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Role of Locoregional Treatment after Good Response to Systemic Chemotherapy in Metastatic Nasopharyngeal Cancer : A Case Report

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원격 전이가 동반된 비인두암에서 항암화학요법 후 치료 반응을 보인 환자에 대한 국소치료의 역할 : 증례보고

서울대학교 의과대학 방사선종양학교실,[1] 내과학교실,[2] 암연구소,[3] 서울대학교 의학연구원 방사선의학연구소[4]
이주호[1] · 우홍균[1,3,4] · 허대석[2]

= 국문초록 =

원격 전이된 비인두암 환자에서 주요한 치료 방법은 고식적 항암화학치료에 국한되어왔다. 그러나 적극적인 항암화학치료로 비인두암 환자 중 많은 환자에서 치료 반응을 보이며, 치료 반응을 보인 환자군에서는 국소 제어가 중요한 문제가 된다. 본 저자들은 원격 전이 된 환자 1예를 보고하고자 한다. 환자는 큰 크기의 다발성 전이가 있었으나 항암화학요법으로 관해 상태를 보였다. 이후 공고화 항암화학방사선요법을 추가하였고 현재 30개월 간 무병상태이다. 원격전이된 비인두암에서 공고화 항암화학방사선 요법의 역할에 대하여 문헌 고찰을 통해 논의하고자 한다.

중심 단어 : 비인두암 · 원격 전이 · 항암화학방사선 요법.

Introduction

Most patients with nasopharyngeal cancer(NPC) present with non-metastatic stage.[1)] The standard treatment as chemo-radiotherapy(CRT) can achieve a high probability of disease control rate up to 70% even in locally advanced NPC.[2)] However, 6% of patients with NPC have distant metastasis at presentation.[1)] The main treatment for patients with metastasis is limited in palliative chemotherapy.[2)]

However, aggressive chemotherapy including cisplatin achieves substantial major and complete response of 70% and 20% in metastatic NPC.[3,4)] As response increase due to the development of effective chemotherapy, locoregional control can be a valuable issue for patients showing major or complete response after initial systemic treatment.[5,6)] We report on a case with metastatic NPC who underwent aggressive systemic treatment followed by concurrent CRT with definitive aim, and suggest a possibility of this approach for a cure in the responsive subgroup of metastatic NPC.

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Case Report

An 18-year-old male patient presented with palpable mass in the left neck area. He was previously healthy without comorbidities. He first noticed the slowly growing mass two years

prior to visiting the otolaryngologist. On physical examination, multiple enlarged lymph nodes were palpated. On the laryngoscopic examination, an exophytic mass was observed in the nasopharynx. A punch biopsy was performed, and the mass was diagnosed as nasopharyngeal undifferentiated carcinoma with positive Epstein-Barr virus. A neck computed tomography(CT) scan with contrast and fluorine-18 fluorodeoxyglucose(F-18 FDG) positron emission tomography (PET)/CT scan were performed to evaluate the extent of disease (Fig. 1). A slightly enhanced mucosal thickening without invasion to adjacent structure was observed in the nasopharynx. The multiple enlarged lymph nodes were observed in the bilateral neck area including supraclavicular fossa, and the length of the largest lymph node was 6.2 cm. Increased FDG uptakes were observed at the same lesion on the CT scan. In addition, abnormal absorption of the F-18 FDG uptakes existed in the liver, left upper lung, portocaval lymph node, skeletal bones including skull base, spines, sacrum, sternum, pelvic bones. An abdomen CT scan with contrast also confirmed the metastatic lesions observed in PET/CT scan. According to the American Joint Committee on Cancer staging system 7th edition, this case was classified as stage

