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REVIEW

Treatment of early stage nasopharyngeal carcinoma: conventional versus new radiation therapy technologies

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Abstract
Introduction In this review article, we highlight the progress made in the staging and treatment techniques for early stage nasopharyngeal cancer (NPC).
Historical context Techniques and limitations of conventional radiation therapy are discussed. While this disease entity has a favorable treatment outcome even with conventional radiation therapy, the majority of patients will suffer some late morbidities. The addition of focal radiation to conventional radiation therapy, either by brachytherapy or stereotactic radiosurgery, may improve local control but may lead to exacerbation of late radiation effects.
Contemporary treatment Contemporary radiation therapy with intensity modulation has been shown to maintain excellent local control rates at the cost of less morbidity and should be considered standard of care currently. Concurrent systemic therapy has been shown in randomized studies to reduce the rate of distant metastases and improve the survival rates of patients with locally advanced NPC. Patients with early stage disease have been less well studied, but may receive similar benefit, especially those with node-positive disease.
Conclusion Lastly, future developments which may improve the therapeutic ratio are discussed.

Keywords Nasopharyngeal neoplasms · Staging · Intensity modulated radiation therapy · Outcomes

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Introduction

Due to a paucity of early or specific symptoms or signs and the absence of an effective screening program, nasopharyngeal carcinoma (NPC) is often diagnosed at a relatively late stage [1]. A large retrospective study from Hong Kong showed that early stage disease (stage I or II) constituted only 21 % of a cohort of 5,037 patients [2]. The prognosis of early stage NPC is favorable, even with conventional radiation therapy, with 5-year survival rates ranging between 87 and 90 % for stage I and 74 and 84 % for stage II disease [3–5]. However, acute toxicity can be substantial [6], and long-term follow-up of patients treated with conventional radiation therapy alone has revealed that the majority of patients cured of cancer continue to suffer some treatment-related sequelae [7, 8]. Over the past two decades, considerable progress has been made in the staging, imaging, radiation therapy, and systemic therapy of this disease. All these advances have contributed to the curability and improved survivorship of patients with early stage NPC and are discussed in this review.

Definition of "early stage"

Staging of NPC has been relatively rapidly changing since the early work of Geist and Portman in 1952 [9]. Because NPC is treated non-surgically, staging has always been clinical. However, with the evolution of clinical staging modalities, from physical examination and plain X-rays to cross-sectional imaging, including computed tomography, magnetic resonance imaging, and positron emission tomography, staging accuracy has improved, but at the cost of stage migration.

Using the current American Joint Committee on Cancer (AJCC)/Union for International Cancer Control staging

classification, stage I and II tumors are considered early stage, whereas stage III and IVA/B are locally advanced and stage IVC denotes tumors that have already demonstrated distant metastatic disease. The staging classification changed substantially with the fifth (1997) AJCC edition compared to prior editions, with the intention of evenly distributing cases across the stages [4, 10]. For the T-category, tumors extending to the oropharynx or nasal cavity were classified as T3 using the 1992 system, whereas they are categorized as T2 currently. Similarly, patients with N1 to N2b adenopathy in the previous system are re-assigned to the N1 category. In China, the Chinese 1992 staging system is commonly used, which is similar but not identical to the current AJCC classification [11]. While the T1/2 classification is broadly similar, N1 of the Chinese system denotes a solitary mobile upper cervical node <4 cm in diameter, compared to the current AJCC system where N1 denotes unilateral metastasis in a node(or nodes), ≤6 cm in greatest dimension, above the supraclavicular fossa. This temporal and regional variation in staging classification has unfortunately hindered the comparability of results published over different eras and in different countries.

