RESEARCH ARTICLE

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Dosimetric Determinants of Locoregional Failure in Nasopharyngeal Carcinoma Treated with Definitive Intensity-modulated Radiotherapy (IMRT) with or without Concomitant Chemotherapy

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Abstract

Purpose: Nasopharyngeal carcinoma (NPC) is a significant head and neck malignancy with rising incidence globally. Despite recent advances in the treatment of NPC, particularly introduction of intensity-modulated radiotherapy (IMRT) in its management, locoregional recurrence remains a major challenge, impacting patient survival and quality of life. This study evaluates the five-year locoregional failure rates and recurrence patterns in NPC patients treated with IMRT with or without Concomitant Chemotherapy. **Methods:** A historical cohort of 65 NPC patients treated at Shohadai-e-Tajrish Hospital in Tehran, Iran, from 2017 to 2019, was analyzed. All patients received definitive IMRT, with a median follow-up of five years. Recurrence patterns were classified as in-field, marginal or out-field recurrences, based on dosimetric parameters. Statistical analyses assessed recurrence associations with clinical and dosimetric factors at the significant level of $p<0.05$. **Results:** Of the 61 patients, 31.2% experienced recurrence including 18.03% with locoregional failure and 13.1% with distant metastasis. Among locoregional recurrences, 60% were in-field, 30% marginal, and 10% out-field. Mean dosimetric values for high-risk, intermediate-risk, and low-risk clinical target volumes were 68.3 Gy, 58.65 Gy, and 51.66 Gy, respectively. **Conclusion:** Locoregional failures in NPC remain a significant clinical issue, with in-field recurrences being the most common. Strategies like dose escalation, functional imaging-guided radiation, and improved clinical target volume delineation are essential to enhance treatment outcomes and reduce recurrence rates. Further research into individualized treatment approaches and long-term toxicity data is needed to optimize patient care.

Keywords: Nasopharyngeal carcinoma- IMRT- Locoregional recurrence- Dosimetric analysis

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Introduction

Nasopharyngeal cancer (NPC) is a malignancy of the head and neck region that originates from the epithelial lining of the nasopharynx. According to GLOBOCAN 2022, around 120,434 new cases of NPC were detected globally, representing a cancer incidence of 0.60%, with 73,482 fatalities, accounting for a cancer mortality rate of 0.75% [1-3]. While age-standardized mortality rates have declined globally, the age-standardized incidence rate of NPC has risen from 1990 to 2019. This trend will continue between 2020 and 2035, signifying that NPC remains a significant health challenge worldwide [4, 5].

NPC treatment depends on the disease stage, including radiotherapy for stage 1 and radiotherapy with or without chemotherapy for stage 2 cancer. For more advanced stages (3 and 4), treatment includes chemoradiotherapy, often combined with induction or adjuvant chemotherapy [6]. Despite significant advancements in early detection and recent innovations in cancer therapies like advanced radiation techniques such as Intensity-Modulated Radiation Therapy (IMRT), which have greatly improved head and neck cancer treatment, locoregional recurrence continues as a considerable challenge for patients diagnosed with NPC. Approximately 10% of patients, especially those initially presenting with T3 or T4 lesions, continue to suffer from local recurrence [6]. Tumor recurrence not only results in increased mortality but also has a substantial negative impact on a patient's quality of life.

NPC recurrences can be classified into three categories based on their anatomical locations: in-field, marginal, and out-field recurrences [7]. Understanding these patterns is crucial for optimizing treatment strategies and improving patient outcomes. In-field recurrence refers to tumor regrowth within the original radiation treatment area. If V

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recur (volume of recurrence) within the 95% isodose curve (V95%) is≥95%, this is the most common pattern observed in NPC recurrence, accounting for approximately 83.3% of cases in some studies [8]. The primary reasons for in-field failure often include intrinsic radioresistance [9]. If the prescribed dose does not adequately cover the tumor volume, residual cancer cells may survive and proliferate. The median time to in-field recurrence can vary, but many patients experience this within the first three years post-treatment. The second form of recurrence is marginal recurrence, which occurs at the edges of the treated area, typically where the radiation dose may have been insufficient [10, 11]. On the other hand, if between 20% and 95% of the recurrent volume received over 95% of the prescribed dose, V95% was less than 95% and not less than 20%. This type of recurrence accounts for 21.1%% of failures in some studies [10]. Contributing factors to marginal recurrence include issues with target volume delineation. Errors in defining the clinical target volume (CTV) can result in inadequate coverage of tumor margins, especially if there are changes in the tumor's size or shape during treatment. Additionally, radiation dose distribution in areas that receive lower doses may not effectively control tumor growth, which can lead to marginal failures [10]. In some studies that applied IMRT, marginal failures were observed predominantly in areas such as the ethmoid sinus and nasal cavity, indicating specific anatomical vulnerabilities [10]. Out-field recurrence is the third form of recurrence. Out-field recurrence is defined as tumor regrowth outside the initially treated area if V95% of the recurrence volume was< 20%. This pattern is rare, representing about 5.6% of all recurrences. Common sites for out-field failures include distant lymph nodes, particularly in regions like the parotid gland and level Ib lymph node, and non-irradiated anatomical sites, which are not included in the radiation field due to initial staging or treatment planning errors [12, 13]. Out-field recurrences are often linked with systemic disease progression rather than localized treatment failure [14].

