

Nasopharyngeal Carcinoma with Skull Base and Intracranial Invasion: Salvage Gamma-Knife Radiosurgery

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Received: 07-Sep-2022, Manuscript No. SCR-22-20146; **Editor assigned:** 09-Sep-2022, Pre QC No. SCR-22-20146 (PQ); **Reviewed:** 21-Sep-2022, QC No. SCR-22-20146 (Q); **Revised:** 23-Sep-2022, Manuscript No. SCR-22-20146 (R); **Published:** 28-Sep-2022, doi: 10.35248/2161-1076.22.12.9.410

Abstract

Because of its deep-seated location, proximity to vital structures, and patient history of high-dose irradiation, recurrent Nasopharyngeal Cancer (NPC) is typically challenging to treat successfully with salvage procedures. Malignancies with skull base and cerebral invasion can be treated with Gamma Knife Radiosurgery (GKS). We performed a retrospective, observational, single-center analysis on 15 patients who had GKS as a salvage procedure for recurrent NPC (stage T4b) involving the base of the skull and cerebral invasion. Twelve years were spent enrolling patients. The TNM classification T4b was divided into T4b1 and T4b2, according to a prior study, based on the involvement of the skull base or cavernous sinus with an intracranial extension of 5 mm and >5 mm, respectively. Age, sex, survival time, MRI presentation, existence of further distant metastases, tumor volume, marginal dosage, maximal dose, and Karnofsky Performance Status (KPS) were examined as prognostic markers that may affect outcomes. Better results following GKS treatment were seen in the patients with T4b1 NPC ($p=0.041$), small tumor volume ($p=0.012$), greater KPS ($p=0.001$), and no additional metastases ($p=0.007$), indicating that GKS is a potential treatment option for NPC.

Keywords: Nasopharyngeal carcinoma • Salvage therapy • TNM staging • Brain imaging

Introduction

In the United States and Western Europe, 2 persons per 100,000 are affected by Nasopharyngeal Cancer (NPC), a rare tumor that develops from the tiny tubular passageway behind the nasal cavity. NPC is primarily an undifferentiated, nonkeratinizing squamous cell carcinoma histologically. The racial and regional distributions of this illness, however, are astounding. Southern Asia, especially Taiwan, is experiencing a noticeably increased incidence of NPC. Radiotherapy continues to be the mainstay of NPC treatment since it is a radiosensitive tumor and a surgical approach is constrained by its anatomical placement. Primary NPC is typically treated with external beam Radiation Treatment (RT), either by itself or in conjunction with chemotherapy, at quite high doses (66 Gy-70 Gy). Randomized trials have demonstrated that RT with or without chemotherapy can achieve excellent locoregional control and avoid distant metastases in individuals with early stage I or II illness. Induction chemotherapy followed by concurrent chemoradiation or concurrent chemoradiation with or without adjuvant chemotherapy are two possible treatments for an advanced stage of the disease. 10%-40% of patients report NPC recurrence after 1-year-2 years of initial treatment, and 7%-15% of patients remain at risk of persistent or recurrent illness even after receiving radical radiation.

Recurrent and metastatic NPC are the most common causes of death in patients with NPC, and both disorders are difficult to treat. The median overall survival for these patients is 10 months-36 months. Regrettably, retreatment using traditional methods is linked to subpar results and/or a high frequency of late problems. The deep-seated nature of NPC and the nearby vital structures make salvage therapy for recurrent NPC typically difficult. Salvage operations with endoscopic nasopharyngectomy should be carried out rather than reirradiation with or without concurrent chemotherapy for the treatment of small recurrent local lesions eligible for resection because this method improved overall survival and decreased long-term toxicity in a phase III trial.

