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Impact of comorbidity on tolerability and survival following curative intent intensity modulated radiotherapy in older patients with nasopharyngeal cancer

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ABSTRACT

Objective: This study aimed to evaluate the predictive factors for survival and acute toxicities in older patients with NPC treated with curative intent IMRT.
Materials and Methods: Older patients aged 65 years and above with non-metastatic NPC treated with curative intent IMRT between 2003 and 2013 were retrospectively analysed. Variables examined were gender, age, overall stage, chemotherapy use, Eastern Cooperative Oncology Group (ECOG) performance status and comorbidity. The comorbidity severity was determined by adult comorbidity evaluation (ACE-27). We considered hospitalization or placement of feeding tube during and up to one month post radiotherapy as surrogate endpoint for significant acute toxicities. Other endpoints examined were: OS (overall survival), DFS (disease free survival), DSS (disease specific survival).
Results: A total of 185 patients were eligible for analysis. Median age was 70 (65–86 years). Most of the patients presented with Stage III and IVA/B ($n = 127$, 68.7%), of good performance status of ECOG 0–1 ($n = 176$, 95.1%) and had low comorbidities with ACE-27 score of 0–1 ($n = 141$, 76.2%). Chemotherapy was delivered to 84 patients (45.4%). OS, DFS, and DSS were 64.5%, 51.4%, and 72.8% respectively. High comorbidity burden but not chemotherapy had significant impact on OS and DFS in patients with advanced stage. Fifty patients (27%) required tube feeding or hospitalization during the course of RT. Males, chemotherapy use and ECOG score ≥2 were significant predictors of tube feeding or hospitalization during RT.
Conclusion: Curative IMRT was associated with excellent survival outcomes in older patients with NPC. Comorbidity but not chemotherapy was associated with prognosis in advanced stage. Careful monitoring and intensive support should be instituted in older males with ECOG score ≥2 receiving chemo-radiotherapy.

1. Introduction

Radiotherapy is the mainstay of treatment in the management of nasopharyngeal cancer (NPC) and there exists a prevalent perception that older patients may not tolerate regular curative treatment as well as their younger counterparts [1,2]. Older patients may be treated less aggressively due to concerns that their tolerance may be impaired and their life expectancy is short [3–5]. Nonetheless, some studies have shown that high dose radiation for head and neck cancers was tolerable in older patients [6–8]. This is highly relevant as there is a second peak of NPC in ages 65–79 [9]. Currently there is a growing body of data regarding the assessment and treatment of older patients with cancer that helps to stratify these patients into their appropriate treatment groups [10]. Chronological age alone cannot be justified as the reason for treatment selection or dismissal. Rather, the biological age of each patient, taking into account other factors including comorbidities and performance status, is considered to be more relevant criteria than chronological age for treatment planning [10,11].

Technological advances such as intensity modulated radiotherapy (IMRT) have significantly improved treatment precision and hold the potential to widen the eligibility for curative treatment in older patients [12–15]. To date, there have been no published studies limited to IMRT in older patients with nasopharyngeal cancer. Previous studies were mostly restricted to older radiotherapy technique such as two dimensional (2D) or three dimensional (3D) conformal radiotherapy [16–18]. The generalizability of these results on this issue is problematic as IMRT is now widely accepted as the standard of care in head and neck cancer. Furthermore, there is also scarcity of data on the incidence of hospitalization or tube feeding during RT in older patients. Hospitalization and tube feeding are both useful and clinically relevant surrogate indicators of severity of acute toxicities during radiotherapy. Therefore, it is prudent to properly select patients for aggressive treatment and to

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anticipate their functional response. To the best of our knowledge, this is the largest series of older patients with NPC treated with curative intent IMRT. This study aimed to evaluate predictive factors for the various survival endpoints and hospitalization or placement of feeding tube rates during RT in patients aged ≥65 years old with nasopharyngeal carcinoma treated in our institution.

2. Methods & Materials

A retrospective review of all patients aged 65 years and above with non-metastatic nasopharyngeal carcinoma treated with curative intent intensity modulated radiotherapy in our Department of Radiation Oncology in the National Cancer Centre Singapore between January 2003 and December 2013 was conducted. This study was approved by our local institutional review board.

The clinical data collected from the medical records included age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), treatment patterns, survival duration, and causes of death. The comorbidity disease severity at diagnosis was determined by adult comorbidity evaluation (ACE-27) and scored retrospectively. ACE-27 is a 27-item comorbidity instrument validated on adult patients with cancer, including 1086 patients with head and neck cancer [19]. It was developed through modification of the Kaplan-Feinstein Comorbidity Index (KFI) [20]. ACE-27 grades comorbidities into one of four scores: none (0), mild (1), moderate (2), or severe (3).

Pre-treatment assessment included a complete history and physical examination, endoscopy, histologic examination, baseline blood tests, magnetic resonance imaging (MRI) of the posterior nasal space and metastatic workup. Metastatic workup included chest X-ray and an ultrasound of the liver or computer tomography (CT) of the chest/abdomen and a bone scan. All patients were restaged according to the American Joint Committee on Cancer (AJCC) 7th edition.

