Review

The Role of Neoadjuvant Chemotherapy in Nasopharyngeal Cancer

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Abstract: Nasopharyngeal cancer is a common cancer in Asia as well as in North Africa. Though concurrent chemoradiation therapy (CCRT) became standard treatment for advanced NPC patients, some high risk patients still have poor survival. Neoadjuvant chemotherapy has been an option in treatment of NPC. Up until now, there was no solid proof that NCT would positively impact the overall survival (OS) in advanced NPC. Different regimens were compared in the literatures, NCT plus radiation (RT) did not show improvement in OS as compared to RT alone, as well as NCT plus CCRT did not show benefit as compared to CCRT or CCRT plus adjuvant chemotherapy (ACT). Some trends of improving disease free survival (DFS) or distant recurrence free survival were observed, especially in certain group of patient with large local tumor or lymph nodes. More studies which focus on standard NCT regimen and narrowing down the target patients will be needed to further investigate the value of NCT in treatment of NPC.

Keywords: Nasopharyngeal cancer (NPC); Neoadjuvant chemotherapy (NCT); Overall survival (OS).

Introduction

Nasopharyngeal cancer (NPC) is a common cancer in southern China and southeast Asia as well as in north Africa1,2. NPC is strongly related to Epstein Barr virus (EBV) infection and highly sensitive to both chemotherapy and radiotherapy. Although early stage NPC has good prognosis, the advanced stage NPC still struggling with local recurrence and poor survival.

As a chemosensitive tumor, it was not a surprise that multiple clinical trials and systematic reviews have demonstrated concurrent chemoradiotherapy (CCRT) has improved the prognosis, while CCRT has become the standard care for advanced NPC patients3-11. However, for certain high risk patients such as patients with bulky locally advanced disease and/or extensive nodal disease, we are not sure if the treatment should be limited to CCRT.

Neoadjuvant chemotherapy (NCT) has been evaluated in many solid
cancers such as ovarian cancer and was an attractive option\(^{12}\), for it eliminates subclinical micrometastases before definitive local treatment and permits chemotherapeutic agents penetrate into tumor tissues without the disruption of native blood vessels after radiotherapy (RT) as well as better tolerance of chemotherapy prior to RT. Our experience with NCT in NPC began decades ago\(^{13}\). Despite the evidence of concurrent chemoradiotherapy in NPC, the role of NCT remains uncertain.

In the present study, we reviewed the literatures and investigated the role of neoadjuvant chemotherapy in treatment of NPC to bring better understanding of value of this method and provide information to future research.

### NCT+RT vs. RT alone

Advantage of NCT setting has not been established in combination with RT alone. Among the published four randomized clinical trials (RCT)\(^{14-17}\), different NCT regimens were implied to the trials and bleomycin and cisplatin were the most frequent drugs used. The drug choices ranged from platinum based regimen to gemcitabine based regimen. Most of the patients got 2 to 3 cycles of neoadjuvant chemotherapy before RT. However, the agents varied from study to study which made it more difficult to draw a clear conclusion on the effectiveness of NCT followed by RT (Table 1).

| Published year | Arms | N | OS | RFS | Local recurrence free survival | Distant metastasis free survival | Comments |
|----------------|------|---|----|-----|-------------------------------|---------------------------------|----------|
| **JCO 2001\(^{17}\)** | RT vs. NCT(cisplatin/bleomycin/5FU) + RT | 456 | 56% vs. 63% | 50 vs. 63% | 74% vs. 80% | 75% vs. 79% | |
| **P value** | | | | | 0.11 | 0.05 | 0.40 | |
| **IJROBP 1996\(^{15}\)** | RT vs. NCT(bleomycin/cisplatin/epirubicin) + RT | 339 | NA | NA | NA | Treatment related death 1% vs. 8% | |
| **Cancer 1998\(^{14}\)** | RT vs. NCT (cisplatin/epirubicin) + RT | 334 | 78% vs. 71% | 48% vs. 42% | NA | NA | In subgroup of 49 patients with bulky neck LN>6 cm, RFS 28% vs. 68%, \(P=0.02\); OS 37% vs. 73%, \(P=0.057\) |
| **Cancer 2002\(^{16}\)** | RT vs. NCT (cisplatin/5FU) + RT | 80 | 48% vs. 60% | 43% vs. 55% | 65% vs. 68% | 56% vs. 74% | But favor in NCT |

\(P>0.5\) \(P>0.5\) \(>0.05\) \(>0.05\)

OS: overall survival; RFS: recurrence free survival; RT: radiotherapy; NCT: neoadjuvant chemotherapy; NA: not available; LN: lymph node.

Up to date there are four RCT compared NCT followed by RT and RT alone. None of these studies found benefit of NCT on overall survival, except one study in 2002 that found two cycles of 5FU and cisplatin showed favorable overall survival in NCT arm as compared to RT alone\(^{16}\). Unfortunately, this study had only 80 patients in total, which might compromise the statistical power on the trend the authors found. In the other three trials, the sample numbers are as large as 300 to 400, yet overall survival improvement has not been
shown in any of these trials. The overall survival varied from 48% to 78%. The raw figure did favor in NCT group, but it did not reach statistical significance.