Conventional radiation therapy and associated late effects

Two-dimensional radiation therapy techniques [12] traditionally were used for the curative treatment of NPC. Targets were defined using bony landmarks, and treatment fields were typically split, with lateral fields superiorly and anterior/posterior fields inferiorly to avoid critical neural structures. Two to three phases were utilized to deliver a lower dose to a larger volume containing sub-clinical-sized disease followed by boosts to smaller volumes containing gross disease. To minimize the dose delivered to the larynx and spinal cord without compromising tumor coverage, some techniques involved changing the head position between treatment phases [13]. Typically, the tumor dose prescribed was 66–70 Gy in 2 Gy per day fractions five times a week.

The use of these fields in a region surrounded by critical structures has been associated with considerable treatment toxicity [7, 8, 14–17]. While acute toxicities are manageable and reversible for most patients, late effects can potentially be debilitating and irreversible. These late toxicities can be broadly divided to neurological or non-neurological categories. Neurological complications are comprised mainly of temporal lobe necrosis or cranial nerve palsies, whereas non-neurological complications include xerostomia, hearing or swallowing dysfunction, endocrinopathy, fibrosis, radionecrosis, and secondary malignancies. There is significant variation in the reported incidence rates of these late effects, and substantial under-reporting is likely. Contributory causes include a long latency period, competing risks of disease recurrence or co-morbidities, loss to follow-up, varying reporting standards and criteria, as well as non-uniform treatment techniques in different centers.

Temporal lobe necrosis has been reported to occur in 1–9 % of patients [8, 17] and is generally related to the high radiation doses delivered to the inferior and medial portions of the temporal lobes with the use of bilateral parallel-opposed portals to treat the nasopharynx. In a series of 1,032 patients with T1–2 NPC, Lee et al. [18] found 51 patients (5 %) with radiologically diagnosed temporal lobe necrosis. Approximately half (26 patients) were asymptomatic. Amongst the symptomatic patients, half (13 patients) had mild symptoms and the remaining 11 patients had severe symptoms, such as marked debilitation, pressure symptoms, epileptic attacks, changes in conscious level, or death. Similarly, treatment of disease in close proximity to or invading the skull base can result in cranial nerve palsies, with reported incidence rates ranging from 0.4 to 47 % [14, 16, 19]. The risk of neurological injury increased markedly with the addition of radiosensitizing chemotherapy [8, 14], dose escalation [7, 8, 14, 16], fraction size [20, 21], dose acceleration [21], or repeat irradiation [7].

Non-neurological complications are heterogeneous and multi-factorial. Chronic xerostomia of varying degrees is commonly reported, related to the inclusion of the salivary glands in the lateral fields required to treat the nasopharynx and upper cervical region [7, 17] Hearing loss is common and has been correlated to radiation dose to the cochlea [8] and the use of chemotherapy [8, 22]. Radiation-induced neck fibrosis can reduce neck motion and is also associated with lower cranial nerve palsies or brachial plexopathy [14, 23]. While neurological complications continue to occur many years after initial treatment, the incidence rate of non-neurological complications appears to plateau about 10 years after treatment [7]. Table 1 summarizes the main complications reported in the literature.

Role of focal radiation techniques

Focal radiation techniques, including brachytherapy and stereotactic radiosurgery, have been used for the treatment of NPC since the radium brachytherapy methods described by Richard and Pierquin in the 1920s [24]. A dose–response relationship above 66 Gy for local control has been shown using either external beam or brachytherapy [25]. However, it has also been shown that 2D planning techniques have definite limitations in trying to match the complex shapes created by nasopharyngeal carcinomas, particularly with locally advanced disease [26]. It is not easy to ascertain if boost techniques merely serve to compensate for inadequate