The management of recurrent NPC requires a nuanced understanding of these recurrence patterns. In-field recurrences are primarily related to radioresistance and dose inadequacies, while marginal recurrences highlight the importance of precise target volume delineation. Out-field recurrences suggest a need for broader systemic approaches. Continuous monitoring and adaptive treatment strategies are essential to mitigate these risks and improve patient survival rates following initial therapy.

The current study investigated five-year local-regional failure and the pattern of failure in patients diagnosed with NPC at stages I to IVa who received IMRT as definitive treatment in a single tertiary referral center in Iran.

Materials and Methods

This is a historical cohort design focusing on 65 patients with NPC who received treatment at Shohadai-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences (SBMU), between October 2017 and October 2019. Our study is a 5-year follow-up of a previously published study by Khandani et al (2023), and the population of the study and all staging work-ups were described comprehensively there [15]. This study was approved by the Research Ethics Committee of Shahid Beheshti University of Medical Sciences (Ethics ID: IR.SBMU.MSP.REC.1401.553). Briefly, patients with non-metastatic NPC who underwent definite radiotherapy using the IMRT technique were included if their medical records were available for follow-up.

Treatment sessions were conducted in a supine position with immobilization using thermoplastic masks under CT simulation guidance. Simulation CT scans were taken from the top of the head down to the arch of the aorta.

The definitions of target volumes for radiotherapy are as follows

The Gross Tumor Volume (GTV) was categorized into two subgroups: Primary GTV (GTV-P), which includes primary nasopharyngeal tumors, and Lymph Nodes GTV (GTV-N), encompassing all cervical metastatic lymph nodes.

The Clinical Target Volume (CTV) was divided into three risk categories

High-Risk Volume CTV1: GTV+10mm. This volume was received 70 Gy in 33 fractions.

Intermediate-risk volume

This included high-risk areas in the nasopharynx and neck, specifically covering the entire nasopharynx, posterior pharyngeal lymph node area, skull base, parapharyngeal space, pterygopalatine fossa, sphenoid sinus, part of the nasal cavity, and one-third of the maxillary sinus. This volume was received 59.4 Gy in 33 fractions.

Low-Risk Area CTV2

This volume covered lower-risk lymph node regions. It received 54 Gy in 33 fractions.

Planning Target Volumes (PTVs) were defined as CTV+ 5mm margin for treatment planning.

Treatment planning was conducted using Eclipse software to design seven co-planar irradiated fields. The treatment plans were required to meet specific criteria: no more than 20% of the PTV could receive over 105% of the prescribed dose; less than 3% could receive under 95%; and no area outside the PTV was allowed to exceed more than twice the prescribed dose. In the current study, IMRT was administered using a Varian linear accelerator (Varian Medical Systems, Palo Alto, CA, USA) operating at 6 MV. To ensure precise dose delivery, an electronic portal imaging device (EPID) was employed for weekly verification.

Chemotherapy was given either before (induction), during (concomitant), or after radiotherapy (adjuvant). Five regimens were used for induction or adjuvant therapy: cisplatin with gemcitabine; cisplatin with fluorouracil; cisplatin with docetaxel; a combination of cisplatin with fluorouracil and docetaxel; paclitaxel combined with carboplatin. Concurrent chemotherapy involves either cisplatin or carboplatin.

After completion of treatment, all patients were

clinically assessed by the radiation oncologist and otolaryngologist at 3-month intervals in the first year and 6-month intervals in the second and third years.

Three months after the completion of radiation therapy, a baseline MRI of the nasopharynx and neck was performed and subsequently repeated every 6 to 12 months. Every clinical or imaging-detected recurrence was confirmed by biopsy.

In this study, patients with locoregional recurrence underwent imaging at the time of recurrence, which was fused with their initial treatment plan. Dosimetric parameters for both the site of recurrence and the original plan were extracted. To minimize interobserver errors, these patients were re-contoured by a single physician based on RTOG (Radiation Therapy Oncology Group) guidelines.

