Concurrent Chemo radiation in Nasopharyngeal Cancer

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Anatomy

The pharynx is a musculomembranous tube. Interior of the pharynx is divided into 3 parts. Oropharynx. Nasopharynx. Laryngopharynx.
Nasopharynx
Present behind the nasal cavity and above soft palate.
Anterior wall is deficient.
Posterior wall and roof supported by sphenoid (body), basilar part of occipital, anterior arch of atlas.
Posterior wall and roof presents following features.

- The nasopharyngeal tonsils
- The pharyngeal bursa (pouch of Luschka)
- The pharyngeal hypophysis

**Floor** communicates with oropharynx through pharyngeal isthmus.

**lateral wall** presents the following features

- Nasopharyngeal opening of Auditory tube
- Tubal elevation
- Pharyngeal recess (Fossa of Rosenmuller)
Cross sectional anatomy of Nasopharynx
Nasopharyngeal Carcinoma (NPC)

- Arise from the epithelial lining of the nasopharynx.
- Fossa of Rosenmuller is the commonest site of origin.
- Results from the interplay of environmental, genetic and viral risk factors
Incidence & Mortality (World)

• 80,000 cases with 50,000 deaths annually
  – < 1 per 100,000/year incidence
  – 23rd most common cancer in the world
• 2-3 fold higher risk for males : females
• Broad racial/ethnic and geographic variation
  – 4th most common cancer in Hong Kong
• Highest incidence in Asian, N African/Mid east, and Arctic populations
Other Etiologies

- Epstein-Barr Virus (EBV)
  EBV DNA detected in ~100% of type II and III NPC
  Type I is not as consistent
  Also detected in NP dysplasia

- Salt-Preserved Fish & Meat

- Smoking causes a 2-6 fold increased risk
  Particularly true for Type I

- Occupational exposures
  - Formalin
  - Heat/combustion exposures
  - Wood dust
  - Chlorophenols
Pathology – WHO classification

• Nasopharyngeal carcinoma
  – Keratinizing squamous cell ca: type I
    • Similar with that in rest of aerodigestive tract

  – Non-keratinizing ca: type II and III
    • Differentiated non-keratinizing ca (type II)
    • Undifferentiated ca (type III)
Symptoms/signs

• Epistaxis and nasal obstruction/discharge
  – Mass in nasopharynx
• Tinnitus and hearing impairment
  – E-tube dysfunction, lateral extension
• Headache, diplopia, facial pain/numbness
  – Skull-base invasion, nerve palsy(5th/6th)
• Neck mass
• Signs of distant metastasis
  – Lung/bone/liver
**Tumour in nasopharynx (T)**

<table>
<thead>
<tr>
<th>T1</th>
<th>Tumour confined to the nasopharynx</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>Tumour extends to soft tissues of oropharynx and/or nasal fossa</td>
</tr>
<tr>
<td>T2a</td>
<td>without parapharyngeal extension</td>
</tr>
<tr>
<td>T2b</td>
<td>with parapharyngeal extension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades bony structures and/or paranasal sinuses</td>
</tr>
</tbody>
</table>

**T4**
Tumour with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, or orbit

**Regional lymph nodes (N)**

The distribution and the prognostic effect of regional lymph node spread from nasopharynx cancer, especially of the undifferentiated type, is different from that of other head and neck mucosal cancers and justifies use of a different N classification scheme.

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa
- N2 Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa
- N3 Metastasis in a lymph node(s)
  - N3a greater than 6 cm in dimension
  - N3b extension to the supraclavicular fossa
<table>
<thead>
<tr>
<th>Stage grouping</th>
<th>T1s</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II A</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II B</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2a</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2a</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV B</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV C</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
### Standard approach to nasopharyngeal carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Denomination</th>
<th>Gold standard therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-2a N0 M0</td>
<td>Early stage</td>
<td>- IMRT alone - Conventional RT alone</td>
</tr>
<tr>
<td>From T2b N0 M0 to T4b N3 M0 also every T</td>
<td>Locally advanced</td>
<td>- Neoadjuvant platinum-based CT followed by IMRT or CCRT (platinum-based) - Concurrent cDDP and RT</td>
</tr>
<tr>
<td>N2/3 M0</td>
<td>Metastatic</td>
<td>- Exclusive CT</td>
</tr>
</tbody>
</table>