Table 1 Late toxicities reported in the literature

First author and year	Tuan 2012	Schinagl 2010	Chen 2009	Lee 2009
Number of patients	771	51	556	422
Median follow-up (years)	7.2	7.6	5.2	4.4
Any complication	565 (73)	36 (71)	NR	122 (29 %)
Temporal lobe necrosis/ encephalopathy	37 (5)	NR	7 (1)	4 (1)
Memory impairment	NR	14 (27)	NR	NR
Cranial nerve palsy	70 (9)	24 (47)	6 (1)	7 (2)
Tinnitus	94 (12)	11 (22)	NR	NR
Otitis media	NR	30 (59)	NR	NR
Otorrhea	101 (13)	NR	NR	NR
Hearing loss	120 (16)	43 (84)	196 (35)	81 (19)
Trismus	45 (6)	2 (4)	82 (15)	1 (0.2)
Dysphagia	116 (15)	NR	NR	3 (0.5)
Permanent tube feeding	61 (8)	NR	NR	NR
Soft palate dysfunction	NR	20 (39)	NR	NR
Nasopharyngeal mucosal injury	NR	25 (49)	NR	2 (0.4)
Neck fibrosis/subcutaneous injury	169 (22)	9 (18)	NR	NR
Skin injury	NR	5 (10)	25 (5)	NR
Primary hypothyroidism	101 (13)	16 (33)	NR	NR
Hypopituitarism	48 (6)	NR	NR	41 (10)
Xerostomia	353 (46)	19 (37)	235 (42)	NR
Osteonecrosis	13 (2)	0	NR	0
Second malignancy	17 (2)	5 (4)[a]	NR	NR

Percentages are reported in brackets

[a]Out of 117 patients

dose delivered via 2D techniques or help to deliver a high tumoricidal dose to relatively radioresistant or hypoxic gross disease. Where the disease encroaches the parapharyngeal space, for example, lateral fields alone (constrained by the tolerance of the adjacent neural tissue) have been insufficient to eradicate the posterolateral disease extent. Consequently, in the 2D era, some practitioners [5, 27] added posterior oblique off-cord fields, with the head tilted, to deliver an additional 10–20 Gy to ensure adequate coverage of this gross disease. As an alternative to a "parapharyngeal boost," the delivery of intra-cavitary brachytherapy for T1 disease might truly represent dose escalation to the primary site, since standard 2D radiation techniques would probably be able to provide sufficient tumor coverage [26].

Both interstitial [28, 29] and intra-cavitary [30–36] brachytherapy techniques have been successfully applied to boost the radiation dose to the nasopharynx. Most comparative series report improved local control with the addition of brachytherapy; however, most series are retrospective. Selection bias may also be significant, given that some physicians offer brachytherapy for clinical or biopsy-proven residual disease, while others routinely offer brachytherapy for all T1–2 tumors [31, 35]. Overall, the magnitude of local control benefit appears to range from 5 to 20 %.

While brachytherapy is able to deliver high radiation doses with a steep fall off, dose coverage is usually inadequate for bulky tumors, especially those with substantial parapharyngeal extension. Excellent local control has been reported with the addition of stereotactic radiosurgery to external beam radiation therapy, with only one local failure reported in a cohort of 82 patients [37] and a 3-year local control rate of 93 % in another report [38].

Regardless of modality, however, the addition of a boost can be associated with long-term toxicity. Hara et al. [37] reported that 10 of 82 patients developed temporal lobe necrosis, although nine of them required intense therapy because of T4 disease. Schinagl et al. [16] reported that 47 % of the patients treated with brachytherapy experienced cranial nerve palsies. Chronic nasopharyngeal ulceration/necrosis was also shown to be more common after the addition of brachytherapy [30]. Serous otitis media was noted in 20 % of patients receiving brachytherapy in one report [34]. In summary, in the era of conventional radiation therapy, there appeared to be a role for focal boost techniques. However, in view of the associated increased risk of toxicity, some authors have suggested restricting this technique to larger tumors [37] or residual disease after conventional therapy [17].

Results of contemporary fractionated radiation therapy

Intensity-modulated radiation therapy (IMRT) has allowed greater conformity of the high-dose regions to tumor volumes while relatively sparing normal structures. This has been shown to be especially useful in complex tumor volumes in close proximity to critical structures [39, 40]. Multiple retrospective [41–48] and prospective [49–53] studies utilizing IMRT have demonstrated excellent locoregional control ranging from 90 to 100 % for all stages of non-metastatic NPC. Studies reporting results for early stage disease alone [47, 49] report local control rates of 98–100 % and overall survival rates of 97–100 %, albeit with a relatively short follow-up. Randomized comparisons between IMRT and conventional radiation therapy have already shown improvements in toxicity [50, 53] and quality of life [50] associated with IMRT, but not efficacy.

