Diagnosis of Post-Radiotherapy Local Failures in Nasopharyngeal Carcinoma: A Prospective Institutional Study

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Abstract

Background: This prospective study was conducted to evaluate and compare the efficacies of nasopharyngoscopy and CT scan in the diagnosis of local failure of external beam radiotherapy (EBRT) for nasopharyngeal carcinoma.

Methods: Total 52 patients of histopathologically proven nasopharyngeal carcinoma treated with external beam radiotherapy (EBRT), were included in this study. For every patient computed tomography (CT), nasopharyngoscopy and nasopharyngeal biopsies were performed 3 months after completion of EBRT.

Results: Three months after completion of EBRT, 9 patients (17.3%) had evident disease on histological examination of biopsies. Nasopharyngoscopy showed 77.78% sensitivity, 93.03% specificity, 70% positive predictive value and 95.24% negative predictive value in diagnosing the residual/recurrence of tumor. There was statistically significant agreement between the endoscopic findings and the histological findings (Kappa reliability coefficient=0.562, $p<0.01$). On the other hand, CT scan showed a 55.56% sensitivity, 39.53% specificity, 16.13% positive predictive value and 80.95% negative predictive value in diagnosing the residual tumor/recurrence. There was no statistically significant agreement between the CT scan findings and the histological findings (Kappa reliability coefficient = 0.038, $p>0.05$).

Conclusion: Nasopharyngoscopy should be considered the primary follow-up tool after radiotherapy of nasopharyngeal carcinoma. CT scan should be reserved for patients with histological or any symptomatic indications. Routine postnasal biopsies are not required.

Keywords: Nasopharyngeal carcinoma; Local failure; Nasopharyngoscopy; CT scan; Biopsy

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Introduction

Nasopharyngeal carcinoma is peculiar among all the head and neck cancers in its marked geographical predilection, highly malignant tumor growth characteristics, special difficulties in detection and staging and high rate of treatment failure despite its radiosensetivity. It is more common in men, with male to female preponderance of 2-3:1. Age of diagnosis shows a bimodal distribution that peaks at 6th decade of life, with a small peak among adolescents in the low to medium incidence area. External Beam Radio Therapy (EBRT) is the only curative treatment modality, radiotherapy alone for early stages and combined chemoradiotherapy for late stages with a dose of 60-70 Gy [1-4]. Despite its radiosensitivity, local residual or recurrent disease is not uncommon. Local residual disease after EBRT has been observed in 8-13% of patients, with a cumulative local failure rate of 21-24% over a 5 year surveillance period [5-6].

Early detection of locoregional failure is crucial for a better chance of salvage, and regular follow-up after completion of primary treatment is recommended. Frequently used methods include manual palpation, rigid nasopharyngoscopy,

nasopharyngeal biopsies and imaging techniques (e.g., CT and MRI).

Thorough examination of the nasopharynx with a fiber-optic nasopharyngoscope is currently considered the most efficient clinical tool [1]. Imaging techniques include Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET). CT scan is the current imaging modality of choice. Post-radiotherapy changes affect the CT and MRI results. CT scan may not be able to differentiate between local failures and postradiotherapy changes, except in the presence of bony erosions. MRI may be promising as a noninvasive method for differentiating radiation fibrosis from local recurrence. However, the signal intensity pattern of the tumor is not specific and may be seen in radiation edema and infection [7, 8]. The disadvantage of PET is that it is optimally undertaken six months after EBRT [9,10,11]. Histopathological examination is the main modality for nasopharyngeal carcinoma detection, but this is expensive and invasive. Hence a minimally invasive and cost-effective test is required which can diagnose recurrence/residual nasopharyngeal carcinoma after EBRT, with good sensitivity and predictive value.

This prospective study was conducted to evaluate and compare the efficacies of nasopharyngoscopy and CT scan in the diagnosis of postradiotherapy local failures in nasopharyngeal carcinoma.

Materials and Methods

Over a 3 year period from April 2010 to January 2013, all patients with histologically proven squamous cell nasopharyngeal carcinoma and selected to receive treatment with EBRT were prospectively included in this study.

Patients less than 25 years of age, patients with distant metastases, previously treated patients and/or inability to comply with study protocol were excluded from the study. Pregnant females and the patients who refused for CT, nasopharyngoscopy or nasopharyngeal biopsy, were also excluded from the study.