However, because to the restricted access to the nasopharynx, salvage surgeries using endoscopic nasopharyngectomy are technically difficult. Reirradiation is still an option for treating larger (T3 to T4) locoregionally recurring nasopharyngeal tumors or those that are untreatable, particularly those that have invaded the area around the base of the skull. The tolerable dose for reirradiation is constrained by prior radiotherapy treatments and the tolerance of healthy tissues; as a result, severe acute and late toxicities must be anticipated. This provides a therapeutic dilemma. Additionally, radioresistance brought on by prior therapy poses a serious issue, especially in patients who have recurrence following initial high radiation doses given as primary therapy in conjunction with chemotherapy. When possible, vigorous treatment should be taken into account because a sizable fraction of patients with local failure can still be effectively saved and attain long-term survival.

Recently, Stereotactic Radiosurgery (SRS) has become a viable treatment option for malignant skull base and intracranial lesions. Several studies have found that SRS is effective in preventing skull base invasion in NPC, though some patients have experienced side effects as a result of the procedure. Stereotactic radiosurgery's dose distribution improves homogeneity, particularly for lesions that involve regions far from the nasopharyngeal mucosa. The efficacy of SRS in comparison to other salvage procedures is uncertain, and information about SRS for saving patients with late-stage relapse is currently lacking. SRS has only been used in a small number of studies to treat late-stage tumor relapse in NPC.

Gamma Knife Radiosurgery (GKS) was recently developed as an alternate treatment for malignancy with skull base and intracranial invasion. It is a very precise form of SRS that focuses on powerful beams of gamma rays with pinpoint accuracy to treat lesions in the brain. According to earlier research, GKS is a viable salvage strategy for individuals with recurrent NPC who have already undergone RT. Few studies have employed GKS to treat the skull base and intracranial invasion (T4) in patients with NPC who have previously received full-dose (brain stem, 54 Gy-56 Gy) radiation, but this condition still has to be managed. Therefore, the purpose of this study was to examine the viability of GKS for cerebral invasion in NPC patients who had already undergone radiation.

Discussion

Even while the survival and local control rates for early and intermediate-stage NPC are good following adequate therapy, only 40%-70% of T3 and 40%-50% of T4 lesions experience long-term local nasopharyngeal control. Isolated local relapse is the typical recurrent pattern, and local recurrence following external beam RT continues to be a significant cause of treatment failure. Additionally, the most frequent causes of death include recurrence and metastasis. Patients who are carefully chosen and given the right care can survive for a long time, and aggressive local salvage therapy can increase the survival rate. The findings may suggest routine thorough MRI scans of the head and neck to evaluate locoregional illness before starting treatment for the

original NPC. Minimal (T4b1) and prolonged (T4b2) cerebral invasion were present in eight and seven patients with NPC, respectively. Since staging in every case was done using thorough enhanced MRIs, it's possible that the initial imaging missed the minor extension of primary lesions. Therefore, accurate imaging investigations may make it easier to identify cerebral invasion early and reduce the likelihood that expanded lesions would go undiagnosed or that the underlying illness stage will be underestimated. Resection of such lesions may be beneficial for patients with minor local recurrences and no distant metastases if the recurrence does not affect the bone or cranial nerves. The goal of surgery in this situation is to obtain an appropriate margin while conserving the neurovascular bundle and reestablishing the vital mucosal barrier. The majority of nasopharyngeal recurrent lesions, however, are more extensive, necessitating reirradiation at frequently high doses. Due to a variety of variables, successful salvage or palliation of NPC recurrence is difficult. The intricate structure of the skull base frequently makes it impossible to completely resect the area or insert a radioactive implant in the ideal location. However, a recent study found that patients with locally recurrent NPC confined to the nasopharyngeal cavity, post-nasal or nasal septum, superficial parapharyngeal space, or base wall of the sphenoid sinus had three-year survival rates as high as 85.8% after salvage endoscopic nasopharyngectomy. Higher T classification of recurrent tumors (involvement of the skull base, cranial nerve, dura, or brain) and the emergence of significant unfavorable consequences are related to a bad prognosis. Chemotherapy following recurrence has poor efficacy because to low response rates, and over half of patients with apparent local recurrence also have concurrent distant metastases.