The site of recurrence in these patients was classified according to the following definitions

In-field recurrence: Over 95% of the recurrent volume received over 95% of the prescribed dose.

Marginal miss: Between 20% and 95% of the recurrent volume received over 95% of the prescribed dose.

Outside miss: Less than 20% of the recurrent volume received over 95% of the prescribed dose.

A p-value < 0.05 was considered statistically significant for all analyses.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics and treatment factors, including frequencies and percentages for categorical variables (e.g., gender, histopathologic type, tumor classification, node classification, total stage, and treatment plan). Mean and range were reported for continuous variables such as age and GTV volumes.

For assessing patterns of recurrence, the relationship between dosimetric parameters (e.g., D98%CTV1, D95%CTV2, D95%CTV1) and recurrence type (in-field, marginal, or out-of-field) was analyzed. Chi-square tests or Fisher's exact tests were applied for categorical comparisons, and independent t-tests or ANOVA were used for comparing continuous variables among recurrence groups. A p-value < 0.05 was considered statistically significant.

Results

A total of 65 patients with NPC were studied. The demographic characteristics, tumor staging, and treatment details are outlined in Table 1. The patient population consisted of 42 men and 23 women, resulting in a male-to-female ratio of approximately 1.82:1. Patients ranged from 15 to 78 years old, with a median age of 43.38 years. Histologically, most patients had undifferentiated carcinoma; only four cases involved keratinizing squamous cell carcinoma. In terms of tumor staging, T1 was found in 18 patients (27.7%), T2 in 21 (32.3 %), T3 in 12 (18.5%), and T4 in 14 (21.5%) patients. For lymph node involvement: N0 occurred in 17 patients (26.2%), N1 in eight (12.3%), N2 dominated with 32 cases (49.2%), and N3 affected 8 patients (12.3%). Overall disease stages were distributed as follows: Stage I accounted for 7 cases (10.8%); Stage II included 13cases (20%); Stage III comprised 11 cases (16.9%)

Furthermore, stage IV represented 34 cases (52.3%). During the 5-year follow-up, three patients were excluded from the study due to incomplete follow-up data, and one patient died from a cause unrelated to cancer. Of 61 patients, 42 remained disease-free (68.8%), while 19 cases experienced recurrence (31.2%) 11 patients (18/03%) with loco-regional recurrence, and 8 patients (13.1%) with distant metastasis without evidence of prior loco-regional recurrence.

No information is available for one patient's plan, so data exists for 10 patients. Six patients experienced local recurrence, and four patients had a recurrence in cervical lymph nodes. Of these four patients, two were those who had more than 12 weeks passed from the end of treatment until achieving a complete clinical response in the neck. The mean initial GTV volume in these patients was 26.84± 8.05 CC, and the mean volume of clinically positive lymph nodes 6.85 ± 6.72CC were recorded. Among 10 patients with loco-regional recurrence, the mean D98% values for high-risk CTV and mean D95% for intermediate-risk CTV, and low-risk CTV are as follows: 68.3±0 .42 Gy, 58.65± 0.84 Gy, 51.66 ± 0.7Gy.

The mean recurrence tumor volume is 22.6+_ 11/7cc. Six (60%) patients had filed failure, three (30%) Cases had

Table 1. Patient Characteristics and Treatment Factors (n = 65)

Characteristic	Category	n (%)
Gender	Male	43 (64.6)
	Female	23 (35.4)
Age (years)	Mean (range)	-
Histopathologic Type	Undifferentiated	41 (63.1)
	Differentiated	2 (3.1)
	Non-keratinizing SCC	15 (23.1)
	Keratinizing SCC	4 (6.2)
	Low-grade adenocarcinoma	1 (1.5)
	Lymphoproliferative	1 (1.5)
	Basaloid SCC	1 (1.5)
Tumor Classification	T1	18 (27.7)
	T2	21 (32.3)
	T3	12 (18.5)
	T4	14 (21.5)
Node Classification	N0	17 (26.2)
	N1	8 (12.3)
	N2	32 (49.2)
	N3	8 (12.3)
Total Stage	I	7 (10.8)
	II	13 (20.0)
	III	11 (16.9)
	IV	34 (52.3)
Treatment Plan	RT alone	6 (7.8)

Abbreviations: SCC, squamous cell carcinoma; T, tumor classification; N, node classification; RT, radiotherapy.