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

Treatment

- *Radiation Therapy is the mainstay*
  - Difficult surgical approach
  - Sensitive to radiotherapy
- *RT volume (field) and dose*
  - Primary tumor: 65-75 Gy
  - Involved neck: 65-70 Gy
  - Uninvolved neck: 50-60 Gy
Fig.1- nasopharyngeal cancer, tumor has spread through pharyngobasilar fascia to involve parapharyngeal fat space.

Fig.2- CT image showing level II neck nodes.
Steps of conventional planning

- Clinical evaluation & assessment
- Patient set up supine
- Immobilised with thermoplastic mask
- Planning X-rays or CT scan done
- Conventional set up: 3 fields; 2 lateral opposed for primary and upper neck, matched to 1 anterior field for lower neck.
Portals for conventional RT

B/L parallel opposed portals for primary & upper neck

• **Superior**: 2 to 2.5 cm above the zygomatic arch and splits the pituitary fossa. In case of base of skull involvement or intracranial extension it is taken 4.0 to 5.0 cm above the zygomatic arch or 1 cm above the pituitary fossa.

• **Inferior**: at the thyroid notch

• **Anterior**: encompasses posterior ½ of nasal cavity or moved forward to cover the extensions if any.

• **Posterior**: kept open to cover the posterior triangle.
Portals for conventional RT

Single anterior portal for lower neck

- **Superior**: matched to the inferior border of the lateral fields.
- **Inferior**: extend below to cover the lower edge of clavicles.
- **Lateral**: cover medial 2/3rd of the clavicle.
Portals for conventional RT
Dose prescription

• Phase I : 40 to 44 GY in 20 to 22 fractions @ 2GY/#.
• Phase II : fields are shrinked to avoid the spinal cord. The primary tumor is boosted to an additional 20 to 25 GY.
  T1 & T2 tumor : 60 to 65 GY
  T3 & T4 tumor : 70 to 75 GY.

Dose to neck nodes : 45 to 50 GY to N0 neck.
  if nodes are palpable, an additional boost is given preferably by Electrons.
Morbidity from RT

• **Acute Toxicity**
  - Mucositis
  - Dermatitis
  - Pharyngitis
  - Otitis

• **Chronic Toxicity**
  - Xerostomia
  - sub cutaneous fibrosis
  - radiation myelitis
  - cranial neuropathy
  - endocrine dysfunction
  - temporal lobe necrosis
  - hearing loss
  - otitis media

• **Dose-limiting organ**
  - Brain stem
  - Spinal cord
  - Pituitary-hypothalamic axis
  - Temporal lobes
  - Eyes
  - Middle/inner ears
  - Parotid glands
Need for newer techniques
- 3DCRT
- IMRT
- IGRT
- SRS (boost)
- Rapid arc
- VMAT
- Proton

- Development of computerized 3D treatment plans is an important technical advance for Nasopharyngeal cancer with its typically concave tumor volume and proximity to critical structures.
Rationale of IMRT in cancer nasopharynx

1. Anatomically complex H&N region
2. Treat target volumes adjacent to critical or sensitive normal tissues
3. Lack of organ motion in the H&N region
4. Allows for dose escalation, allows for concomitant boost.
Steps of IMRT

- Clinical evaluation & assessment
- Simulation
- Planning CT/MRI/PET-CT scan
- Target volume Delineation: Gross target volume, Clinical target volume, Planning target volume.
- Dose prescription: PTV dose and Organ at risk (OAR) constraint
- IMRT Planning, Dose Volume Histogram
- Quality Assurance
- Execution of IMRT
Steps of IMRT
Contouring guidelines

