



# Salvage Endoscopic Nasopharyngectomy for Recurrent Nasopharyngeal Cancer: an Institutional Experience

Original Investigation

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## Abstract

**Objective:** This study aims to present the surgical and oncological long-term outcomes of patients with locally recurrent nasopharyngeal cancer (NPC) following endoscopic endonasal nasopharyngectomy (EEN).

**Methods:** The medical records of 11 patients who underwent EEN due to recurrent NPC were retrospectively reviewed.

**Results:** The mean age of the patient cohort, consisting of 10 males (90.9%) and one female (9.1%), was 44±13.01 years at the time of initial diagnosis. Seven patients (63.7%) had local recurrence, and four patients (36.3%) had loco-regional recurrence. The mean time to first recurrence from the initial diagnosis was 40.3 months, with a 5-year overall survival (OS) rate of 72.7% and a disease-free survival (DFS) rate of 27.3%. There were no significant differences between the concurrent chemoradiotherapy (CRT) and induction chemotherapy+concurrent CRT treatment groups in terms of DFS and OS as a first-line treatment (p=0.645).

**Conclusion:** EEN is a viable alternative approach for selected cases of locally recurrent NPC, considering the morbidities associated with re-irradiation.

**Keywords:** Nasopharyngeal carcinoma, local neoplasm recurrence, natural orifice endoscopic surgery, salvage therapy, treatment outcome, survival analysis

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## Introduction

Nasopharyngeal cancer (NPC) is a disease with an epidemiological pattern commonly observed in China, Hong Kong, and Southeast Asia (1). According to the World Health Organization's 5<sup>th</sup> edition classification of head and neck cancers, NPC is classified into three subtypes: non-keratinizing squamous cell carcinoma, keratinizing squamous cell carcinoma, and basaloid squamous cell carcinoma (2).

The treatment of NPC involves radiotherapy (RT) alone in early-stage disease, while concurrent chemoradiotherapy (CCRT) is administered in advanced stages (3). Advanced RT techniques such as intensity-modulated radiotherapy (IMRT) have shown 5-year local control rates ranging from 76% to 91% (4, 5).

NPC is an aggressive tumor that often leads to bilateral or multiple neck metastases and the reported rates of local recurrence after initial treatment range from 8.4% to 10.9%



(6-8). Surgical resection, re-irradiation, and chemotherapy are options for the management of recurrent NPC (9). Despite the advancements in IMRT, re-irradiation can result in high morbidity and mortality, including complications such as osteoradionecrosis, trismus, transverse myelitis, brain abscesses, and osteomyelitis. Chemotherapy is generally used as a palliative treatment in advanced cases (9).

Salvage nasopharyngectomy (SNP) has shown better outcomes in terms of 5-year survival rates (40-60%) compared to patients treated with re-irradiation (8-36%) (10). SNP can be applied in recurrent cases of NPC, especially in patients with rT1, rT2, or limited rT3 tumors (11). The success of the surgical procedure is highly correlated with the clinical stage of NPC (12). Various surgical approaches can be used for SNP, including trans-palatal, trans-mandibular, maxillary swing, and infratemporal approaches (13). These surgical approaches are currently less frequently used because of the potential for significant complications and the need for large incisions. The development of endoscopic imaging technology and surgical instruments specifically designed for endoscopic surgery has brought new approaches to this field. Endoscopic endonasal nasopharyngectomy (EEN) offers a solution to the morbidities associated with open approaches (14, 15).

In this study we aimed to present the surgical and oncological long-term outcomes of patients with locally recurrent NPC following EEN.

## Methods

Before starting our study, we obtained approval from the ethical committee of the Hacettepe University Non-Invasive Clinical Research Ethics Committee (decision no.: 2023/09-38, date: 21.02.2023). The medical records of 11 patients who underwent EEN due to recurrent NPC at the Hacettepe University, Department of the Otorhinolaryngology in the years between 2011 and 2019 were retrospectively reviewed. Informed consent was obtained from the patients.

The demographic characteristics of the patients, year of initial diagnosis, first, and if applicable, second recurrence status (local, regional, or distant), and treatments received were noted. Histopathological examination results after EEN and additional treatments administered to the patients were documented. The last follow-up dates were recorded, and survival data were collected by contacting the patients or their relatives via telephone for late survival analysis. The patients were restaged using magnetic resonance and positron emission tomography imaging.

## Statistical Analysis

In the statistical analysis of the study, Kaplan-Meier analysis was utilized to obtain both overall survival (OS) and disease-free survival (DFS) rates.