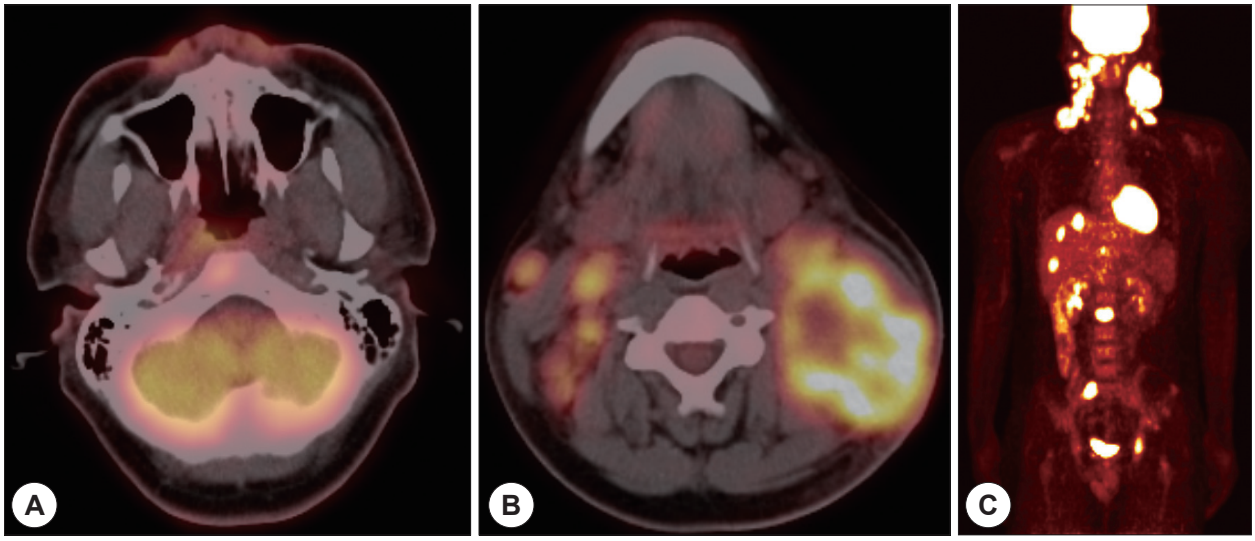

Fig. 1. Fluorine-18 fluorodeoxyglucose(F-18 FDG) at positron emission tomography(PET)/Computed tomography scan at diagnosis. Abnormal F-18 FDG uptakes in the right nasopharynx(A), neck nodes(B) and distant organs(C) were observed.

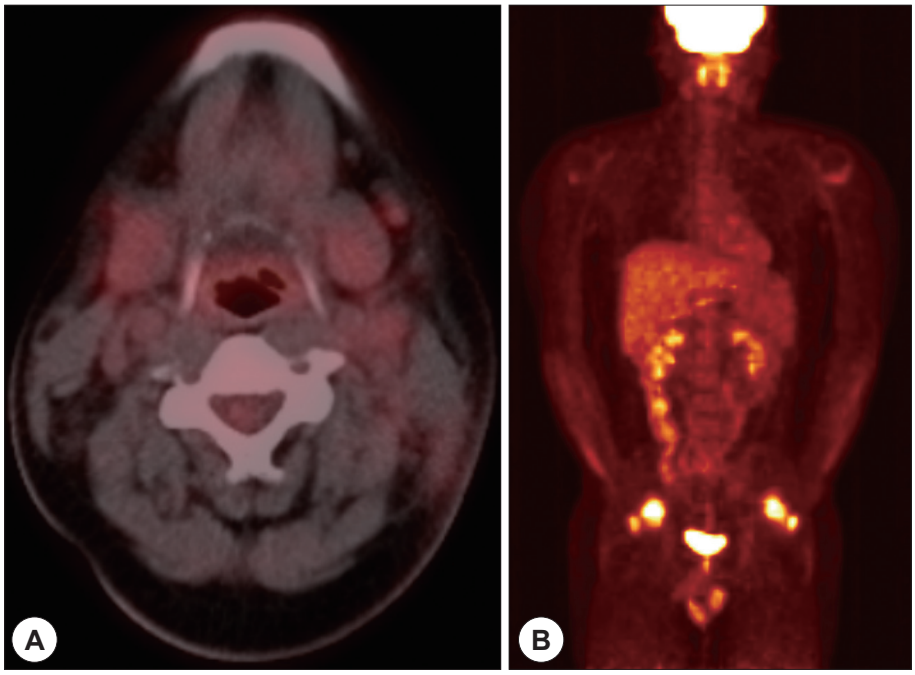

Fig. 2. Fluorine-18 fluorodeoxyglucose(F-18 FDG) at positron emission tomography(PET)/Computed tomography scan after 6 cycles of chemotherapy with docetaxel, cisplatin, and 5-fluorouracil(A). Faint F-18 FDG uptakes remained at the neck lymph nodes(B). However, the other abnormal uptakes of distant metastatic lesions were disappeared after chemotherapy.