Table 2. Summary of Treatment Outcomes and Recurrence Patterns

Case	GTV.P Volume (cc)	GTV.LN Volume (cc)	D98% CTV1 (Gy)	D95% CTV2 (Gy)	D95% CTV1 (Gy)	Recurrent Volume (cc)	V95% Recurrent (%)	D100 Recurrent (Gy)	Miss Type
T1N2	18	11	68.6	58.9	51.3	30	22	40	Marginal miss
T4N0	18.7	0	68.2	57.9	51.1	23.6	96	59	In-field miss
T1N0	43.7	0	69.2	60.5	51.5	30.3	100	60.4	In-field miss
T4N2	30.1	17.1	68.7	59.1	51.7	43.2	73	49.1	Marginal miss
T2N2	21.4	13	68.9	58.1	51.7	21	95.1	58.4	In-field miss
T4N2	19.9	15.1	68.3	58.3	51.5	11	96.3	59.1	In-field miss
T3N0	33.33	0	68	58.3	52	8	83	49.6	Marginal miss
T2N1	25.1	4	69	58.6	53.1	28.1	98	58.1	In-field miss
T3N1	27.7	6.5	68.1	59.2	52.1	29.2	99.1	58.3	In-field miss
T4N1	31.4	5.9	68.3	57.6	52.9	9	11	17	Out-field miss

Abbreviations: GTV.P, primary gross tumor volume; GTV.LN, lymph node gross tumor volume; D98%/D95%, dose to 98%/95% of CTV; V95% recurrent, % of recurrence receiving ≥95% dose; D100 recurrent, dose to 100% of recurrence. Miss types: Marginal (20–95% coverage), In-field (≥95% coverage), Out-field (outside target).

marginal failure, and one (10%) case had an out-of-field failure. Most sites of failure were in radiotherapy, but in marginal recurrence, the site of recurrence was the ethmoid sinus in two of three cases. The mean V95% for marginal failure was 47.92 ±36.6% and 97.42± 1.92% for in-filed failure. D100 for marginal failure was 36.3 ±20.46 Gy, And In58.8± 0.84 Gy in field failure. V95 % typically refers to the volume receiving 95% of the prescribed dose in radiation therapy, while D100 refers to the minimum dose received by 100% of a specific volume (e.g., a tumor).

The details of the dosimetric data are summarized in Table 2.

Discussion

NPC is a relatively common head and neck malignancy in East and Southeast Asia, known for its sensitivity to radiotherapy. Advancement of radiation techniques such as IMRT has dramatically improved treatment outcomes, resulting in five-year overall survival rates of about 80% for most patients. Nevertheless, local recurrence is a significant challenge, impacting roughly 5-15% of individuals after treatment (1). A thorough understanding of the local failure patterns is essential for refining treatment protocols and improving patient outcomes.

The current study investigated a five-year follow-up analysis of locoregional failure patterns in patients with NPC at stages I to Iva, who received definitive IMRT. The results indicate that 60% of local failures occurred within the initially irradiated field, commonly termed in-field failures. This finding is in accordance with the study of X.-T. Xiao et al. [10] who noted that 63.2% of recurrences were within the previously irradiated volume, indicating potential tumor radio resistance . Similarly, S. Chen et al. found that local failures were predominantly located in the GTV defined during initial treatment, emphasizing the importance of accurate contouring and optimized dose distribution [8]. Despite adequate radiation coverage, the persistence of in-field recurrence suggests the need for novel strategies to enhance tumor control, including dose escalation and targeted radiation boosts guided by functional imaging [16]. Several studies of dose escalation in NPC produced promising treatment results [17, 18]. In these studies, conventional anatomical imaging was used to delineate the targets with simultaneous integrated boost treatment of the GTV. Escalated regimens typically had hypofractionated doses of 2.17–2.42 Gy per fraction over total nominal radiation doses of 66–76 Gy [17].

The short-term loco-regional control rates were as high as 87–91% [19]. However, there are not enough comparative studies regarding the advantages of this technique over the standard non-escalated regimens. Furthermore, long-term toxicity data were lacking due to inconsistent reporting and limitations regarding follow-up periods.