## Results

Of the 11 patients included in the study, 10 (90.9%) were male and one (9.1%) was female. The mean age at the initial diagnosis was  $44 \pm 13.01$  years. The minimum follow-up time was 42 months (median 82, min 42-max 242 months). CCRT alone was administered to four (36.4%) patients as the initial treatment, while induction chemotherapy (IC) followed by CCRT (IC+CCRT) was administered to seven (63.6%) patients. The mean time to first recurrence from the initial diagnosis was 40.3 months. Seven patients (63.7%) had local recurrence, whereas four patients (36.3%) had loco-regional recurrence. When the patients were restaged, five patients were rT2N0M0, three patients were rT3N1M0, one patient was rT1N0M0, one patient was rT4N0M0, and one patient was rT3N2M0. All patients with recurrent neck disease underwent salvage neck dissection. In cases with rT3 involvement, skull base involvement was observed, and resection was performed until reaching healthy bone. In the single case with rT4 involvement, resection, and duraplasty were performed due to dural involvement.

Preoperative biopsies were obtained from all patients who underwent nasopharyngectomy, confirming the presence of recurrence pathologically. According to the multidisciplinary tumor board's decisions, four (36.4%) patients received re-irradiation (three patients received stereotactic radiosurgery), three (37.2%) patients received additional CCRT, and four (36.4%) patients did not receive any additional treatment (Table 1).

The five-year DFS rate for our patients with NPC was 27.3%, with the latest recurrence observed in the 96<sup>th</sup> month (Figure 1). The OS rates were 72.7% at five years and 53% at 10 years (Figure 1). Mortality was observed in three patients with rT1N0M0, one patient with rT2N0M0, one patient with rT3N0M0, one patient with rT3N2M0, and one patient with rT4N0M0. When comparing the groups that received IC+CCRT or CCRT alone after the initial diagnosis, no statistically significant difference was found in terms of OS ( $p=0.645$ ). The 5-year OS rate was 75% in the group receiving concurrent treatment, whereas it was 71.4% in the IC+CCRT group (Figure 2). Finally, when comparing the 5-year DFS rates between these two treatment groups, the concurrent treatment group had a rate of 50%, while the IC+CCRT group had a rate of 14.3%, but the difference was not statistically significant ( $p=0.123$ ). None of the patients underwent surgery more than once, and there were no major complications.

## Discussion

Although NPC is a radiosensitive malignancy, local or regional recurrence remains a significant cause of treatment failure (16). Various treatment modalities, including re-

irradiation and surgery, are preferred for recurrent disease. In addition to these two treatments, with the advancement of medical technology, proton therapy, targeted therapies, and immunotherapies can also be applied (17). To the best of our knowledge, our study is the first to be reported from Turkey regarding salvage endoscopic nasopharyngectomy.

Patients with NPC require close monitoring during the first five years following the primary treatment. Studies have reported local recurrence rates of 60-65% within the first three years, increasing to 80% within the first five years (18, 19). While in our study, the mean time between the initial

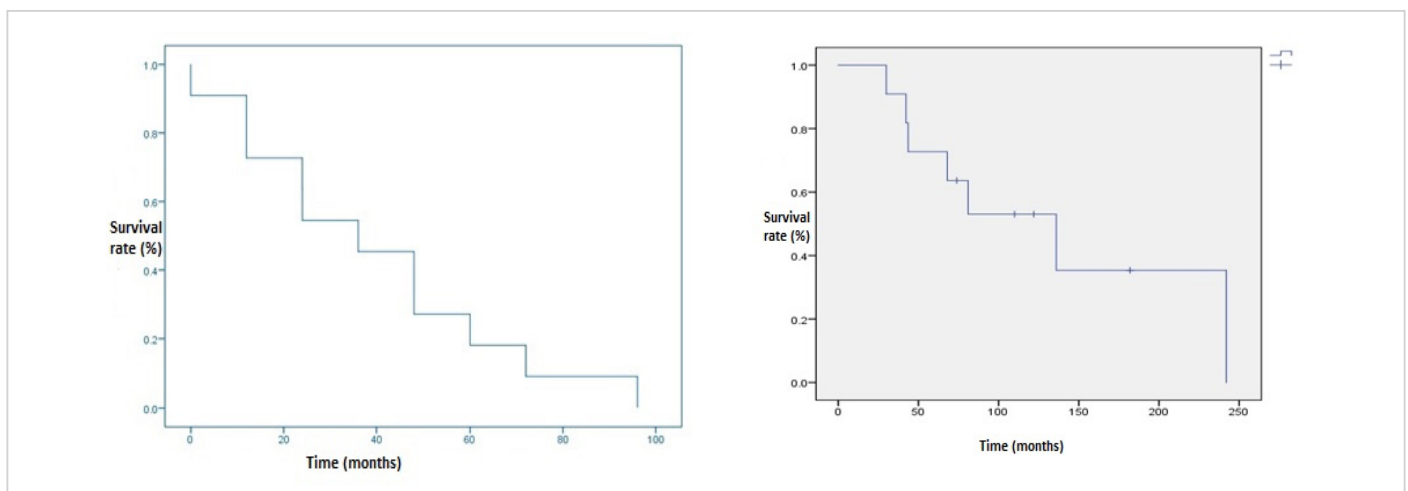
treatment and first recurrence was 40.3 months, Wong et al. (20) reported this time as 30 months. Another study found a mean time of 33 months between the primary disease and local recurrence (21). In our study, local recurrence was observed in three patients as the first recurrence, while regional and distant metastasis was observed in seven (63.6%) and one (9.1%) patients, respectively.