- GTV = gross disease
- CTV = entire nasopharynx, sphenoid sinus, cavernous sinus, base of skull, posterior ½ of nasal cavity, posterior 1/3 of maxillary sinuses, post. Ethmoid sinus, pterygoid fossa, lateral & posterior pharyngeal wall, retropharyngeal nodes, & b/L cervical nodes including level V & SCF.
- PTV = 5mm to 1cm.
Contouring of primary disease and palpable neck nodes
Dose prescription

- PTV 1: 70GY/35# @ 2GY/#
- PTV2: 61.25GY/35# @ 1.75GY/#
- PTV 3: 52.5 GY/30# @ 1.75GY/#

**OAR Constraints**

<table>
<thead>
<tr>
<th>OARs</th>
<th>Constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord</td>
<td>Dmax ≤ 40 Gy</td>
</tr>
<tr>
<td>Brainstem</td>
<td>Dmax ≤ 54 Gy&lt;br&gt;V55 &lt; 5 cc&lt;br&gt;V50 &lt; few cc</td>
</tr>
<tr>
<td>Optical nerves</td>
<td>Dmax ≤ 50 Gy</td>
</tr>
<tr>
<td>Chiasma</td>
<td>Dmax ≤ 50 Gy</td>
</tr>
<tr>
<td>Mandible</td>
<td>Dmax ≤ 66 Gy (Dmax ≤ 100% prescribed dose – no hot spots)</td>
</tr>
<tr>
<td>Parotids</td>
<td>V15 ≤ 67%&lt;br&gt;V30 ≤ 50%&lt;br&gt;V45 ≤ 25%&lt;br&gt;Dmean &lt; 30 Gy&lt;br&gt;...as low as possible with priority for PTV coverage</td>
</tr>
</tbody>
</table>

**OARs**

<table>
<thead>
<tr>
<th>OARs</th>
<th>Constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larynx</td>
<td>V20 ≤ 60%&lt;br&gt;V30 ≤ 50%&lt;br&gt;V50 ≤ 20%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>V45 ≤ 50%&lt;br&gt;V60 ≤ 40%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>V20 ≤ 60%&lt;br&gt;V30 ≤ 30%&lt;br&gt;V50 ≤ 20%</td>
</tr>
<tr>
<td>Mucosa</td>
<td>V20 ≤ 50%&lt;br&gt;V30 ≤ 40%&lt;br&gt;V50 ≤ 20%</td>
</tr>
<tr>
<td>Lung apex</td>
<td>V30 ≤ 50%</td>
</tr>
<tr>
<td>Inner Hear</td>
<td>Dmax ≤ 50 Gy</td>
</tr>
<tr>
<td>Bone</td>
<td>Dmax ≤ 65 Gy&lt;br&gt;V55 ≤ 20%</td>
</tr>
</tbody>
</table>

Try to optimize “as low as possible” without compromising the PTV coverage.
Plan evaluation and Treatment
Comparison of different treatment plans

Axial dose distributions through the center of the nasopharynx and neck for the intensity-modulated radiation therapy (IMRT) [(a), (b)], three-dimensional (3D) conformal [(c), (d)], and traditional [(e), (f)] treatment plans. Note the relatively poor coverage of the skull base and medial nodal regions using the traditional plan and the improved dose conformity of the IMRT plan.
Results of Radiotherapy alone

<table>
<thead>
<tr>
<th>STAGE</th>
<th>5 Yr SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>EARLY DISEASE</td>
<td>90 – 95%</td>
</tr>
<tr>
<td>LOCALLY ADVANCED</td>
<td>50%</td>
</tr>
</tbody>
</table>

To improve the results in locally advanced cases chemotherapy was incorporated.
Chemoradiation in Cancer
Nasopharynx

• It is the most chemo and radiosensitive entity of all head & neck cancer.
• High incidence of distant metastasis.
• Integration of chemotherapy in radiotherapy has resulted in improved disease outcomes.
Chemo radiotherapy

- An improved therapeutic index is the goal
  - More effect of chemo radiotherapy on the tumor compared to the effect of chemo radiotherapy on normal tissue toxicity

