CASE REPORT

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Pediatric nasopharyngeal cancer with repeated oligometastases involving the bone, liver and distant lymph nodes who achieved cure after radiotherapy

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ABSTRACT

Systemic chemotherapy is a standard treatment for Stage IVc nasopharyngeal carcinoma (NPC). Stage IVc NPC patients with oligometastases have a better prognosis, and local therapy has an important role in further development of the disease. However, the efficacy of local therapy to the metastases in patients with multiple-site and/or multiple-organ metastases is limited due to the aggressive behavior of the tumor. We report a NPC case in a pediatric patient with repeated oligometastases involving the bone, liver and distant lymph nodes who achieved 10-year disease free status after initial chemotherapy and radiotherapy to all the metastases. This very rare case demonstrated that radiotherapy to oligometastatic lesions have a potential to cure repeated oligometastases which involved multiple-organ metastases in a pediatric NPC with stage IVc.

Keywords: nasopharyngeal, bone metastasis, radiotherapy, oligometastases, head and neck

Abbreviations:
NPC: nasopharyngeal carcinoma
OS: overall survival
CT: computed tomography
MRI: magnetic resonance imaging

INTRODUCTION

As most cases of stage IVc nasopharyngeal carcinoma (NPC) are not curable, the standard management of these patients has been systemic chemotherapy. However, recent treatment results in a large number of patients with stage IVc NPC indicated that the outcomes are heterogeneous

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with a wide range of survival.[1-3] Hellmann et al defined the term "oligometastases" as a limited metastasis with a maximum of 3–4 clinically detectable metastases.[4] Patients with oligometastases have a better prognosis, and local therapy (i.e. radiotherapy and surgery) has an important role in further development of the disease.[5-11] Tian et al retrospectively analyzed the patients initially diagnosed with stage IVc NPC, and local therapy to metastases yielded significantly better overall survival (OS) rate, while patients with ≧6 lesion metastases and multiple-organ metastases showed poor OS rates.[12] Therefore, the efficacy of local therapy to the metastases in patients with multiple-site and/or multiple–organ metastases may be limited, and cure or long-term survival usually cannot be achieved in patients with those factors. We describe herein the rare pediatric case with stage IVc NPC with repeated oligometastases involving the bone, liver and para-aortic lymph nodes who achieved over 10 years disease-free survival time after radiotherapy to all the metastatic lesions.

CASE PRESENTATION

A 15-year-old woman with no significant past medical history presented with a 3-month history of a painless right neck lump. The Computed Tomography (CT) images and Magnetic Resonance Imaging (MRI) showed a nasopharyngeal tumor lesion involving the base of skull, multiple right side lymph nodes swelling of the neck and a solitary left side lymph node swelling of the left upper jugular area (Fig. 1a and 1b). Biopsy of the primary confirmed the diagnosis of undifferentiated carcinoma (Fig. 2). Chest CT and bone scintigraphy demonstrated a solitary bone metastasis of the sternum (Fig. 1c). Chest and abdominal CT did not show disease elsewhere. She was initially staged as T4N2cM1. She was commenced on carboplatin and infusional fluorouracil chemotherapy. Objective tumor response based on CT after one cycle of the chemotherapy was stable disease. Although further cycles of the chemotherapy were recommended, patients and family refused the continuation of the chemotherapy. Three months after the chemotherapy, the enlargement of the tumor was recognized. Definitive radiotherapy for primary and lymph nodes metastases (72Gy/60 fr., two daily fractions, with a 6-hour interval, of radiation of 1.2Gy), whole neck irradiation as elective neck irradiation (43.2Gy/36fr.), and the solitary bone metastasis of the sternum (40.8Gy/17fr.) was enforced (Fig. 3a). Concurrent chemotherapy of daily carboplatin (25mg/m^2) during radiotherapy was also performed.