More recently, a network meta-analysis in 2015 also looked into this topic and found that including the four clinical trials listed above along with another Chinese study which published in 1996, the hazard ratio (HR) for NCT+RT versus RT alone was 0.84 (95% CI, 0.66–1.08) with 3-year OS rate of 53%, which again failed to show improvement of overall survival[18].

Despite the failure of improving overall survival, in those RCTs, there was a clear favorable recurrence free survival (RFS) in NCT group in 2 trials with one trial showing marginal disease free survival (DFS) benefit. Increase in RFS could be a result from the local control as well as from a decreased distance recurrence in these local advanced cancers. In the largest trial, the local recurrence (74% vs. 80%) and distant metastases (75% vs. 79%) were significantly less in the NCT arm as compared to RT alone arm[17]. Interestingly, in the trial which found NCT+RT arm had better RFS, the local and distant recurrence rates had no difference between two arms[15]. One of the possible explanations of the discrepancy of the findings would be that when local advanced patient developed distant recurrence many of them had have local recurrence or progression in the same time. When selectively comparing the local recurrence and distant recurrence only, the difference would possibly be diluted. In a meta-analysis published in 2004, NCT did reduce distant metastasis when added to RT[10].

Notably, when stratifying down to subgroup of 49 patients with bulky neck lymph nodes larger than 6 cm, RFS was 68% in NCT arm as compared to 28% in RT alone arm, (P = 0.02) while OS was 73% compared to 37% in RT arm (P = 0.057)[14]. It indicated that within local advanced diseases, patients with large lymph nodes may benefit most from NCT. The underlying reasons and selection criteria needed to be further investigated.

Also, there was one trial pointed out that treatment related death increased 7% in the NCT+RT group[15]. The extra toxicity certainly is one of the concerns of adding NCT to RT.

**NCT+CCRT vs. CCRT alone**

CCRT has been shown to significantly improve survival in advanced NPC patients, and now it has become the standard care for NPC[10,11,19]. However, in certain patients, multiple interventions seem to be needed, especially in those with large local tumor or multiple lymph nodes involved patients. When CCRT was established for NPC patients, researchers have started to investigate if NCT would add further benefit to these aggressive diseases.

As shown in a network meta-analysis which compared NCT+CCRT with RT alone, NCT plus CCRT had more favorable survival[20]. As we have discussed previously, NCT did not show OS improvement as compared to RT alone, this survival gain seen in NAT+CCRT regimen might result from concurrent chemotherapy rather than NCT. In 2015, a phase III randomized study compared NCT+RT+ACT with CCRT+ACT and the authors found no overall survival differences between these two arms while metastasis free survival rate was significantly improved in the CCRT group[21].

These results reinforced the role of concurrent chemotherapy. However, there wasn’t a definite answer to the question that whether NCT is meaningful when CCRT is applied to the patient. Fountzilas and Hui firstly put insight on this question with their randomized clinical trials, then Tan and colleagues updated their work on this topic (Table 2).

In these RCTs, progress free survival and overall survival were the two main endpoints. The OS varied from 63% to 94.3%, which might be the results of heterogeneity in patient selection. All three RCTs reported 3 years overall survival instead of 5 years due to the limited follow up time (3.2 to 4.6 years). One study found improvement of survival in NCT arm as compared to CCRT alone arm in the 3 years OS (94.1% vs. 67.7%, P = 0.012), though only 65 patients enrolled the study, which had impact on its statistical power[22]. Other two studies did not find NCT added to CCRT would bring patients benefit in overall survival. The network meta-analysis also concluded that the NCT-CCRT had no survival benefit with HR of 0.92 (95% CI, 0.29–2.97)[18].

When looking into other endpoints such as PFS or DFS, all of these studies failed to show advantages in NCT plus CCRT regimen. In Fountzilas’ study in 2012, the local recurrence and distant recurrence were studied in details. Neither local recurrence rate nor
distance recurrence rate were different in two arms. In the meanwhile, the side effect did not increased in combination of NCT and CCRT with merely slightly increased tolerable events during treatment\textsuperscript{[23]}. As mentioned above, the drugs used for NCT were not consistent among studies while some imply cisplatin, and other studies used docetaxel, whereas, some studies applied 3 drugs and other study used 2 drugs. Cisplatin was the most common choice due to its effect shown in CCRT, whereas, gemcitabine and newer platinum drugs such as carboplatin and nedaplatin became more popular in solid tumors. These factors certainly cloud the conclusion on the effect of NCT in NPC patients.