- Classically there are 4 ways to define the interaction
  - spatial cooperation
  - toxicity independence
  - radioprotectors
  - radiation sensitizers
    - Steel & Peckham IJROBP 5:85, 1979
Locally advanced disease

- Various trials and meta-analysis have shown a clear advantage in terms of locoregional control, disease free & overall survival in favour of addition of chemotherapy to radiation.
Incorporate chemotherapy

- Induction (neo adjuvant)
- Concurrent
- Adjuvant
- Combination

Induction → Concurrent

Concurrent → Adjuvant
## Chemo-radiation trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Pts</th>
<th>Study design</th>
<th>Main end-point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin JC et al[4]</td>
<td>III</td>
<td>284</td>
<td>Exclusive RT alone vs cDDP-5FU + RT</td>
<td>5-year DFS</td>
<td>Experimental arm better (P &lt; 0.0012)</td>
</tr>
<tr>
<td>Chan AT et al[5]</td>
<td>III</td>
<td>350</td>
<td>Exclusive RT alone vs cDDP-5FU + RT</td>
<td>2-year PFS</td>
<td>Experimental arm better (P &lt; 0.016)</td>
</tr>
<tr>
<td>Zhang L et al[12]</td>
<td>III(m)</td>
<td>1608</td>
<td>Exclusive RT alone vs cDDP based CT + RT</td>
<td>5-year OS</td>
<td>Experimental arm better (P &lt; 0.001)</td>
</tr>
<tr>
<td>Yang AK et al[13]</td>
<td>III(m)</td>
<td>1993</td>
<td>Exclusive RT alone vs cDDP based CT + RT</td>
<td>5-year OS</td>
<td>Experimental arm better (P &lt; 0.05)</td>
</tr>
<tr>
<td>Lu H et al[17]</td>
<td>II</td>
<td>22</td>
<td>IMRT + cDDP</td>
<td>1 year OS</td>
<td>96%</td>
</tr>
<tr>
<td>Ekenel M et al[24]</td>
<td>II</td>
<td>100</td>
<td>IMRT + cDDP-Cet</td>
<td>ORR</td>
<td>100%</td>
</tr>
</tbody>
</table>

RT: Radiotherapy; IMRT: Intensity modulated RT; CT: Computed tomography; ORR: Overall response rate; DFS: Disease-free survival.
The main objective of this meta-analysis was to determine the clinical benefit of concurrent chemoradiotherapy (CCRT) compared with radiation alone (RT) in the treatment of nasopharyngeal carcinoma (NPC) patients in endemic geographic areas.

This is the first meta-analysis of CCRT vs. RT alone in NPC treatment which included studies (7 TRIALS, 1608 PTS) only done in endemic area. The results confirmed that CCRT was more beneficial compared with RT alone.

The role of concurrent chemoradiotherapy in the treatment of locoregionally advanced nasopharyngeal carcinoma among endemic population: a meta-analysis of the phase III randomized trials
Published online 2010 October 15.
## 5 years Overall Survival

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CCRT Events</th>
<th>CCRT Total</th>
<th>RT Events</th>
<th>RT Total</th>
<th>Weight</th>
<th>Risk Ratio M-H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan (11,25)</td>
<td>52</td>
<td>174</td>
<td>73</td>
<td>176</td>
<td>37.9%</td>
<td>0.72 [0.54, 0.96]</td>
</tr>
<tr>
<td>Wee (12)</td>
<td>24</td>
<td>111</td>
<td>42</td>
<td>110</td>
<td>22.1%</td>
<td>0.57 [0.37, 0.87]</td>
</tr>
<tr>
<td>Lee 9901 (13,18)</td>
<td>55</td>
<td>172</td>
<td>63</td>
<td>176</td>
<td>32.6%</td>
<td>0.89 [0.67, 1.20]</td>
</tr>
<tr>
<td>Lee 9902 (15,17)</td>
<td>11</td>
<td>51</td>
<td>13</td>
<td>42</td>
<td>7.5%</td>
<td>0.70 [0.35, 1.39]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>508</strong></td>
<td><strong>504</strong></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.74 [0.62, 0.89]</td>
</tr>
</tbody>
</table>

Total events: 142 CCRT, 191 RT

Heterogeneity: Chi² = 3.14, df = 3 (P = 0.37); I² = 5%

Test for overall effect: Z = 3.29 (P = 0.001)
Another meta-analysis included 18 trials enrolling a total of 1993 patients from China. Yank AK, Liu TR, Guo x, Qi gl, Chen FJ. 

