotherapy scheme. In a phase II trial, Jian et al\(^15\) investigated the activity of hyperfractionated radiotherapy and concomitant platinum-based chemotherapy. As a result, three-year overall survival rate was 72%, with 73% of patients showing grade 3 mucositis, 31% of patients experiencing severe weight loss and 15% requiring a feeding tube. In view of such an unfavorable toxicity profile, further investigation in this direction does not seem justified.

IMRT is widely employed as an alternative to conventional RT in NPC patients with stage I-II disease, but its role in association with chemotherapy is still unknown. Lu et al\(^16\) evaluated the feasibility and efficacy of a weekly cisplatin (40 mg/m\(^2\)/wk) regimen given concurrently with definitive IMRT in twenty-one locally advanced NPC patients, obtaining a good safety profile and an excellent one-year overall survival of 95.5%\(^17\). In another similar trial, the association of three-weekly cisplatin and weekly cetuximab was employed together with standard IMRT.
therapy plus adjuvant chemotherapy yielded better results with respect to RT alone in terms of survival and activity, at the cost of higher toxicity. Similar results were seen in another phase III trial enrolling only non-keratinizing locally advanced NPC patients randomized to concurrent chemo-radiotherapy followed by adjuvant cisplatin and 5-fluorouracil or to RT alone. In this trial, concurrent chemo-radiotherapy was superior in terms of efficacy but also more toxic than RT alone.

PARK et al.21 carried out a retrospective analysis in forty-three locally advanced NPC patients treated with concurrent chemo-radiotherapy using cisplatin and 5-fluorouracil followed by adjuvant chemotherapy consisting of three cycles of cisplatin, epirubicin and bleomycin. The overall response rate (ORR) was 95% after concurrent chemo-radiotherapy and 100% after adjuvant therapy. The main toxicities observed were grade 3/4 neutropenia and mucositis occurring during concurrent chemo-radiotherapy.

In a prospective phase II trial conducted by Hu et al.25 fifty-four patients were treated with concomitant weekly paclitaxel and external beam radiation therapy (concurrent chemo-radiotherapy) followed by three cycles of cisplatin (30 mg/m² on days 1-3) and paclitaxel (135 mg/m² on day 1), both given every three weeks. An excellent 100% ORR was obtained after the entire treatment with a complete response (CR) rate of 85%. An acceptable toxicity profile was seen with no grade 3/4 side effects.

In view of the conflicting results reported on the role of adjuvant chemotherapy after concurrent chemo-radiotherapy, it is presently unclear whether the addition of adjuvant therapy may improve the efficacy of concurrent chemo-radiotherapy. Interestingly, a combined analysis of two large studies (NPC-9901 and the NPC-9902) revealed that the dose of cisplatin during the concurrent phase of concurrent chemo-radiotherapy had a significant impact on locoregional control, while additional adjuvant chemotherapy with a fluorouracil-containing combination contributed to improving distant control. Table 3 shows the results of clinical trials assessing the efficacy and/or activity of adjuvant chemotherapy followed concurrent chemo-radiotherapy.

ROLE OF NEOADJUVANT CHEMOTHERAPY FOLLOWED BY CONCURRENT CHEMO-RADIOThERAPY

The role of neoadjuvant chemotherapy followed by concurrent chemo-radiotherapy or RT is a matter of outstanding interest. Several clinical phase III trials from Western countries have proved that induction chemotherapy based on the administration of cisplatin, 5-fluorouracil and taxanes, may significantly improve treatment outcomes in patients with squamous cell carcinoma of the head and neck. An interesting approach may be to employ the same chemotherapy or a similar regimen in locally advanced NPC patients. AMMO et al.23 treated 110

Table 2  Chemo-radiation trials

| Trial | Phase | Ps | Study design | Main endpoint | Results |
|-------|-------|----|--------------|---------------|---------|
| Lin JC et al.24 | III | 284 | Exclusive RT alone vs CDDP, SFU + RT | 5-year DFS | Experimental arm better (P < 0.0012) |
| Chan AT et al.25 | III | 350 | Exclusive RT alone vs CDDP, SFU + RT | 2-year PFS | Experimental arm better (P < 0.016) |
| Zhang L et al.26 | III | 1608 | Exclusive RT alone vs CDDP based CT + RT | 5-year OS | Experimental arm better (P < 0.001) |
| Yang AK et al.27 | III | 1993 | Exclusive RT alone vs CDDP based CT + RT | 5-year OS | Experimental arm better (P < 0.05) |
| Lu H et al.27 | II | 22 | IMRT + CDDP | 1 year OS | 96% |
| Ekenel M et al.28 | II | 100 | IMRT + CDDP, Cet | ORR | 100% |

RT: Radiotherapy; IMRT: Intensity modulated RT; CT: Computed tomography; ORR: Overall response rate; DFS: Disease-free survival.