52 patients (39 males and 13 females), with a mean age of 54 years (range 29-65 years) fulfilling the inclusion and exclusion criteria were enrolled in the study and delivered EBRT. Before starting EBRT, 16 (30.77%) patients had stage I, 21 (40.38%) had stage II, 13 (25%) had stage III and only 2 (3.8%) had stage IV disease, according to the TNM staging system of American Joint Committee on Cancer (AJCC) [12]. For every enrolled patient, CT, nasopharyngoscopy and nasopharyngeal biopsy were performed 3 months post-treatment. The last day of EBRT was considered as the end of treatment.

Treatment Protocol

All patients were treated with EBRT through two lateral opposing fields and a Lower Anterior Neck (LAN) field on Theratron-780C and 780E ^{60}Co teletherapy machine. The total tumor dose delivered was 66-70 Gy. The dose per fraction was 2 Gy, with 5 daily fractions per week. Concurrent chemotherapy was administered to patients with stage II disease onwards. The chemotherapy regimen was consisting of five to six cycles of injection cisplatin 40mg/m^2 (ceiling dose 50 mg) weekly with premedication and adequate hydration.

Follow-up of the patients was done 3 months after completion of treatment. Contrast enhanced CT scan was performed in every patient. A mass or asymmetry in the nasopharynx in CT scan was considered as positive finding. Nasopharyngoscopy was performed using a rigid endoscope. The nasopharynx was judged to be normal if it appeared to be smooth, and suspicious if growth, nodule, ulcers, submucosal bulges or irregular mucosa were seen. The otolaryngologist was blinded to the radiological findings at the time of examination. The nasopharyngeal biopsy was taken under endoscopic control from the most suspicious area of the nasopharynx. The pathologist was blinded to the endoscopic and CT findings at the time of assessment.

Statistics

The sensitivity, specificity, negative and positive predictive values were calculated for nasopharyngoscopy and CT scan and compared with results of histological examination of nasopharyngeal biopsy specimens. The statistical analysis was done by Kappa reliability test. Value of $p<0.05$ was considered significant. To improve the consistency of results and to eliminate interobserver bias, all the histological, radiological and endoscopic examinations were done by the same pathologist, radiologist and otolaryngologist respectively.

Results

In the 3 months follow-up period after EBRT, 9 patients (17.31%) had residual/recurrent nasopharyngeal malignancy on histological examination. The nasopharyngeal endoscopic appearance was normal in 42 patients (80.77%), of whom only 2 were discovered to have residual/recurrent malignancy on examination of nasopharyngeal biopsies. 10 patients had a suspicious endoscopic appearance; of these, 7 were found to have evidence of malignancy. The

sensitivity, specificity, positive predictive value and negative predictive value of nasopharyngeal follow-up endoscopy were 77.78%, 93.03%, 70% and 95.24% respectively. There was statistically significant agreement between the endoscopic and histological findings (Kappa reliability coefficient=0.562, p<0.001). Table 1 shows the nasopharyngeal endoscopic findings versus the histological findings.

Table 1. Nasopharyngeal endoscopic *vs.* Histological findings

Endoscopy	Histology		Total
	Malignancy	No malignancy	
Suspicious	7	3	10
Normal	2	40	42
Total	9	43	52

CT scan results were suspicious in 31 (59.62%) patients, of whom 5 had histological evidence of disease. Of the 21 patients with normal CT scans, 17 were histologically disease-free. The sensitivity, spectificity, positive predictive value and negative predictive value of CT were 55.56%, 39.53%, 16.13% and 80.95% respectively. There was no statistically significant agreement between the CT and histological findings (Kappa reliability coefficient = 0.038, p=0.785). Table 2 shows the CT findings versus the histological findings.

Table 2. CT *vs.* Histological findings

CT	Histology		Total
	Malignancy	No malignancy	
Suspicious	5	26	31
Normal	4	17	21
Total	9	43	52

Discussion

Because long-term survival can be achieved for a substantial proportion of patients with early locoregional recurrence and useful palliation for those with extensive disease, aggressive salvage treatment is usually advocated. Several approaches can be used successfully, including surgery and re-irradiation by brachytherapy or EBRT. Chemotherapy is generally used in conjugation with local treatment in patients with advanced disease. A significant proportion of these patients can still achieve long-term disease control (up to 87%) and survival (up to 85%) [13-17]. Prognosis for patients with local failure depends on the extent of disease at the time of detection [17-23]. So, early detection and management of post-radiotherapy local residual and recurrent nasopharyngeal carcinoma is very important.