Four months after the chemoradiotherapy, painful bone metastases of the sacrum and left femur were recognized on CT (Fig. 1d and 1e). Radiotherapy for the bone metastases of the sacrum (48Gy/18fr.) and left femur (30Gy/10fr.) was enforced (Fig. 3b and 3c). Six months after the radiotherapy to the bones, a solitary liver metastasis, 4cm in size, was seen on CT (Fig. 1f). Because the other recurrence or metastasis was not recognized in the neck, chest, abdominal and pelvic CT and bone scintigraphy, radiotherapy for the solitary liver metastasis (60Gy/40fr., two daily fractions, with a 6-hour interval, of radiation of 1.5Gy) was performed (Fig. 3d). Although concurrent chemotherapy of docetaxel during the radiotherapy was planned, infusion reaction occurred in the initial administration and the chemotherapy was discontinued. Three month after the radiotherapy to the liver metastasis, a solitary paraaortic lymph node metastasis, 2 cm in size, was detected on CT (Fig. 1g). The other recurrences nor metastasis was not recognized on neck, chest, abdominal and pelvic CT. Salvage radiotherapy for the paraaortic lymphnode metastasis (42Gy/21fr.) was administrated (Fig. 3e). Eight months after the radiotherapy to paraaortic lymphnode metastasis at the level of right renal hilus, a solitary paraaortic lymph node metastasis, 3 cm in size, at the level of lower pole of the right kidney was seen (Fig. 1h). No other metastases nor recurrence were detected on neck, chest, abdominal

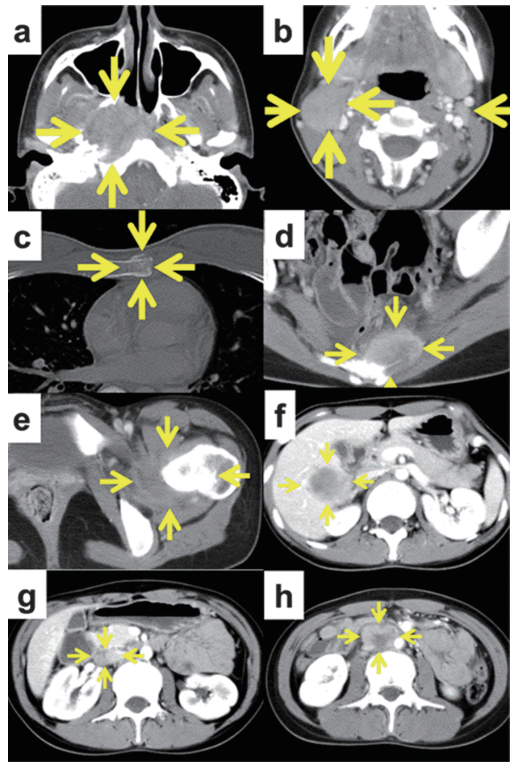

Fig. 1 Imaging features
A huge nasopharyngeal tumor extending to the skull base (a), cervical lymphnode metastases (b) and solitary bone metastasis of the sternum (c) before the initial chemoradiotherapy. Bone metastases of the sacrum (d) and left femur (e) were seen 4 months after the initial chemoradiotherapy. Solitary liver metastasis emerged 11 months after the initial chemoradiotherapy (f). Solitary paraaortic lymph node metastasis at the revel of right renal hilus was recognized 14 months after the initial chemoradiotherapy (g). Solitary paraaortic lymph node metastasis at the level of lower pole of the right kidney occurred 24 months after the initial chemoradiotherapy (h).