The ability of IMRT to deliver varying doses per fraction to multiple volumes, known as simultaneous integrated boost or simultaneous modulated accelerated radiation therapy (SMART) [54], has allowed a higher biologically effective dose (BED) to be delivered to the tumor at a larger dose per fraction, while delivering a lower BED to critical structures such as the parotid glands or neural structures. IMRT plans have been shown to be superior to 3D conformal RT with a brachytherapy boost [55], but it is as yet unclear whether such radiation would improve the clinical outcomes of patients treated with more homogeneous IMRT to 66–70 Gy. Recent series utilizing IMRT with [38, 41, 42] or without [45, 49, 52] boost have both shown excellent efficacy results, and it is unlikely that a sufficiently powered, i.e., large enough-sized, randomized comparison would be feasible in a reasonable timeframe. Moreover, there are limits to the degree of acceleration permissible using a SMART technique. A recent prospective study delivering 70.2 Gy in 2.34-Gy fractions has reported an in-field temporal lobe necrosis rate of 12 % [20], whereas contemporary studies appear to indicate that this complication has become relatively rare with IMRT using fraction sizes of 2.0–2.12 Gy [56].

Role of chemotherapy

Twelve randomized trials [6, 57–66] and four meta-analyses [67–70] have been published demonstrating the efficacy of concurrent chemoradiation therapy over radiation therapy alone for locally advanced NPC with an absolute survival benefit of approximately 6 % at 5 years (from 56 to 62 %) [69]. Currently, the National Comprehensive Cancer Network [71] provides a category 1 recommendation for concurrent chemotherapy for all non-metastatic NPC patients except those with stage I disease. Using the American Society of Clinical Oncology terminology, the European Head and Neck Society–European Society for Medical Oncology–European Society for Radiotherapy and Oncology Clinical Practice Guideline [72] recommends radiation therapy alone for stage I and considers concurrent chemoradiation therapy for stage II NPC as level III evidence with a grade B recommendation.

Of the randomized trials, none has included stage I tumors, and only three have included stage II (by the current definition) tumors [6, 58, 64]: migrated stage tumors in the Intergroup 0099 study, the Taiwanese Veterans General Hospital study, and the Sun Yat Sen University Cancer Center work in China. The Intergroup and the Taiwanese studies used the 1988/1992 AJCC staging to accrue stage III and IV patients, hence recruited a minority of patients currently classified as having stage II disease. Chen et al. enrolled stage II patients using the China 1992 staging system, but on reclassification to the 1997 AJCC system, noted that 13.5 % were AJCC stage III. All three trials showed improved overall survival for the entire cohort with the addition of concurrent chemotherapy compared to conventional radiation therapy, though the magnitude of benefit for the subset with stage II disease is unclear. Chen et al. reported an impressive 8.7 % improvement in the 5-year overall survival rate, from 85.8 to 94.5 %, with the addition of low-dose (30 mg/m^2) weekly cisplatin concurrently with radiation therapy. While locoregional control rates were similar across both arms, the arm receiving chemotherapy had fewer distant metastases, suggesting that the role of systemic therapy in this setting was effective in eliminating micrometastases. This appears consistent with the sub-group analysis by Chua et al. [73] which looked at two induction chemotherapy randomized trials and concluded that only T1–2N0–1 patients benefited from chemotherapy, by the reduction in the rate of distant metastases.