Re-irradiation has been used in the treatment of local recurrence, either with external RT or stereotactic radiosurgery. However, it can lead to serious morbidities, including complications such as osteoradionecrosis, cranial

**Table 1.** Distribution of patients' demographic characteristics and oncological data

Features	Frequency (%), n=11
Age at the first diagnosis (mean±SD, years)	44±13.01
<b>Gender</b>	
Male	10 (90.9)
Female	1 (9.1)
<b>The first treatment</b>	
Concurrent CRT	4 (36.4)
Induction CT + concurrent CRT	7 (63.6)
Time to relapse (mean±SD months)	40.3±6.1
<b>Re-staging</b>	
rT1N0M0	5 (45.4)
rT2N0M0	1 (9.1)
rT3N1M0	3 (27.2)
rT3N2M0	1 (9.1)
rT4N0M0	1 (9.1)
<b>Adjuvant treatment after nasopharyngectomy</b>	
Re-irritation	3 (27.2)
Concurrent CRT	4 (36.4)
None	4 (36.4)

SD: Standard deviation, CRT: Concurrent chemoradiotherapy, CT: Chemotherapy



**Figure 1.** Kaplan-Meier curves of the 5-year a) disease-free survival (27.3%) and b) overall survival (72.7%) rates

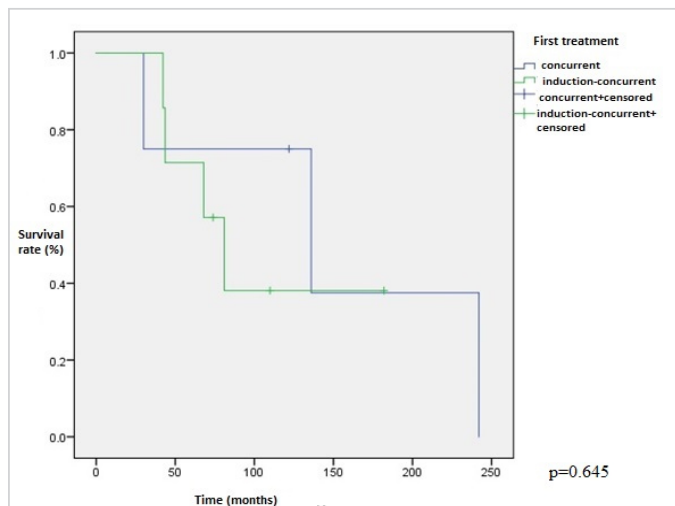
nerve neuropathies, brain abscesses, and mortality. Although there were no complications in our patient cohort, surgery-associated morbidities should always be kept in mind. Success rates are lower in advanced-stage recurrent tumors (rT3, rT4) (6). With the development of advanced RT techniques, reports have started to emerge regarding better outcomes with fewer complications. Studies on patients with rT3 and rT4 tumors reported OS rates of 35-36% and 19-30.2% for 5-year periods, respectively (22-24).

In our study, the OS rate at five years was 72.3%, and at 10 years, it was 53%. The 5-year OS rates in cases where nasopharyngectomy was performed as the treatment for local recurrence of NPC vary between 39% and 75.1% in the literature (18, 20, 21, 25, 26). Wong et al. (27) reported a 2-year OS rate of 66.7% following EEN, while Peng et al. (28) reported a rate of 66.3% (Table 2). The 5-year DFS rate in our study was 27.3%, slightly lower than the literature (Table 2). In the study conducted by Li et al. (29), the 3-year OS rate was reported as 55.2%, and the DFS rate as 29.4%. Furthermore, factors such as low body mass index, advanced

age, stage rT+, tumor necrosis, and invasion of the internal carotid artery by the tumor were identified as predictors of poorer OS. Additionally, low body mass index and stage rT4 were associated with worse DFS outcomes. Endoscopic nasopharyngectomy, like all endoscopic surgeries, is a procedure that requires advancement along the learning curve. As experience in the anatomy of this head region increases, even advanced-stage surgeries are becoming feasible. Initially, it is advisable to start this surgery with cases that do not extend to the posterior cranial fossa dura and do not cross laterally beyond both carotid arteries. Recurrence of NPCs particularly limited to the nasopharynx without widespread involvement at the skull base can be more suitable for SNP instead of IMRT.