IVC, NPC. Chemotherapy was performed after initial diagnosis. The first chemotherapy regimen consisted of intravenous docetaxel(75 mg/m^2) and cisplatin(75 mg/m^2). After the first chemotherapy, the size of the largest neck lymph node was decreased from 6.2 cm to 5.6 cm on the following neck CT scan. To enhance treatment efficacy, 5- fluorouracil was added to chemotherapy regimen. Additional 6 cycles of chemotherapy were performed with docetaxel(70 mg/m^2), cisplatin(40 mg/m^2), and 5-fluorouracil(1,200 mg/m^2)(TPF) in 3 daily doses for each cycle. A PET/CT scan was repeated to evaluate the treatment response after one cycle of DP and six cycles of TPF chemotherapy. The maximal length of the residual lymph nodes was 2.4 cm. Abnormal F-18 FDG uptakes were decreased at nasopharynx and bilateral neck lymph node. The metastatic lesions were disappeared, and any abnormal uptake was not found except primary and regional lymph nodes(Fig. 2). Re-evaluation through a fine needle aspiration to residual neck nodes was performed, and the pathologic result was negative. His case was discussed at the head and neck oncology multidisciplinary meeting, where it was decided consolidation concurrent CRT to the nasopharynx and regional area. The patient was simulated in a supine position with a thermoplastic head mask. The gross tumor volume (GTV) encompassed the gross residual lesion at nasopharynx and neck lymph nodes. Clinical target volume-reduced field(CTV-RF) comprised GTV plus 15 mm isotropic margin. Clinical target volume-large field(CTV-LF) encompassed the nasopharynx, para-nasopharynx, skull base, pterygopalatine fossa, nasal cavity, posterior one-third of the sphenoid sinus, posterior maxillary sinus, and bilateral neck nodes level II, III, IV, V. Additional margin 3 mm from CTV-LF was adopted for planning target volume-large field(PTV-LF), and additional margin from CTV-RF was not for planning target volume-reduced field(PTV-RF). Simultaneous integrated boost technique with intensity modulated radiotherapy was applied to him. The dose fractionation was 2.25 Gy/fraction for PTV-RF and 1.8 Gy/fraction for PTV-LF with 30 fractionations. The concurrent chemotherapy was intravenous cisplatin 35 mg/m^2 every week. Grade 3 acute mucositis occurred during concurrent CRT. However, he completed concurrent CRT as scheduled. In the 30 months of follow-up since the initiation of chemotherapy, there have been no signs of recurrence, and no abnormal lesion has been observed on image studies.

Discussion

The present case with undifferentiated NPC had bulky tumor size and multiple metastases at the presentation but achieved complete response after combination chemotherapy with TPF. NPC, especially undifferentiated type, is more responsive to chemotherapy than other upper aerodigestive tract cancer.[2,7] In addition, neoadjuvant TPF chemotherapy achieved a high level of major response with about 90% in locally advanced NPC[8] and better survival ourcome than the combination of cisplatin and fluouracil in squamous cell carcinoma of the head and neck.[9] The substantial patients who received aggressive chemotherapy for metastatic NPC could have a period with clinically disease-free status.[3] Fandi and colleagues presented a small cohort of 20 patients with metastatic NPC could have long-term disease free survival (82 to 190 months) after complete response of chemotherapy.[7] The data of Fandi et al. suggested a subgroup with complete response could be cured despite initial advanced stage. Those who have responsive nature to anti-cancer treatment might need intensive approach to enhance a cure rate.

The present case underwent aggressive chemotherapy followed by CRT to nasopharynx and regional area. After major response after chemotherapy, we recommended local CRT because initial bulky tumor size was reported as a prognosticator predicting worse locoregional control.[10] In addition, the patient with young age, good performance, and no comorbidity was expected to have long survival time if nasopharyngeal cancer is controlled. When distant disease control can be secured after chemotherapy in selected patients with metastatic NPC, local control in those patients could be a notable issue to maintain long-term disease control.

Two retrospective studies suggested the potential role of local disease control for metastatic NPC.[5,6] The first retrospective study studied 105 patients with metastatic NPC.[6] The all patients underwent radiotherapy following systemic chemotherapy. However, the practice of radiotherapy was heterogeneous, and additional local treatment to metastatic foci was followed by the physicians' discretion. The data reported that radiation dose greater than 65 Gy to the primary region was prognostic factor for overall survival(5-year overall survival, 50% versus 17%), but multivariate analysis was not performed. The second retrospective study compared chemotherapy alone with chemotherapy followed by radiotherapy.[5] It concluded additional radiotherapy is independent prognostic factor for overall survival(5-year overall survival 38% versus 0%). However the criteria of patient selection for additional local treatment were not described in those two studies. Statistical bias might affect the results due to the nature of retrospective methods. Although those studies suggested the potential role of local disease control for metastat-

ic nasopharyngeal cancer, aggressive local treatment for curative aim could not be a reasonable option unless systemic disease is controlled with systemic chemotherapy.