<table>
<thead>
<tr>
<th>ARM</th>
<th>3Yr SURVIVAL</th>
<th>5Yr SURVIVAL</th>
<th>DISTANT METS. RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>56.38%</td>
<td>41.09%</td>
<td>38.71%</td>
</tr>
<tr>
<td>CT + RT</td>
<td>68.74%</td>
<td>51.91%</td>
<td>26.19%</td>
</tr>
</tbody>
</table>

The result demonstrated that chemoradiotherapy increased overall survival by 12% at 3 years, and 11% at 5 years after treatment. After chemoradiotherapy, the rate of distant metastasis was reduced by 12%.
Drugs used in Chemoradiation trials

- Cisplatin alone or in combination with 5-FU, Paclitaxel.
- Dose schedule: Cisplatin $30\text{mg/m}^2$/weekly for 6 to 7 cycles or, $100\text{mg/m}^2$ 3 weekly.

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 chemoradiotherapy had a significant impact on locoregional control.
<table>
<thead>
<tr>
<th>Center</th>
<th>N</th>
<th>Stage</th>
<th>FU (mo)</th>
<th>LC</th>
<th>DM-Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bucci</td>
<td>118</td>
<td>50% T3-4</td>
<td>30</td>
<td>96%</td>
<td>72% (4-year data)</td>
</tr>
<tr>
<td>Kam</td>
<td>63</td>
<td>51% T3-4</td>
<td>29</td>
<td>92%</td>
<td>79% (3-year data)</td>
</tr>
<tr>
<td>Wolden</td>
<td>74</td>
<td>51% T3-4</td>
<td>35</td>
<td>91%</td>
<td>78% (3-year data)</td>
</tr>
</tbody>
</table>
The Intergroup-0099 was the first randomized trial to compare concurrent chemo-radiotherapy followed by adjuvant chemotherapy with RT alone.

In this study, concurrent chemo-radiotherapy consisted of cisplatin (100 mg/m$^2$ every 21 d) for three cycles, followed by adjuvant cisplatin (80 mg/m$^2$ on day 1) and 5-fluorouracil (1000 mg/m$^2$ on days 1-4 every 4 wk).

A statistically significant advantage in the chemo-radiation arm was seen in terms of overall survival, disease-free-survival, locoregional failure rate and time to distant metastases.
### Adjuvant chemotherapy trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Pts</th>
<th>Study design</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Al-Sarraf M et al[18]</td>
<td>III</td>
<td>147</td>
<td>Exclusive RT alone vs CCRT followed by cDDP-5FU</td>
<td>3-year PFS</td>
<td>Experimental arm better ($P &lt; 0.01$)</td>
</tr>
<tr>
<td>Chen Y et al[19]</td>
<td>III</td>
<td>316</td>
<td>Exclusive RT alone vs CCRT followed by cDDP-5FU</td>
<td>2-year OS</td>
<td>Experimental arm better ($P &lt; 0.003$)</td>
</tr>
<tr>
<td>Lee AW et al[20]</td>
<td>III</td>
<td>348</td>
<td>Exclusive RT alone vs CCRT followed by cDDP-5FU</td>
<td>5-year PFS</td>
<td>Experimental arm better ($P &lt; 0.035$)</td>
</tr>
<tr>
<td>Park KH et al[21]</td>
<td>II</td>
<td>43</td>
<td>cDDP-5-FU + RT followed by cDDP-Epi-Ble CT</td>
<td>ORR</td>
<td>100%</td>
</tr>
<tr>
<td>Hu W et al[22]</td>
<td>II</td>
<td>54</td>
<td>w Pac + RT followed by cDDP-Pac CT</td>
<td>ORR</td>
<td>100%</td>
</tr>
<tr>
<td>Leung TW et al[19]</td>
<td>II</td>
<td>48</td>
<td>HFRT + cDDP based CT followed by cDDP-5FU CT</td>
<td>3-year DFS</td>
<td>71%</td>
</tr>
</tbody>
</table>