in 100 locally advanced NPC patients. The complete + partial response rate achieved was 100% and the toxicity profile was very low, except for a 64% rate of grade 2 acneiform rash. Clinical studies assessing the efficacy and activity of exclusive concurrent chemo-radiotherapy in locally advanced NPC patients are shown in Table 2.
patients with induction cisplatin and epirubicin followed by a radical course of radiotherapy with three cycles of concurrent cisplatin, and obtained encouraging results in terms of safety and effectiveness. Italian investigators used the same treatment schedule in 40 patients and obtained an overall response rate of 100% and a 5-year disease-free survival of 77%\textsuperscript{[24]}. In another Italian phase II study, Ferrari \textit{et al.}\textsuperscript{[25]} treated thirty-four patients with concurrently administered cisplatin and 5-fluorouracil, followed by concurrent cisplatin and RT. As a result, the overall response rate was a satisfactory 85.3% and the 3-year overall survival rate was 80%.

In the last five years, taxanes have been employed in several phase II and III clinical trials in patients with squamous cell carcinoma of the head and neck, showing a good activity and manageable toxicity profile. Lu \textit{et al.}\textsuperscript{[26]} carried out a trial to compare two different schedules of induction chemotherapy, namely carboplatin-5-fluorouracil (CF) \textit{vs} docetaxel-carboplatin (TC). Fifty-eight patients with locally advanced NPC were enrolled and randomized to receive CF or TC induction chemotherapy, both followed by concurrent carboplatin and RT. There was no significant difference in terms of response rate and 1-year survival rate. More grade 3/4 neutropenia events were reported in the TC group than in the CF group, whereas less grade 3/4 thrombocytopenia and emesis occurred with the TC regimen than with the CF regimen. An Egyptian study enrolled thirty-six patients who were treated with three cycles of induction paclitaxel (175 mg/m\textsuperscript{2}) and cisplatin (80 mg/m\textsuperscript{2}) given every three weeks, followed by concomitant cisplatin-radiotherapy. The overall response rate after the entire treatment schedule was 89% and the 3-year overall survival was 68%. The main toxicity encountered was grade 3/4 neutropenia which was observed in 25% of patients\textsuperscript{[27]}. Hui \textit{et al.}\textsuperscript{[28]} published the results of a randomized phase II trial in which stage III-IVb NPC patients, not previously treated, were randomly assigned to receive either neoadjuvant docetaxel and cisplatin for two cycles followed by concurrent chemoradiotherapy, or concurrent chemoradiotherapy alone. A positive impact on survival was observed, since the 3-year overall survival for the neoadjuvant versus the control arm was 94.1% \textit{vs} 67.7% (\textit{P} = 0.012). Bossi \textit{et al.}\textsuperscript{[29]} recently presented data of a study on docetaxel, cisplatin and 5-fluorouracil as induction chemotherapy followed by concomitant cisplatin/RT. After completion of treatment, the ORR was 98%, with a complete response rate of 70%. Other authors showed that the same combination had similar results with a 93% response rate and a median time to progression of 39 months\textsuperscript{[30]}. In a phase II study, induction docetaxel, cisplatin and capecitabine followed by chemo-radiation was tested in 40 patients, and resulted in an ORR of 98% and a complete response rate of 48%\textsuperscript{[31]}. In a phase II clinical study, Bae \textit{et al.}\textsuperscript{[32]} treated thirty-three patients with induction cisplatin (70 mg/m\textsuperscript{2}), 5-fluorouracil (1000 mg/m\textsuperscript{2} in i.c of 4 d) and docetaxel (75 mg/m\textsuperscript{2}) followed by cisplatin (100 mg/m\textsuperscript{2}) and RT. Twenty-seven patients achieved a partial response and five patients achieved a complete response. An excellent ORR of 98% was achieved and the three-year overall survival rate was 86.1%. Nonetheless, a 72.7% rate of grade 2/3 neutropenia and a 9.1% rate of febrile neutropenia were reported. Xie \textit{et al.}\textsuperscript{[33]} administered induction cisplatin (80 mg/m\textsuperscript{2}) and docetaxel (70 mg/m\textsuperscript{2}) to fifty-seven patients and randomized them to receive either concomitant RT and single agent cisplatin (80 mg/m\textsuperscript{2}) or concomitant cisplatin (80 mg/m\textsuperscript{2}) and docetaxel (60 mg/m\textsuperscript{2}) with RT. After completion of treatment, the complete response rates were very similar in both treatment arms (about 93%), but the occurrence of grade 3/4 neutropenia was significantly higher in the concomitant docetaxel, cisplatin and RT group (\textit{P} > 0.05). In a recent phase II clinical study, fifty-nine locally advanced NPC patients were treated with neoadjuvant cisplatin (75 mg/m\textsuperscript{2}), docetaxel (75 mg/m\textsuperscript{2}) and 5-fluorouracil (500 mg/m\textsuperscript{2} on days 1-5 in i.c) for three cycles, followed by concomitant weekly cisplatin (40 mg/m\textsuperscript{2}) and conventional RT or IMRT. The overall response rate three months after RT was 90.2% and the 1-year overall survival was 100%. The rate of grade 3/4 myelosuppression during induction CT was 55.9% and the corresponding rate during concomitant chemotherapy and RT was 11.9%\textsuperscript{[40]}. More recently, Ekelnel \textit{et al.}\textsuperscript{[41]} published the preliminary results of a phase II trial in which patients with locally advanced NPC received induction cisplatin (75 mg/m\textsuperscript{2}) and docetaxel (75 mg/m\textsuperscript{2}) for three cycles, followed by definitive RT and concomitant cisplatin (100 mg/m\textsuperscript{2}). Fifty-nine patients were evaluable and the ORR obtained after RT was 95%. Three-year overall survival was 93% and the treatment was generally well tolerated with a 10% rate of grade 3/4