Since the earlier trials were performed with conventional radiation techniques, it is unclear whether the magnitude of benefit would be similar in patients who are treated with IMRT. Retrospective series [47, 74, 75] using IMRT have demonstrated excellent results, both for local control and overall survival, for early stage disease. However, Su et al. noted that the 5-year distant metastases-free survival (DMFS) rate for T2N1 disease was 94 % compared to 99–100 % for T1–2N0 or T2N0 NPC. In another study looking at cervical node-negative patients treated with IMRT, those without retropharyngeal node involvement had a DMFS rate of 95.9 vs. 88.1 % for those with retropharyngeal lymphadenopathy (P=0.04) [48]. From these studies, we propose that early stage patients with cervical or retropharyngeal nodal metastases (particularly T2N1) could have a higher risk for distant micrometastases that require systemic therapy, but local control may be adequate with radiation therapy alone.

Concurrent chemoradiation therapy is associated with more acute toxicity than radiation therapy alone. Across the randomized studies, estimates of acute toxicity rates (grade 3 and above) range from 64 to 84 % for chemoradiation therapy versus 40–53 % for radiation therapy alone. Data for late toxicities are less comprehensive, given the long latency and relatively short follow-up of these studies. In addition, the studies were powered for efficacy rather than toxicity end points. While none of the randomized trials for NPC so far have shown a significant increase in severe late toxicities with the addition of chemotherapy, the grade 3–4 late toxicity rates can be considerable, approaching 24–30 % in the Hong Kong NPC 99–01 study [76]. Given that more than two thirds of patients would get moderate-to-severe acute toxicity and close to a third would experience late toxicity, it is likely that we are close to the limit of "tolerability" for concurrent chemoradiation therapy particularly for early stage tumors that presumably would benefit the least [77].

Future developments

A newly diagnosed patient with early stage NPC treated with contemporary techniques has an excellent chance of cure. However, the probability of suffering adverse effects from treatment remains considerable. Efforts to improve the therapeutic ratio include improving the technical delivery of radiation therapy and individualizing therapy, possibly by substituting a systemic therapy for some radiation therapy

If the main goal of combining chemotherapy in early stage disease is spatial cooperation, where cure rates are improved by eliminating micrometastases rather than radiosensitization for locoregional control, sequential systemic therapy may be a viable alternative. Neoadjuvant chemotherapy might minimize the risk of enhancing radiation-related toxicity and yet allow "full doses" of systemic therapy to be delivered. Xu et al. [65] compared neoadjuvant versus concurrent chemotherapy strategies in a randomized trial and showed a reduction in acute toxicities using the neoadjuvant approach without loss of efficacy. Using neoadjuvant chemotherapy and IMRT, Lin et al. [78] reported a high 3-year overall survival of 89 % in a cohort of 370 patients with stage IIB–IVB NPC. Whether this has any relevance to early stage disease remains to be seen.

Over the 6- to 7-week course of radiation therapy, changes in size and configuration of both tumor and normal structures occur. In particular, weight changes can result in a change in body contour, and radiosensitive organs, such as the parotid glands, can shrink in size. Adaptive planning, where repeat planning accounts for changes in contours, can potentially ameliorate toxicity [79] and improve efficacy. Additionally, technical advances in photon delivery techniques, such as the use of rotational therapy [80–83], might also marginally improve dose distributions. The use of particles such as in proton beam therapy (PBT), instead of photons, might lead to more dramatic dosimetric improvements. A treatment planning study comparing PBT and IMRT has shown that doses to critical structures can be significantly reduced using PBT without loss of tumor coverage [84]. However, demonstration of clinical benefit is still awaited.

Conclusion

Advances in staging, imaging, and treatment of early stage NPC have resulted in a high cure rate. The role of focal radiation therapy techniques in the primary treatment of this cohort is less clear, due to the excellent locoregional control attainable with IMRT. These techniques may best be reserved for treating residual or recurrent disease, in view of the potential late effects reported. The efficacy of concurrent chemotherapy has been demonstrated in randomized trials of more advanced disease, but at the cost of increased toxicities, and may represent overtreatment of early stage tumors, especially when node negative. Adaptive radiation therapy may reduce the toxicity burden for these patients while improving efficacy slightly.

Conflict of interest The authors declare that they have no conflict of interest.

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