RT: Radiotherapy; CT: Computed tomography; ORR: Overall response rate; CCRT: Concurrent chemoradiotherapy; DFS: Disease-free survival.

Neo-adjuvant chemotherapy

• The role of neo-adjuvant chemotherapy followed by concurrent chemo-radiotherapy or RT is a matter of outstanding interest.

• Several clinical phase II 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.
# Neoadjuvant chemotherapy trials

<table>
<thead>
<tr>
<th>Trial</th>
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<tr>
<td>Al-Amro A et al[23]</td>
<td>II</td>
<td>110</td>
<td>Neo cDDP-Epi and followed by cDDP + RT</td>
<td>ORR</td>
<td>100%</td>
</tr>
<tr>
<td>Airoldi M et al[24]</td>
<td>II</td>
<td>30</td>
<td>Neo cddca-Pac followed by RT + cddca-Pac</td>
<td>ORR</td>
<td>87%</td>
</tr>
<tr>
<td>Ferrari D et al[25]</td>
<td>II</td>
<td>34</td>
<td>Neo cDDP-5FU followed by RT + cDDP</td>
<td>ORR</td>
<td>85.3%</td>
</tr>
<tr>
<td>Lu X et al[26]</td>
<td>II</td>
<td>58</td>
<td>Neo cddca-Tax followed by cddca + RT (arm A) vs neo cddca-5FU followed by cddca + RT (armB)</td>
<td>1-year DFS</td>
<td>no difference between arm A and B</td>
</tr>
<tr>
<td>Mosatata E et al[27]</td>
<td>II</td>
<td>36</td>
<td>Neo cDDP-Pac followed by cDDP-RT</td>
<td>ORR</td>
<td>89%</td>
</tr>
<tr>
<td>Hui ZP et al[28]</td>
<td>II</td>
<td>65</td>
<td>Neo cDDP-Tax followed by cDDP + RT (arm A) vs cDDP + RT (arm B)</td>
<td>3-year OS</td>
<td>Arm A better than arm B (P &lt; 0.012)</td>
</tr>
<tr>
<td>Bossi P et al[29]</td>
<td>II</td>
<td>45</td>
<td>Neo cDDP-Tax-5FU followed by cDDP + RT</td>
<td>ORR</td>
<td>98%</td>
</tr>
<tr>
<td>Cho S et al[30]</td>
<td>II</td>
<td>19</td>
<td>Neo cDDP-Tax-5FU followed by cDDP + RT</td>
<td>ORR</td>
<td>93%</td>
</tr>
<tr>
<td>Bae WK et al[32]</td>
<td>II</td>
<td>33</td>
<td>Neo cDDP-Tax-5FU followed by cDDP + RT</td>
<td>ORR</td>
<td>99%</td>
</tr>
<tr>
<td>Kong L et al[37]</td>
<td>II</td>
<td>52</td>
<td>Neo cDDP-Tax-5FU followed by cDDP + RT</td>
<td>ORR</td>
<td>90.2%</td>
</tr>
<tr>
<td>Ekenel M et al[34]</td>
<td>II</td>
<td>59</td>
<td>Neo cDDP-Tax followed by cDDP + RT</td>
<td>ORR</td>
<td>95%</td>
</tr>
<tr>
<td>Lin S et al[35]</td>
<td>II</td>
<td>370</td>
<td>Neo cDDP based CT followed by IMRT</td>
<td>3-year OS</td>
<td>90%</td>
</tr>
</tbody>
</table>

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

Conclusion

- 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/neo-adjuvant setting.