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ORIGINAL ARTICLE

Local definitive intensity-modulated radiation therapy recommended for patients initially diagnosed with nasopharyngeal carcinoma with distant metastasis after an effective systemic chemotherapy*

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Abstract

Objective The aim of the study was to propose a hypothesis that local definitive intensity-modulated radiation therapy (IMRT) should be recommended for initially diagnosed metastatic nasopharyngeal carcinoma (NPC) and demonstrate its feasibility.

Methods Recently published papers on local definitive radiotherapy for initially diagnosed metastatic NPC were reviewed to propose a hypothesis.

Results Several studies revealed the survival benefits of adding local definitive radiotherapy to the systemic chemotherapy in patients initially diagnosed with metastatic NPC.

Conclusion We suggested that local definitive IMRT should be recommended in patients initially diagnosed with NPC with distant metastasis after an effective systemic chemotherapy, which may possibly prolong their survival time and potentially treat the disease.

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Key words: nasopharyngeal carcinoma (NPC); metastasis; intensity-modulated radiation therapy (IMRT)

Nasopharyngeal carcinoma (NPC) is one of the most common head and neck cancers in southern China. In endemic areas, the NPC incidence is approximately 25–30 per 1 000 000 persons per year [1]. About 4% of patients are initially diagnosed with distant metastasis, especially those with locally advanced disease [2].

Despite the significant progress in long-term disease control in patients with early stage and locally advanced disease, metastatic NPC is still conventionally regarded as incurable. Palliative chemotherapy is the primary and frequently used therapeutic strategy for metastatic NPC. Although chemotherapy yields high objective response rates, the median survival in patients with metastatic NPC is merely 12–20 months after various chemotherapy regimens [3]. Most patients who undergo chemotherapy have persistent locoregional disease. This condition often accelerates disease progression after the first-line systemic chemotherapy. The 5-year overall survival (OS) rate in patients with metastatic NPC is only 20%, which is in contrast to > 80% in patients without metastasis [4]. Therefore, managing NPC patients with metastasis remains a therapeutic challenge.

No consensus is currently available among oncologists with regard to the optimum treatment modality for metastatic patients with initially diagnosed NPC. Radiotherapy has been the mainstay treatment for patients with nonmetastatic NPC; however, its role in patients with metastatic disease remains controversial [5].

The addition of local therapy, such as radiation, to the systemic chemotherapy for metastatic cancer has been practiced for metastatic rectal, esophageal, breast, and lung cancers [6–9]. With the rapidly emerging oncologic concept of using local treatment for limited metastatic disease, several studies recently reported the survival benefit of adding local definitive radiotherapy to systemic chemotherapy in metastatic patients with initially

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diagnosed NPC [10–19].

Hypothesis

In this study, we hypothesized that local definitive intensity-modulated radiation therapy (IMRT) should be recommended after an effective systemic chemotherapy for patients with initially diagnosed NPC who developed distant metastasis. The current systemic chemotherapy merely leads to a short median survival time of 12–20 months, and the radiotherapy dose for the primary tumor and cervical disease is often palliative. This condition fails to prolong the survival time. Recent studies show that patients diagnosed with NPC with distant metastasis who received curative local radiotherapy after an effective systemic chemotherapy had improved survival compared with those who did not.

Discussion and conclusion

Radiotherapy is usually the mainstay treatment for patients with nonmetastatic NPC because of its anatomic location and relatively high radiosensitivity. However, the role of local radiotherapy in NPC patients with metastasis remains unclear.

First, many oncologists consider local radiotherapy unnecessary because of distant metastasis, which signifies clinical incurability. Palliative chemotherapy is currently the most frequently used therapeutic strategy. The single systemic chemotherapy treatment modality for metastatic NPC is largely insufficient, especially for diseases with primary bulky tumor and those that occur close to the critical organs, such as the brainstem, carotid arteries, and optic chiasm. Persistent locoregional disease is often observed in these patients after receiving systemic chemotherapy treatment alone. With disease progression, the primary tumor may cause severe symptoms and complications, such as massive hematuria, severe headache, hearing impairment, blindness, and brainstem injury. These factors will compromise the patients' quality of life and even lead to death. A subgroup of patients with NPC will eventually die of local failure of treatment after a systemic chemotherapy because the oncologists are not concerned of the distant foci [20]. In addition, the current NPC tumor-node-metastasis classification has drawbacks in the M stage, which is still a "catch-all" classification in patients who differ in terms of the specific organs involved and the number and location of lesions in each organ. Subdividing the M1 stage in patients with metastatic NPC may help oncologists stratify patients according to prognosis and guide treatment decisions. Many reports showed that a single lesion confined to an isolated organ or oligometastasis is associated with prolonged survival time compared with widespread metastatic lesions in isolated or multiple locations [13–16]. Moreover, many reports showed that selective patients with NPC and limited metastatic lesions are potentially treated using the appropriate combination of systemic chemotherapy and definitive local radiotherapy [10–19]. Zou *et al* successfully subdivided the M1 stage into three groups: M1a, oligometastasis without liver involvement; M1b, multiple metastases without liver involvement; and M1c, liver involvement irrespective of metastatic lesions. The 3-year OS was 54.5%–72.8% for M1a, 34.3%–41.6% for M1b, and 22.6%–23.6% for M1c [13]. Shen *et al* developed an M categorization system based on factors related to the prognosis of patients with metastatic NPC. They defined the following groups based on liver involvement and number of metastatic lesions: M1a, single lesion confined to an isolated organ or location except the liver, which had the best prognosis; M1b, single lesion in the liver and/or multiple lesions in any organs or locations except the liver, which had the modest prognosis; and M1c, multiple lesions in the liver, which had the worst prognosis [16]. These studies indicated that patients with more than three metastatic sites had significantly poorer OS than those with three or fewer metastatic sites. Compared with liver metastases, lung or bone metastasis was demonstrated as a positive factor of survival, which may lead to long-term survival. The reason of poor survival in liver metastasis may be related to the rich blood supply of the liver and the low response rate to the systemic chemotherapy. Therefore, local radiotherapy should be included after effective systemic chemotherapy, especially in patients with single or limited metastatic sites without liver involvement.