Patient selection might be crucial to find patients who might gain benefit from additional local CRT. In the other types of chemosensitive and radiosensitive tumors, consolidation radiotherapy with or without concurrent chemotherapy has been applied to patients showing good response to initial chemotherapy. This response-based consolidation radiotherapy presented significant benefit of disease control or survival in small cell lung cancer, lymphoma, and germ cell tumor.[11-13] In Hodgkin's lymphoma, the benefit of consolidation radiotherapy was particularly profound in patients with high risk of local recurrence such as bulky tumor size[12] as the present case. The residual risk of local recurrence, as well as treatment response, general health status of patients, and the other risk factors[14,15] might also need to be considered for the patient selection. However, evidence is insufficient for consolidation treatment based on response in metastatic NPC, and retrospective studies described above had no clue for the patient selection.

Based on this case, we suggest a possibility that local CRT following chemotherapy for metastatic NPC might be beneficial to patients showing good response after initial chemotherapy. Prospective studies are necessary to evaluate this approach as a standard treatment strategy and to search the appropriate criteria of patient selection for aggressive local treatment.

References

1) Lee AW, Poon YF, Foo W, Law SC, Cheung FK, Chan DK, et al. *Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976-1985: Overall survival and patterns of failure. Int J Radiat Oncol Biol Phys. 1992;23:261-270.*
2) Loong HH, Ma BB, Chan AT. *Update on the management and therapeutic monitoring of advanced nasopharyngeal cancer. Hematol Oncol Clin North Am. 2008;22:1267-1278, x.*
3) Ji JH, Yun T, Kim SB, Kang JH, Park JC, Cho IS, et al. *A prospective multicentre phase II study of cisplatin and weekly docetaxel as first-line treatment for recurrent or metastatic nasopharyngeal cancer(KCSG HN07-01). Eur J Cancer. 2012;48: 3198-204.*
4) Song CH, Wu HG, Heo DS, Kim KH, Sung MW, Park CI. *Treatment outcomes for radiotherapy alone are comparable with neoadjuvant chemotherapy followed by radiotherapy in early-stage nasopharyngeal carcinoma. Laryngoscope. 2008;118:663-670.*
5) Lin H, Cai X, Jin T, Guo L, Wang H, Sun R, et al. *Chemotherapy plus radiotherapy makes curability a possibility in nasopharyngeal carcinoma patients with distant metastasis at diagnosis. Head Neck Oncol. 2013;5:1.*
6) Lin S, Tham IW, Pan J, Han L, Chen Q, Lu JJ. *Combined high-dose radiation therapy and systemic chemotherapy improves survival in patients with newly diagnosed metastatic nasopharyngeal cancer. Am J Clin Oncol. 2012;35:474-479.*
7) Fandi A, Bachouchi M, Azli N, Taamma A, Boussen H, Wibault P, et al. *Long-term disease-free survivors in metastatic undifferentiated carcinoma of nasopharyngeal type. J Clin Oncol. 2000;18:1324-1330.*
8) Kong L, Hu C, Niu X, Zhang Y, Guo Y, Tham IW, et al. *Neoadjuvant chemotherapy followed by concurrent chemoradiation for locoregionally advanced nasopharyngeal carcinoma: Interim results from 2 prospective phase 2 clinical trials. Cancer. In press 2013.*
9) Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, et al. *Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med. 2007; 357:1705-1715.*
10) Schrijvers D, Van Herpen C, Kerger J, Joosens E, Van Laer C, Awada A, et al. *Docetaxel, cisplatin and 5-fluorouracil in patients with locally advanced unresectable head and neck cancer: A phase I-II feasibility study. Ann Oncol. 2004;15:638-45.*
11) Jeremic B, Shibamoto Y, Nikolic N, Milicic B, Milisavljevic S, Dagovic A, et al. *Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: A randomized study. J Clin Oncol. 1999;17:2092-2099.*
12) Laskar S, Gupta T, Vimal S, Muckaden MA, Saikia TK, Pai SK, et al. *Consolidation radiation after complete remission in Hodgkin's disease following six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy: Is there a need? J Clin Oncol. 2004;22:62-68.*
13) Kretschmar C, Kleinberg L, Greenberg M, Burger P, Holmes E, Wharam M. *Pre-radiation chemotherapy with response-based radiation therapy in children with central nervous system germ cell tumors: A report from the Children's Oncology Group. Pediatr Blood Cancer. 2007;48:285-291.*
14) Patil V, Noronha V, Joshi A, Muddu Krishna V, Juvekar S, Pantvaidya G, et al. *Is There a Limitation of RECIST Criteria in Prediction of Pathological Response, in Head and Neck Cancers, to Postinduction Chemotherapy? ISRN Oncol. 2013;2013:259154.*
15) Fang WJ, Lam KO, Ng SC, Choi CW, Kwong DL, Zheng SS, et al. *Manual contouring based volumetric evaluation for colorectal cancer with liver limited metastases: A comparison with RECIST. Asian Pac J Cancer Prev. 2013;14:4151-4155.*