2.1. Radiotherapy

The radiotherapy procedures have been previously described [14]. All patients were immobilized in a supine position with neutral neck position in a thermoplastic shell. Contrast enhanced planning CT scans were performed at 3 mm intervals in the nasopharyngeal region and 5 mm intervals in the rest of the neck region. Registration of diagnostic MRI with planning CT images was performed for all patients to aid in the delineation of target volumes and critical structures. When neoadjuvant chemotherapy was given, fusion of pre- and post-chemotherapy MRI or CT image sets was also performed to delineate the pre-chemotherapy tumor volume.

The gross target volume (GTV) included all known gross disease (primary and lymph nodes) determined by clinical examination and imaging findings. A clinical target volume at 70 Gy (CTV_70) includes the entire nasopharynx and GTV with a three to 5 mm margin. A further margin of three to 5 mm was added to generate planning target volume at 70 Gy (PTV_70). This margin was allowed to be compromised when the PTV_70 would overlap with critical structures (i.e. Brainstem, spinal cord, optic nerves, optic chiasm). CTV at 60 Gy (CTV_60) covers the CTV_70, local structures at risk of microscopic spread (i.e. The inferior half of sphenoid sinus, cavernous sinus, base of the skull, anterior half of the clivus, retropharyngeal nodes, parapharyngeal space, pterygoid fossae, the posterior third of the maxillary sinus and nasal cavity) and regional lymphatics (bilateral retropharyngeal lymph nodes, level II–V). Neck level Ib was electively irradiated if there were nodal involvement on the ipsilateral level II. PTV at 60Gy (PTV_60) would cover PTV_70 and CTV_60 with 3 mm margin.

Critical normal structures were contoured, which included brainstem, spinal cord, optic nerves, optic chiasm, temporal lobes, inner ear structures, parotid glands, thyroid glands, lens and eyeballs.

The contoured images were transferred to our Varian Eclipse treatment planning system. All patients were treated with IMRT. The entire volume encompassing the nasopharynx and both sides of the neck were treated in 1 volume. This was done with a simultaneous integrated boost to the primary tumor and involved lymph nodes. The dose to PTV_70 was treated to a dose of 69.96 Gy in 33 fractions with 2.12-Gy fractions, whereas the PTV_60 received 60 Gy in 1.82-Gy fractions over the same period. All treatment was delivered once daily, five days per week.

2.2. Chemotherapy

Patients with Stage III and Stage IVA/IVB cancer received concurrent chemotherapy with or without sequential chemotherapy (neoadjuvant or adjuvant). The chemotherapy regimen was not protocolized and was used at the discretion of the attending medical oncologist of individual cases. Chemotherapy was not administered in some patients due to either patient and family refusal or contraindication from medical comorbidities. Concurrent chemotherapy consisted of paclitaxel or cisplatin administered weekly or three-weekly cisplatin given on weeks one, four and seven of radiotherapy. Adjuvant chemotherapy consisted of cisplatin with 5-flurouracil every three weeks for three cycles. Neoadjuvant chemotherapy consisted of cisplatin with gemcitabine given three times a week for three cycles. In patients for whom cisplatin was contraindicated because of hearing loss or renal impairment, carboplatin-based treatment was substituted.

2.3. Follow-up

Patients were reviewed at least once a week during the course of radiotherapy. Following completion of treatment, patients were followed up regularly every month for the first year, every two months for the second year, every three months for the third year and every six months for the fourth and fifth year and annually thereafter. Acute and late morbidity were assessed according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE). At each follow up visit, history and clinical examination, including flexible endoscopy were performed. Annual CT or MRI scans of the head and neck were performed for the first five years. In addition, an annual thyroid function test was performed for the first five years. Additional tests were ordered when indicated to evaluate for local or distant recurrence.

2.4. Statistics

All statistical analyses were performed using STATA version 14.2 statistical software (Stata Corp, College Station, TX). The clinical endpoints for tumor control were local recurrence free survival (LRFS), disease free survival (DFS), disease specific survival (DSS) and overall survival (OS). OS was calculated from the date of diagnosis to the death from any cause, DFS was calculated from date of diagnosis to relapse or death from any cause, whichever occurred earlier and DSS was calculated from date of diagnosis to date of death from NPC. We considered hospitalization or placement of feeding tube during and up to one month post radiotherapy as surrogate parameters for significant acute toxicities. Variables included in statistical analysis were age (≤70 years vs >70 years), gender (male vs. female), ECOG performance status (two to three vs. zero to one), ACE-27(two to three vs zero to one), overall stage (III/IVAB vs I/II) and chemotherapy use (yes vs. no). Independent factors predicting survival were analysed using Cox regression analysis. Logistic regression was used to determine predictors of tube feeding or hospitalization during RT. A two sided $p < 0.05$ was considered statistically significant.

3. Results

There were a total of 185 patients included in the analysis. The median follow up was 4.3 years (range: 0.3–9.1). The median age was 70 years old (range: 65–86). Most of the patients presented with

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