Recent research has shifted from escalating radiation doses across entire anatomically defined tumors to employing targeted, image-guided dose painting techniques. This approach focuses on functionally active or radio-resistant areas within the tumor [18, 20]. A small randomized control trial utilized 18FDG-PET as

pre-treatment imaging for locally advanced NPC. In this investigation, regions exhibiting a standardized uptake value (SUV) of ≥2.5 were escalated to 77 Gy over 32 fractions. The results showed a superior 3-year disease-free survival rate of 95.2% compared to conventional radiotherapy's rate of 79.2%, providing preliminary evidence supporting dose escalation guided by functional imaging [19]. Diffusion-weighted (DW) MRI sequences were also used for dose painting techniques in NPC. Some studies showed that a low apparent diffusion coefficient (ADC) value on DW-MRI is linked to poor treatment outcomes, independent of clinical stage and other prognostic factors [21, 22]. A recent randomized controlled trial involving 260 patients demonstrated improved disease-free survival using DW-MRI-guided dose-painting IMRT compared to standard IMRT in loco-regionally advanced NPC. After induction chemotherapy, patients in the experimental group received doses of 70.4–72.6 Gy in 32–33 fractions for the gross tumor volume, with an additional simultaneous boost of 75.2–77.6 Gy targeting areas with ADC values below the mean from pre-induction images. This approach significantly improved all survival endpoints, including a remarkable two-year local recurrence-free survival rate of 100%. Notably, there was no significant increase in acute or late adverse events reported during this study [21].

The influence of CTV delineation on local failure patterns remains a topic of considerable debate. While some studies emphasize the importance of precise CTV delineation in minimizing recurrence rates, others suggest that individual patient anatomy and tumor biology may necessitate a more flexible approach to target definition [23]. For instance, X. Yang et al. reported that reducing the scope of CTV during initial radiotherapy could alleviate side effects without compromising treatment effectiveness, given that most recurrences occur in high-dose areas, implying that strict adherence to guidelines may not always lead to improved outcomes [14].

Despite advancements in imaging and treatment planning technologies, inter-observer variability in CTV delineation continues to pose challenges. A multicenter study by Y.-l. Peng et al. highlighted significant discrepancies among radiation oncologists in defining target volumes for NPC [24]. These inconsistencies can result in variable treatment delivery and clinical outcomes [25]. Addressing such variations through standardized training programs and consensus guidelines is essential to enhance the consistency and quality of treatment planning.

In the current study, 30% of patients experienced marginal recurrences, with the majority occurring locally in the nasopharynx, including the ethmoid sinus and skull base. The staging details for these cases are provided in Table 2, with one patient classified as T4N2 and another as T3N0. The mean D100 for these recurrences was 36.3 ± 20.46 Gy, while the mean V95% was 47.92 ± 36.6%. These findings suggest that limitations imposed by organ-at-risk constraints may restrict radiation dose coverage around GTVs. In such scenarios, induction chemotherapy has a critical role by reducing the size of GTVs and improving the separation from adjacent critical structures, thereby facilitating more effective radiation coverage.

In the current study, we noted that 10% of locoregional recurrence was out-of-field recurrence. This finding aligns with observations from other studies, which noted that extra-nasopharyngeal recurrences can complicate management and necessitate re-evaluation of treatment protocols [10].

In our analysis, there were 11 local recurrences during a five-year period; three between years three and five, and eight in the first three years. This pattern aligns with findings from other research, which indicate that a significant proportion of recurrences manifest within the initial years following treatment. For instance, a study analyzing recurrence patterns in nasopharyngeal carcinoma found that approximately 50–60% of recurrences occurred within the first 24 months post-treatment [26]. These findings underscore the importance of vigilant follow-up.

This study revealed important insights regarding recurrence patterns after definitive IMRT for NPC; nonetheless, it has several limitations. First, the sample size is relatively small, and data are derived from a single institution, limiting generalizability. Second, while the study identified recurrence patterns, further investigation is needed to explore the molecular and genetic mechanisms underlying radioresistance. Future studies should focus on prospective trials incorporating biomarker-driven treatment approaches, as well as the role of immunotherapy in reducing recurrence rates.

In conclusion, while IMRT has revolutionized the management of NPC, local failure remains a significant challenge due to various factors, including tumor biology, treatment planning discrepancies, and inter-observer variability in CTV delineation. Future research should focus on developing individualized treatment strategies that consider these complexities and aim to enhance local control while minimizing toxicity.

Author Contribution Statement

Maryam Kalantari Khandani contributed to data collection and manuscript drafting. Seyed Alireza Javadinia was responsible for data analysis, interpretation of results, and critical revision of the manuscript. Masoumeh Nouri (corresponding author) conceptualized the study, supervised all stages of the project, and finalized the manuscript for submission. All authors reviewed and approved the final version of the manuscript.

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Scientific Body / Student Thesis

This study was conducted as an approved institutional research project and was not part of a student thesis.

Ethics Approval

The study was approved by the Research Ethics Committee of Shahid Beheshti University of Medical

Sciences (Ethics ID: IR.SBMU.MSP.REC.1401.553).

Data Availability

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Study Registration

As this was a retrospective observational study, it was not registered in a clinical trial registry.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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