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**Table 3 Adjuvant chemotherapy trials**

| Trial                  | Phase | Pts | Study design                  | Main end-point | Results |
|-----------------------|-------|-----|-------------------------------|----------------|---------|
| Al-Sarraf M et al\textsuperscript{[34]} | III   | 147 | Exclusive RT alone \textit{vs} CCRT followed by cDDP-SFU | 3-year PFS Experimental arm better \(P < 0.011\) |
| Chen Y et al\textsuperscript{[35]}         | III   | 316 | Exclusive RT alone \textit{vs} CCRT followed by cDDP-SFU | 2-year OS Experimental arm better \(P < 0.003\) |
| Lee AW et al\textsuperscript{[36]}         | III   | 348 | Exclusive RT alone \textit{vs} CCRT followed by cDDP-SFU | 5-year PFS Experimental arm better \(P < 0.035\) |
| Park KH et al\textsuperscript{[37]}        | II    | 43  | cDDP-5-FU + RT followed by cDDP-Epi-Ble CT | ORR | 100% |
| Hu W et al\textsuperscript{[38]}           | II    | 54  | w Pac + RT followed by cDDP-Pac CT | ORR | 100% |
| Leung TW et al\textsuperscript{[39]}       | II    | 48  | HFRT + cDDP based CT followed by cDDP-SFU CT | 3-year DFS 71% |
Table 4 Neoadjuvant chemotherapy trials

| Trial                          | Phase | Pts | Study design | Main end-point | Results |
|-------------------------------|-------|-----|--------------|----------------|---------|
| Al-Amro A et al[30]           | II    | 110 | Neo cDDP-Epi and followed by cDDP + RT | ORR | 100% |
| Airoldi M et al[30]           | II    | 30  | Neo cbcda-Pac followed by RT + cbcda-Pac | ORR | 87% |
| Ferrari D et al[30]           | II    | 34  | Neo cDDP-5FU followed by RT + cDDP | ORR | 85.3% |
| Lu X et al[30]                | II    | 58  | Neo cbcda-Tax followed by cbcda + RT (arm A) = neo cbcda-5FU followed by cbcda + RT (armB) | 1-year DFS | no difference between arm A and B |
| Mosatafa E et al[30]          | II    | 36  | Neo cDDP-Pac followed by cDDP-RT | ORR | 89% |
| Hui EP et al[30]              | II    | 65  | Neo cDDP-Tax followed by cDDP + RT (arm A) = neo cDDP + RT (arm B) | 3-year OS Arm A better than arm B (P < 0.012) |
| Bossi P et al[30]             | II    | 45  | Neo cDDP-Tax-5FU followed by cDDP + RT | ORR | 98% |
| Cho S et al[30]               | II    | 19  | Neo cDDP-Tax-5FU followed by cDDP + RT | ORR | 93% |
| Bae WK et al[30]              | II    | 33  | Neo cDDP-Tax-5FU followed by cDDP + RT | ORR | 99% |
| Kong L et al[30]              | II    | 52  | Neo cDDP-Tax-5FU followed by cDDP + RT | ORR | 90.2% |
| Ekenel M et al[30]            | II    | 59  | Neo cDDP-Tax followed by cDDP + RT | ORR | 95% |
| Lin S et al[30]               | II    | 370 | Neo cDDP-5FU followed by IMRT | DFS 3-year OS | 90% |

RT: Radiotherapy; IMRT: Intensity modulated RT; CT: Computed tomography; ORR: Overall response rate; DFS: Disease-free survival.

CONCLUSION

This review reported in detail the available clinical data regarding the use of chemotherapy in combination with radiotherapy for locally advanced NPC. Although several cytotoxic agents have been used both in the neoadjuvant and adjuvant setting with promising results, exclusive concurrent chemo-radiotherapy remains the recommended approach at the present time, as additional evidence is required to support the use of chemotherapy in the adjuvant/neoadjuvant setting.

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