Second, several oncologists are concerned about radiotherapy-related toxicities, which might compromise the patients' quality of life or even shorten the patients' survival time. However, this treatment concept and concern are from the conventional two-dimensional (2D) radiotherapy era. With the development of radiobiology and radiophysics, IMRT has been used worldwide because of its improved tumor target conformity, good local control, and low radiation side effects [21]. The conventional 2D radiotherapy has already been replaced by IMRT in NPC treatment. Therefore, the role of IMRT in patients newly diagnosed with metastatic NPC should be re-evaluated.

The significance of local definitive radiotherapy for patients initially diagnosed with metastatic NPC has been evaluated in many studies. Verma *et al* [10] used the National Cancer Database (NCDB) to analyze the outcomes in patients with metastatic NPC who received chemoradiotherapy versus those who received chemotherapy alone. Among the 555 patients, 296 (53%) underwent chemotherapy alone, and 259 (47%) received definitive chemoradiotherapy. The median OS rates in

the chemotherapy alone and chemoradiotherapy groups were 13.7 and 25.8 months, respectively ($P < 0.01$). With the multivariate analysis, the treatment with additional radiotherapy was independently predicted to significantly improve the OS time ($P < 0.01$). Rusthoven *et al* [11] also used the NCDB to evaluate the outcomes in patients with metastatic NPC receiving chemotherapy with and without local radiotherapy. In this largest reported analysis on chemotherapy with and without local radiotherapy for metastatic NPC, 718 NPC patients with metastasis were identified (39% chemotherapy alone and 61% chemotherapy + radiotherapy). At a median follow-up of 4.4 years, radiotherapy was found to be associated with improved survival time (median OS of 21.4 vs. 15.5 months; 5-year OS of 28% vs. 10%; $P < 0.001$). Long-term survival of > 10 years was only observed in the radiotherapy group. This result supported the strategies incorporating the local radiotherapy with chemotherapy for metastatic NPC. Hu *et al* [12] used the Surveillance Epidemiology and End Results database to examine the role of radiotherapy in treating metastatic NPC and identified 679 patients (66% chemotherapy + radiotherapy and 34% chemotherapy alone). Radiotherapy was associated with significantly improved OS [hazard ratio (HR): 0.50, $P < 0.001$] and cancer-specific survival (HR: 0.50, $P < 0.001$).

Third, in clinical practice, some oncologists merely provide palliative radiation dose to the primary tumor of NPC with distant metastasis. Palliative radiotherapy aims to control local symptom and improve the quality of life but not prolong the survival time. In the analysis of 718 NPC patients with metastatic reported by Rusthoven *et al* [11], radiotherapy dose was found to be an independent prognostic factor both as a continuous and categorical variable, with OS benefits observed among patients receiving ≥ 50 Gy. Patients receiving ≥ 70 Gy achieved the longest survival time. In a retrospective study by Hu *et al* [12], most patients with distant metastasis completed the full course of curative dose of IMRT (> 70 Gy) with estimated median OS time of 31.2 months. These studies indicated that using definitive IMRT combined with systemic chemotherapy to treat primary tumor might prolong the survival time in patients newly diagnosed with metastatic NPC.

The mechanisms underlying the survival benefit of the local definitive radiotherapy on metastatic NPC remains unclear. First, eliminating the primary tumor burden of NPC close to the critical organs could reduce the probability of death by uncontrolled local disease progression. Second, the primary tumor volume is closely related with survival rates in NPC and is a significant prognostic indicator of NPC treatment [22–25]. Local definitive radiotherapy reduces the primary tumor volume and leads to excellent local disease control and further survival benefit. Finally, other potential mechanisms in favor of radiotherapy for primary tumors could be the removal of immunosuppressive cytokines and enhancement of immune recognition [26].

In conclusion, we suggested that local definitive IMRT should be recommended in patients with initially diagnosed NPC with distant metastasis after an effective systemic chemotherapy to possibly prolong their survival time and potentially treat the disease.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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