There are numerous therapy options available to rescue local NPC recurrences. SRS is a successful therapy for patients with low treatment-related morbidity who need palliative care. The primary benefit of SRS is a quick dose reduction surrounding the target volume, sparing delicate nearby critical structures and previously radioactive tissue. Intense gamma ray beams are pinpoint-accurately focused using GKS, a very precise kind of SRS, to treat brain lesions, improving dose uniformity. It has become a different option for treating tumors that have invaded the intracranial space and have a skull basis.

In our investigation, 15 patients with recurrent NPC affecting the skull base and cerebral invasion participated. A dose of at least 12 Gy is advised based on prior scholarly papers and our experience; there is no conventional marginal prescription dose for recurring malignancies. When patients had no tumors involvement in these tissues, we made sure that radiation doses to the optic nerve, optic chiasm, and brain stem were less than 8 Gy.

The T4b classification was separated into two grades: T4b1 (involvement of the skull base or cavernous sinus with little cerebral extension; 5 mm) and T4b2 (involvement of the intracranial region; 5 mm). Small tumor volume ($p = 0.012$), high KPS ($p = 0.001$), the absence of any systemic metastases ($p = 0.007$), and the T4b1 stage ($p = 0.041$) in the MRI taken before to GKS treatment were all found to be significant predictors of positive outcomes. A prior study likewise showed the findings about the small tumor volume and absence of systemic metastases. Furthermore, a KPS of at least 90 is linked to a 50% chance of surviving for at least 40

orbital months. Following reirradiation of locally recurrent nasopharyngeal carcinoma, a recent study using fractionated robotic stereotactic body radiosurgery showed that the prognostic factors for local failure-free survival were cumulative total radiotherapy dose, gross tumor volume, and recurrence time interval, and that treatment-related mortality was vascular in nature. These results validate ours and show that SRS is a promising therapeutic approach for recurrent NPC.

NPC that affects the intracranial area always invades the neural foramina and base of the skull. The invasion of the cavernous sinus segment of the cranial nerves III and VI, the trigeminal ganglion, the cranial nerves in the cistern, the inferior orbital fissure, the orbital apex, and the superior fissure are among the intracranial and orbital extensions that are frequently linked to intracranial nerve involvement found on MRI. Malignancies with cranial nerve involvement identified by MRI have a high probability of distant metastases and a low survival rate. Within the lymphatic system of the epineurium and perineural sheaths, cancer cells develop along the nerves. Given that it has been proven to be a bad prognostic factor in many cancers, including head and neck, colon and rectum, and prostate cancers, perineural invasion is a crucial clinicopathological finding in such instances. The similar approach applies to NPC, where cranial nerve involvement is also a bad prognostic indicator.

Our findings show that the T4b1 lesions had a greater overall survival rate than the T4b2 lesions. Patients with T4b2 NPC were more likely to develop recurrence at distant sites, which could be explained by the hypothesis that tumor proliferation within the lymphatic system may enhance the likelihood of distant metastasis. Contrarily, the cerebral region, particularly the cavernous sinus, is rich in the venous plexus and is traditionally regarded to be a potential pathway for hematogenous dissemination for recurrent NPC, which is presumably another factor contributing to the low survival rate of T4b2 patients. The requirement of the T4b1/T4b2 subclassifications is supported by these findings.

There are a few restrictions on this study. First of all, it was a single-center, retrospective observational study. Patients involved in our trial were primarily from the oncology department because they had no other better therapy alternatives, and the standard salvage treatment for the recurrent high T stage has not yet been defined. Second, there weren't too many cases, and NPC incidence is not common. Recurrent disease with invasion of the skull base and cranium has only occasionally been described, especially in terms of the inclusion criteria of this investigation. Therefore, additional research would be required.

Conclusion

In particular, patients who are inoperable, have limited intracranial extension, a smaller tumor volume, a higher KPS, and no distal metastases should consider GKS as a suitable therapy option. Furthermore, according to our preliminary findings, GKS offers T4b1 NPC patients good tumor control with low side effects. Prior to beginning NPC treatment, comprehensive brain imaging examinations may make it easier to identify intracranial invasion early. Future research should, however, corroborate our findings in terms of long-term outcomes and late problems.