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Review Article

Role of neo-adjuvant chemotherapy in locally advanced nasopharyngeal carcinoma

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ABSTRACT

Nasopharyngeal carcinoma (NPC) is a rare type of tumor which arises from the surface and lining epithelium of nasopharynx. Management of nasopharyngeal carcinoma is one of the greatest clinical challenges but it is radiosensitive and chemosensitive; excellent tumor control can be attained with radiotherapy with or without adjuvant therapies concurrent chemoradiation therapy. This review will focus on role of neoadjuvant chemotherapy in nasopharyngeal carcinoma on disease free survival (DFS), distant metastases free survival and overall survival (OS) and systemic toxicities, indications and choice and number of cycles of regimen for neoadjuvant chemotherapy.

1. Introduction

Nasopharyngeal carcinoma (NPC) is a rare type of tumor which arises from the surface and lining epithelium of nasopharynx. It was first illustrated in 1921 by Regaud and Schmincke.[1,2] Epidemiologically NPC is found as an age-standardized ratio being 0.6–2.0/100,000 in males and 0.2–0.8/100,000 females worldwide. It has distinct geographical distribution with the greatest occurrence in Southeast Asia up to 2.4/100,000 females and 6.4/100,000 males.[3] The etiopathogenesis of NPC appears to trail a multi-step process in which an important role is played by Epstein Bar Virus (EBV), cultural background, and environmental carcinogens.[4] In adults, the other causative factors comprises of genetic predisposition, consumption of food (in particular salted fish) containing carcinogenic volatile nitrosamines, and as in children, EBV.[5–10]

Clinically patients may present with trotters triad (unilateral deafness, neuralgia affecting branches of trigeminal nerve and defective mobility of soft palate), pain, trismus, nasal regurgitation, hearing loss, otitis media or cranial nerve palsies due to tumor growth. Larger growth may produce nasal bleeding or obstruction or 'nasal twang'. Initial presentation in many patients is cervical lymphadenopathy.[4] Histologically,[11] there are 3 subtypes (WHO classification) of NPC -

- Type 1 – Squamous cell carcinoma.
- Type 2 – non-keratinizing carcinoma.
- Type 3 – undifferentiated carcinoma.

Epstein-Barr virus titers are associated with type 2 and type 3, but not with type 1.[12] In particular, plasma Epstein-Barr virus (EBV) DNA has been used for population screening, prognostication, predicting treatment response for therapeutic adaptation, and disease surveillance.[13] Diagnostic criteria includes clinical evaluation of cervical

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lymph nodes, direct nasopharyngoscopy to evaluate primary tumor, biopsy of either cervical lymph nodes or primary tumor to assess histology of the tumor, EBV DNA and viral capsid antigen, radiographic assessment (PET/CT/ MRI/ Bone scintigraphy) for tumor size, extent, structures involved, to assess base of skull erosion and to rule out distant metastasis (bones, lung and liver) for staging and treatment planning.[4]

Management of nasopharyngeal carcinoma is one of the greatest clinical challenges but it is radiosensitive and chemosensitive; excellent tumor control can be attained with radiotherapy with or without adjuvant therapies concurrent chemoradiation therapy. Primary treatment modality is radiotherapy, and using radiation therapy in combination with chemotherapy is recommended for the treatment of locoregionally advanced tumors.[14] This review will focus on role of neoadjuvant chemotherapy in nasopharyngeal carcinoma on disease free survival (DFS), distant metastases free survival and overall survival (OS) and systemic toxicities, indications and choice and number of cycles of regimen for neoadjuvant chemotherapy.

2. Materials and Methods

A systemic review was conducted and the protocols of this review was established before beginning of the documentation and review process. Criteria for eligibility. All the case reports, systemic reviews and meta-analyses published from Jan 2010 to Feb 2021 that described the role of neoadjuvant chemotherapy in nasopharyngeal carcinoma. Only review of human studies and that were published in English were considered. (Table 1)

2.1. Inclusion criteria

1. Meta- analysis of randomized or non- randomized controlled trials.
2. PubMed indexed studies only.

2.2. Exclusion criteria

Data published before 2010 on neoadjuvant chemotherapy for nasopharyngeal carcinoma.

2.3. Search strategy

A pilot search was made on PubMed (National Library of Medicine, NCBI) about neo-adjuvant chemotherapy for nasopharyngeal carcinoma. In March 2020, a widespread search was made on PubMed and result was screened by title and abstract and duplicate and irrelevant reports were excluded. Full text of the remaining articles was read and was assessed to include or exclude according to the criteria discussed.

2.4. Data Collection

Only Pubmed indexed studies on the neoadjuvant chemotherapy for nasopharyngeal carcinoma were collected and studied to evaluate the risk factors, presentation, treatment options and complications.