Endoscopic endonasal surgery is a less complicated surgical approach compared to open procedures. In a study by Salom et al. (21), open nasal and endoscopic surgery approaches were compared, and moderate to severe complications were found to be more frequent in open surgeries. We did not encounter any significant complications in our patient series. The main disadvantage of EEN is the inability to clearly evaluate the surgical margins. As a result, some patients require adjuvant treatment after surgery. In our study, adjuvant treatment was administered to seven (63.6%) patients after surgery. In a study by Peng et al. (28), additional treatment was given to 19 (33.9%) patients.

In their randomized, controlled trial, one of the largest studies in the literature, Liu et al. (30) compared IMRT (71 of the 100 patients received cisplatin-based chemotherapy) and SNP. Three-year OS, DFS, and locoregional recurrence-free survival rates were significantly higher in the SNP group. However, 5-year OS and DFS rates did not reach statistical significance despite being better in the SNP group compared to the IMRT group. In our study, seven (63.6%) patients received IC+CCRT, while four (36.4%) patients received CCRT. The OS rates were 75% and 50%, and DFS rates were 50% and 14.3% in these groups, respectively, with no statistically significant difference.



**Figure 2.** Comparison of overall survival rates between concurrent chemoradiotherapy (CCRT) and induction chemotherapy+CCRT groups (75% vs 71.4%, respectively) (p=0.645)

**Table 2.** Overall and disease-free survival rates from various studies in the literature

	Number of cases	5-year overall survival rate (%)	5-year disease-free survival rate (%)
Salom et al. (21)	8	75	-
Castelnuovo et al. (25)	27	75.1	58.1
Wong et al. (20)	15	50	25
Liu et al. (18)	91	38.3	30.2
Sun et al. (26)	71	39	39.9
Wong et al. (27)	15	66.7 (2- years)	40 (2- years)
Peng et al. (28)	56	48.6	42.6
Liu et al. (30)	100	73.8	59
Li et al. (29)	120	55.2 (3-years)	55.2 (3-years)



The limitations of our study include its retrospective nature and a relatively small patient population. Furthermore, we lack sufficient long-term information on the duration of medical treatment and drug doses. The presence of patients with recurrent neck disease and those receiving additional treatment has also contributed to the heterogeneity of the patient group. Finally, the uneven distribution of patient T stages hindered our ability to present stage-specific survival rates.

## Conclusion

Our study highlighted that EEN is a viable alternative approach for selected cases of locally recurrent NPC, considering the morbidities associated with re-irradiation. Although the results of OS and DFS support the use of the EEN approach, randomized controlled studies with long-term follow-up and larger patient populations are needed. With the advancements in endoscopic imaging systems and surgical instruments, it is expected that better results will be reported in this field in the future.

**Ethics Committee Approval:** Before starting our study, we obtained approval from the ethical committee of the Hacettepe University Non-Invasive Clinical Research Ethics Committee (decision no.: 2023/09-38, date: 21.02.2023).

**Informed Consent:** Informed consent was obtained from the patients.

## Authorship Contributions

Surgical and Medical Practices: S.Ö., T.M.Ö., Concept: E.E., S.Ö., T.M.Ö., Design: E.E., A.E.P., S.Ö., Data Collection and/or Processing: E.E., A.E.P., Analysis and/or Interpretation: E.E., A.E.P., S.Ö., T.M.Ö., Literature Search: E.E., A.E.P., Writing: E.E., A.E.P., S.Ö., T.M.Ö.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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## Main Points

- Considering the morbidities associated with re-irradiation, endoscopic endonasal nasopharyngectomy is a good alternative treatment option for locally recurrent nasopharyngeal cancer (NPC).
- Recurrence of NPCs, particularly those limited to the nasopharynx without crossing laterally beyond both carotid arteries, can be more suitable for salvage nasopharyngectomy.
- With the advancement of endoscopic surgical techniques in the future, 5-year overall and disease-free survival rates may improve.

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