After treatment of nasopharyngeal carcinoma, frequently used follow-up methods include manual palpation, rigid nasopharyngoscopy, nasopharyngeal biopsies and imaging techniques (e.g., CT and MRI). Flexible and rigid fibre-optic endoscopes are the currently accepted clinical tools for examining the nasopharynx. In our study, rigid endoscopy was chosen as our clinical tool. Its sensitivity and specificity for prediction of local failures were 77.78% and 93.03% respectively and its positive and negative predictive values were 70% and 95.24% respectively. The high specificity and negative predictive value imply that it would be unnecessary to pursue further radiological or histological examination. This will reduce patient discomfort and decrease associated morbidity.

Kwong DL et al. reported a low sensitivity (40.4%) and a low positive predictive value (16.3%), and a specificity and negative predictive value of 84.4% and 95% respectively by using flexible endoscopy to detect local failures after nasopharyngeal carcinoma treatment [24]. Our results were much better, which could be explained by the following. First, Kwong DL et al. study had very wide variation in the time period between end of radiotherapy and endoscopic examination, which ranged between 4 and 16 weeks. Second, the outcome of that study depended on the six-week endoscopic findings is very difficult at this time due to radiation-induced mucosal changes; this is clearly shown by the very low sensitivity and positive predictive value, in contrast with the specificity and negative predictive value. Third, we used rigid

endoscopy, which gives better illumination, a wider field, excellent resolution and a sharper image compared with flexible endoscopy; these properties assist detection of subtle residual and recurrent disease [25].

In Ragab SM et al. prospective trial, computed tomography, rigid nasopharyngeal endoscopy and nasopharyngeal biopsies were performed 12 weeks after EBRT to detect local failures after nasopharyngeal carcinoma treatment. Nasopharyngeal endoscopy showed a sensitivity, specificity, positive predictive value and negative predictive value of 66.6%, 95%, 66.6% and 95% respectively. Computed tomography showed a sensitivity, specificity, positive predictive value and negative predictive value of 50%, 45%, 12% and 85.7% respectively [25]. Our results are comparable and better than this trial.

Post-radiotherapy changes like edema, loss of tissue planes and fibrosis may interfere with the detection of recurrent/residual disease. CT scan cannot differentiate between inflammation, post-radiotherapy fibrosis, and recurrent/residual tumor, and thus cannot reliably indicate the presence or absence of recurrent/residual nasopharyngeal carcinoma [26, 27]. On the other hand, it is not ethical to repeat CT scanning during every follow-up visit, since this exposes patients to significant radiation hazards. Its use as a follow-up tool should be reserved for patients with histological or symptomatic indication, rather than being routine.

Histological examination is the gold standard method in the detecting residual and recurrent nasopharyngeal carcinoma. In Ragab SM et al. study, the sensitivity, specificity, positive predictive value and negative predictive value of single, targeted endoscopic biopsy were 83.3%, 100%, 100% and 97.5% respectively, when compared with multiple biopsies [25]. In our study, single targeted endoscopic biopsy was performed as it is cost-effective, less invasive and time-sparing.

Taking biopsies earlier than 3 months post-treatment had showed a high rate of false positive results. Kwong DL et al. reported that 66.5% patients with positive histological findings in the 6th week after radiotherapy achieved spontaneous remission over time and had negative histological findings in subsequent biopsies. Authors also found that 95.4% patients with positive histological findings who achieved spontaneous histological remission had done so by the end of the 10th week [24].

Conclusion

Rigid nasopharyngoscopy should be considered the primary follow-up tool for evaluating postradiotherapy nasopharyngeal carcinoma patients. CT should be reserved for patients with histological or symptomatic indication. Routine postnasal biopsy is not necessary, considering the excellent specificity and negative predictive value of rigid nasopharyngoscopy.

Acknowledgment

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Conflict of Interest

The authors have no conflict of interest in this study.

Authors' Contribution

Puneet Kumar Bagri designed and wrote this article, collected and analyzed the data. Mukesh Kumar Singhal, Daleep Singh and Akhil Kapoor collected the data. Shankar Lal Jakhar, Neeti Sharma, Surender Beniwal, H S Kumar, Ajay Sharma and M R Bardia analyzed the data. All authors read and approved the final manuscript.

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