| Author          | Arms                | N   | NCT                      | CCRT                     | PFS          | OS          | Side Effect Local recurrence | Distance recurrence |
|-----------------|---------------------|-----|--------------------------|--------------------------|--------------|-------------|-----------------------------|---------------------|
| Fountzil et al. | NCT+CCRT vs. CCRT   | 141 | cisplatin+epirubicin+ paclitaxel | cisplatin weekly          | 3 yr 64.5%   vs. 3 yr 63% | 71.8%  P=0.652 | Similar, but more pt get EPO treatment, P=0.002 | 13 vs. 8, 7 vs. 13, P=0.15 |
| Hui et al.      | NCT+CCRT vs. CCRT   | 65  | docetaxel+cisplatin weekly | cisplatin weekly          | 3 yr 88.2%   vs. 3 yr 94.1% | 67.7%  P=0.012 | No difference for acute toxicities | NA                   |
| Tan et al.      | NCT+CCRT vs. CCRT   | 172 | gemcitabine, carbo, cisplatin paclitaxel weekly | cisplatin weekly          | DFS 94.3%   vs. 92.3% | 52%  vs. 37% | NCT arm has more G3 and 4 leukopenia, Distance metastases-free survival | NA | P= 0.547 |

NCT: neoadjuvant chemotherapy; CCRT: concurrent chemoradiotherapy; DFS: disease free survival; PFS: progression free survival; OS: overall survival; EPO: erythropoietin

Meanwhile, two phase III randomized studies published as abstract had promising results that favorable PFS and OS had been seen in NCT plus CCRT as compared CCRT alone. Doaud et al., selected taxotere and 5FU as NCT for 3 cycles in locally advanced NPC patients, whereas Ma et al used a three-drug regimen (docetaxel, cisplatin and fluorouracil). Doaud’s study was stopped early due to poor accrual with a total inclusion of 83 patients. Ma’s study included 241 patients from China, and showed significant improvement in PFS and distant failure free survival in NCT plus CCRT arm as compared to CCRT alone arm. We are looking forward to the final results being updated\textsuperscript{[25,26]}. It’s worth to mention that The PARADIGM study included broader selection of patients as an open-label phase III study comparing the use of docetaxel, cisplatin, and fluorouracil (TPF) induction chemotherapy followed by concurrent chemoradiotherapy with cisplatin-based concurrent chemoradiotherapy alone in patients with locally advanced head and neck cancer. In this study, 145 patients were randomized into two arms. After a median follow-up of 49 months, 3-year overall survival was 73% in the NCT plus CCRT arm and 78% in the CCRT alone arm (hazard ratio 1.09, 95% CI 0.59–2.03; \(P=0.77\)).Though this study did not include nasopharyngeal cancer, the survival results were good in both arms, however, again, NCT did not additional benefit\textsuperscript{[27]}.

**NCT+CCRT vs. CCRT+ACT**

Knowing NPC is a tumor sensitive to chemotherapy, it still remains unknown if further chemotherapy would help giving after CCRT, such as addition chemotherapy as ACT or introduction chemotherapy as NCT. A RCT in 2012 involving CCRT-ACT...
comparing CCRT alone, showed no survival difference between the two groups after a 2 years follow up[28]. If adding chemotherapy after CCRT did not show improvement of survival, would NCT that given before CCRT help?

Ruste and colleagues randomized 30 patients into two groups to compare NCT+CCRT and CCRT+ACT[21]. Cisplatin plus fluorouracil were used both as NCT regimen and ACT regimen. Median PFS was 19.6 months (CCRT+ACT) versus 25.7 months (NCT+CCRT). Neither PFS nor OS showed differences as 3-year PFS rates were 25% and 63%, respectively, with hazard ratio 2.64 (P=0.176) whereas 3-year survival rates were 36% and 25.4%, respectively, with hazard ratio 0.92 (P=0.889). This was a relatively small RCT, and its result did not favor in additional chemotherapy. A much larger phase III trial had multiple arms to compare different NCT regimen and NCT+CCRT with CCRT+ACT. In NCT, one arm used cisplatin plus fluorouracil and the other arm used cisplatin and capecitabine. This trial enrolled 706 patients and became the largest randomized trial to evaluate NCT. Unfortunately, both regimens of NCT did not show better 3 years PFS or 3 years OS[21]. More RCTs with larger sample size are need to address this question in the future.

Conclusion

Theoretically, NCT would be a good choice for advanced NPC patients, yet no solid evidence supports it effectiveness on OS or PFS, though some studies showed trend of better PFS or local/distant recurrence free survival. On the other hand, none of other treatment choices such as CCRT plus ACT overweight NCT plus CCRT. It will be a continuous discussion on what is the best treatment for advanced NPC, especially when it seems adding ACT to CCRT won’t improve survival. Those findings discussed above made the interpretation more complex and we eagerly await the unpublished data from four phase III randomized trials (Taiwan, NCT00201396; Singapore, NCT00997906; China, NCT01245959 and France, NCT00828386). Moreover, consistence in drug selection, newer regimens, and targeting more on those patients who most likely benefit from adding extra chemotherapy to CCRT should be further studied.

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