3. Results

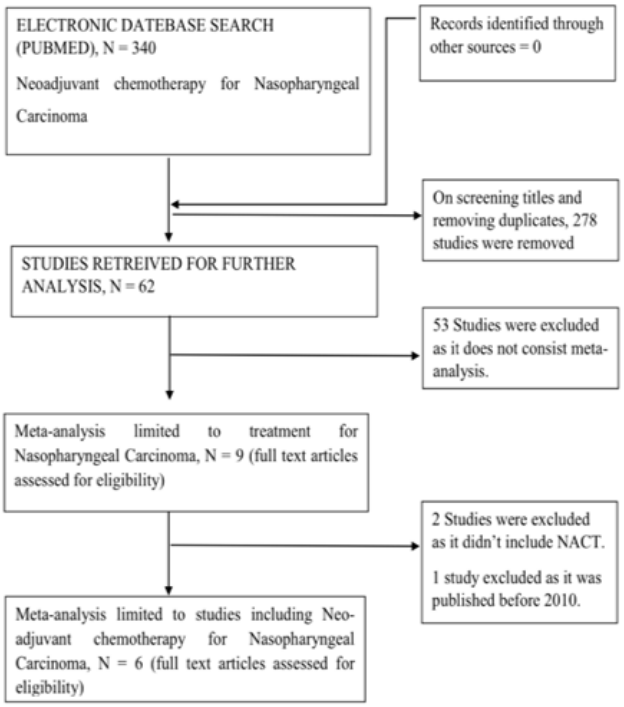

Chart 1: Prisma Guideline

4. Discussion

Nasopharyngeal carcinoma (NPC) is a squamous-cell carcinoma especially prevailing in Southern China. Radiotherapy (RT) is the mainly standard treatment,[15] but it just successfully controls 50%– 70% locoregional advanced tumors.[16] Despite that intensity-modulated radiotherapy (IMRT), a revolutionary technique of RT, has achieved an excellent locoregional control,[17–19] overall survival (OS) and especially distant metastasis-free survival are still limited by RT alone. Then ample studies were carried out to test the use of chemotherapy [neoadjuvant (NACT), concurrent and adjuvant chemotherapy (AC)] in combination with RT for the management of locoregional advanced NPC. Clinical trials,[20,21] meta-analyses[22,23] and systematic review 21 have thoroughly demonstrated concurrent chemoradiotherapy (CCRT) to be most efficacious. However, the significant roles of NACT and AC in OS, locoregional control and distant metastasis control still remain controversial, here are the few recent studies

with their conclusion on role of NACT in locally advanced NPC.

4.1. Role of NACT on PFS, OS, DC, LRC

NCCN guidelines promoted the level of evidence of neoadjuvant chemotherapy stage II-IVa to 2A as a result of the findings in four studies from Hong Kong, Singapore, and Guangzhou. This four randomized control trials for locoregionally advanced NPC evaluated role of induction chemotherapy with concurrent chemotherapy v/s concurrent chemotherapy alone, this pooled analysis of the studies included 1,193 patients of which primary end point was progression free survival (PFS) and secondary end points included overall survival (OS), distant control (DC) and locoregional control (LRC). This study concluded significant improvement in progression free survival, distant control and overall survival in induction chemotherapy arm but no significant difference in LRC (Chart 2).[24]

Liu LT et al in 2019 conducted a retrospective study on 2263 patients with stage III-IVB NPC treated with CCRT, NACT or ACT and evaluated distant metastasis–free survival (DMFS), overall survival, and progression-free survival. They divided patients into three groups – low risk group (N0–1, and EBV DNA <4,000 copies/mL), Intemediate risk group (N0–1, and EBV DNA ≥4,000 copies/mL; N2–3, and EBV DNA <4,000 copies/mL) and high risk group (N2–3, and EBV DNA ≥4,000 copies/mL). Out of 2263, 970 patients were treated with CCRT alone, 1,073 patients were treated with 2 or 3 cycles of NACT followed by CCRT, and 220 received CCRT followed by 1 to 4 cycles of adjuvant PF (cisplatin, 80 mg/m2 on day 1 with 5-fluorouracil, 800–1,000 mg/m2 for 96 hours of continuous intravenous infusion). This study established that in low-risk group who received NACT + CCRT had significantly lower risk of distant metastasis when compared with the paients who received CCRT alone. Patients in the low-risk group who received NACT followed by CCRT attained significantly better 5-year DMFS than those who received CCRT alone (96.2% vs 91.3%; P5.008). Multivariate analyses also confirmed that NACT as an addition was the only independent prognostic factor for DMFS (hazard ratio, 0.42; 95% CI, 0.22–0.80; P5.009). In both the intermediate-risk group and the high-risk group assessment of NACT or ACT + CCRT versus CCRT alone indicated no significantly better survival for all end points. The short comings of this study were relatively smaller sample size in each group and lack of integrated toxicity data.[25] Role of Chemotherapy in neck node negative and neck node positive locally advanced NPC.

Xiang ZF et al in 2021 conducted a study to show factors associated with chemotherapy usage and assess chemotherapy's advantages in patients with stage III NPC stratified by lymph node status. This study included 1,452 patients with stage III NPC who began radiotherapy with (n=1361) or without (n=91) chemotherapy and were identified in the SEER database. This study performed a comparision of all-cause mortality (ACM) and cancer-specific mortality (CSM) using Kaplan-Meier method and concluded that chemotherapy in patients at stage III NPC with node- positive disease increases survival benefits (Chart 3). The extent of chemotherapy advantage in node-negative stage III NPC requires more research (Chart 4).[26]

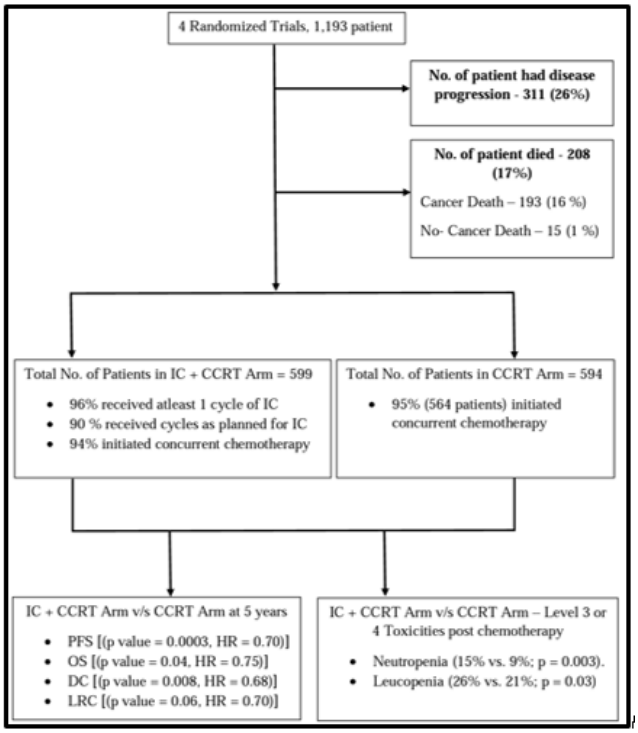

Chart 2: Role of NACT on PFS, OS, DC, LRC. [Abbreviations – IC = Induction chemotherapy, CCRT = concurrent chemo-radiation therapy, PFS = Progression free survival, OS = Overall Survival, DC = Distant Control, LRC = Loco-regional control, HR = Hazard's Ratio]

5. Conclusion

This review paper revealed that chemotherapy meaningfully increases overall survival and decreases NPC-related deaths in stage III NPC. Nevertheless, this findings should be viewed as theory-creating ones. To validate this findings, more prospective clinical trials are in imperative need. With all of these exhilarating recent advances, we are eyeing more advancement and clear picture in future studies which further progress our understanding of NPC and further treatment guidelines should be improved for these patients.

6. Conflict of Interest

The authors declare no relevant conflicts of interest.

Table 1: NACT – neoadjuvant chemotherapy, AC – adjuvant chemotherapy, DMR – distantmetastasis rate, LRR - locoregional recurrance rate, HR – hazard ratios, RCTs – Randomised control trials, CCRT - concurrent chemo-radiation therapy, OR - odds ratio, N-CRT – neoadjuvant + concurrent chemoradiotherapy, CRT - concurrent chemoradiotherapy, CRT-A - concurrent chemoradiotherapy + adjuvant chemotherapy, (A - Adjuvant chemotherapy, C - Concurrent chemotherapy, N - Neo-adjuvant chemotherapy, NCT - neoadjuvant chemotherapy, OS – overall survival.

Authors and Year	Type of Study	Methodology	Results	Conclusion
Ou Yang PY et al[27], 2013	Meta-analysis	(n = 1418) in NACT group. (n = 1187) in AC group.	DMR in NACT group (P = 0.0002; RR 0.69, 95% CI 0.56–0.84). LRR in AC group (P = 0.03; RR 0.71, 95% CI 0.53–0.96)	There was significant decrease in DMR in NACT group when compared to AC. There is no benefit on LRR in NACT group. AC group had significant decrease in LRR, but no benefits on OS and DMR.
Chen YP et al[28], 2015	Meta-analysis	Total patients included from different studies (n = 1988)	DMR (RR=0.54, 95% credible interval [CrI] = 0.27–0.94).	NACT+CCRT was associated with favorable distant failure control when compared with CCRT alone.
Yan M et al[29], 2015	Meta-analysis	25 RCTs (n = 5576 patients)	N-CRT versus CRT, the HR was 1.03 (0.69–1.47). CRT-A versus CRT (0.98; 95% credible regions: 0.71–1.34).	Efficacies of CRT, CRT-A and N-CRT all appeared to be parallel.
He X et al[30], 2015	Meta-analysis	(n = 1277 patients)	Recurrence rate (OR) = 0.65, P < 0.05) Metastasis rate (OR = 0.61, P < 0.05) 5 years overall survival and 5 years disease free – P value > 0.05)	Significantly lower in the neo-adjuvant chemotherapy plus radiation group compared to radiotherapy group
He J et al[31], 2017	Meta-analysis	52 studies (n = 10,081 patients)	**Control Group** 5 year survival = 0.131 3 year survival = 0.181 1 year survival = 0.191 CR = 0.018 **A** 5 year survival = 0.058 3 year survival = 0.092 1 year survival = 0.144 CR = 0.298 **C** 5 year survival = 0.647 3 year survival = 0.680 1 year survival = 0.832 CR = 0.670 **A+ C** 5 year survival = 0.792 3 year survival = 0.851 1 year survival = 0.723 CR = 0.512 **N** 5 year survival = 0.423 3 year survival = 0.469 1 year survival = 0.285 CR = 0.622 **N+A** 5 year survival = 0.883 3 year survival = 0.597 **N+C** 5 year survival = 0.566 3 year survival = 0.631 1 year survival = 0.824 CR =0.864	Reduced HR when compared with the control group. C, C+A and N+C should be considered as the first-line treatment.
Yuan C et al[32], 2018	Meta-analysis	31 RCTs (n=4062) Neo-Adjuvant chemotherapy in locally advanced NPC.	1 year OS for Paclitaxel, carboplatin, and gemcitabine 2 year OS for cisplatin, calcium folinate, and 5-fluorouracil. 3 year OS for for vinorelbine and cisplatin (NP) 5 year OS for cyclophosphamide, cisplatin, and 5-fluorouracil. Complete remission rate for primary tumor by Gemcitabine and cisplatin.	NCT regimens can decrease toxicity of CRT to lowest, such as NP for anemia, mucositis, and thrombocytopenia, paclitaxel, epirubicin, and cisplatin for neutropenia and skin toxicity.

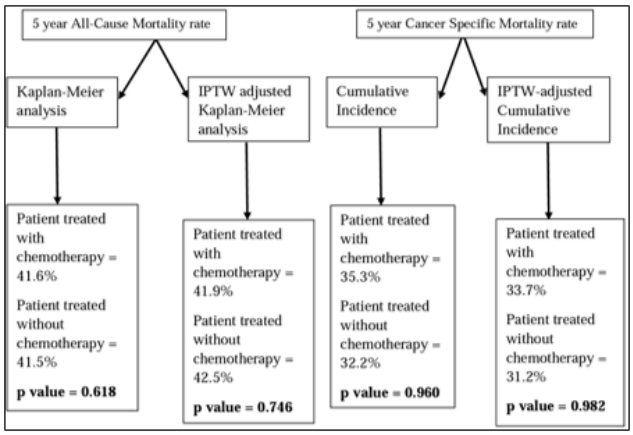

Chart 3: Survival Benefits of Chemotherapy in Clinically N0 Stage III (T3N0M0). Abbreviation: IPTW – inverse probability of treatment weighting

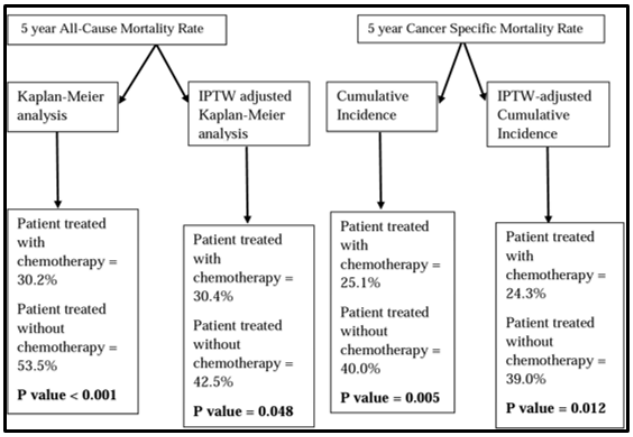

Chart 4: Survival Benefits of Chemotherapy in Clinically Node positive Stage III (T3N1M0/T13N2M0).

7. Source of Funding

None.

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