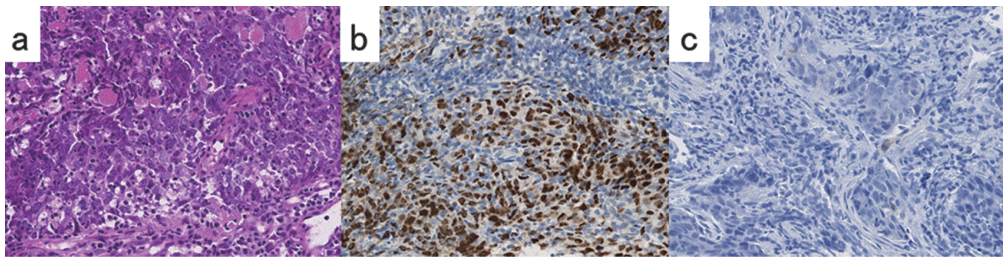

Fig. 2 Histological and immunohistological features of the nasopharyngeal biopsy
Fig. 2a: Microscopy shows undifferentiated carcinoma of nasopharynx (H&E × 400).
Fig. 2b: The carcinoma cells were positive for Epstein-Barr virus-encoded ribonucleic acid in-situ hybridization (×400).
Fig. 2c: P16 immunohistochemical staining in the carcinoma cells was negative (×400).

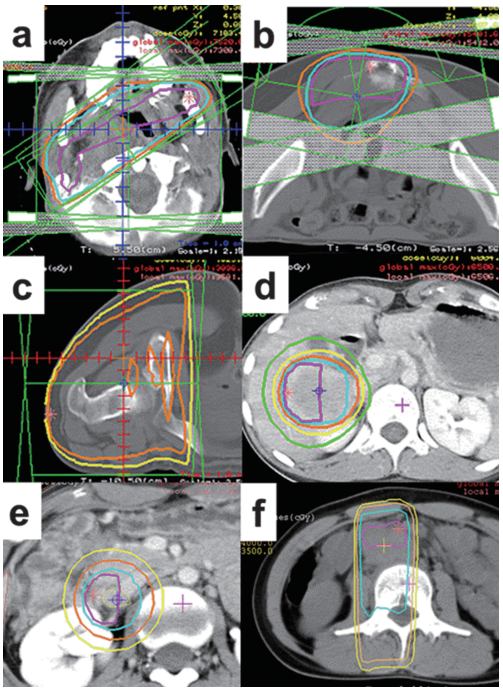

Fig. 3 CT images with radiation dose distribution
(a) For the primary nasopharyngeal tumor, magenta and orange lines denote 72 and 60 Gy, respectively. (b) For the bone metastasis of the sacrum, magenta and orange lines denote 40 and 30 Gy, respectively. (c) For the bone metastasis of the left femur, orange and yellow lines denote 30 and 25 Gy, respectively. (d) For the solitary liver metastasis, magenta and orange lines denote 60 and 50 Gy, respectively. For the paraaortic lymphnode metastases at the revel of right renal hilus (e) and lower pole of the right kidney (f), magenta and orange lines denote 50 and 40 Gy, respectively.

and pelvic CT. Again, salvage radiotherapy for the paraaortic lymphnode metastasis (50Gy/25fr.) was performed (Fig. 3f). The irradiated field could be planned without overlapping the previous irradiated field in the paraaortic lymph node area. No further any treatments were administrated. Follow-up clinical examination and CT was performed at 4-month intervals during the first year after the last salvage radiotherapy, at 6-month intervals during the second, third and fourth years, and thereafter 12-month intervals. No recurrence nor metastasis had been recognized for ten years of follow-up after the last radiotherapy, and follow-up was terminated with no evidence of the disease (Fig. 4). For acute toxicity, Grade2 mucositis, Grade 1 dermatitis and Grade 1 diarrhea was seen during radiotherapy. For late toxicity, Grade 2 xerostomia was recognized.

DISCUSSION

The current case with stage IVc NPC, refusing the continuation of the systemic chemotherapy, could be salvaged after the repeated oligometastases were treated with radiotherapy as they arose. This very rare case is considered to be significant not only fostering discussion for an approach for oligometastatic NPC but also bringing attention to the possibility of cure.

NPC is an uncommon malignancy in children, and treatment recommendations for pediatric

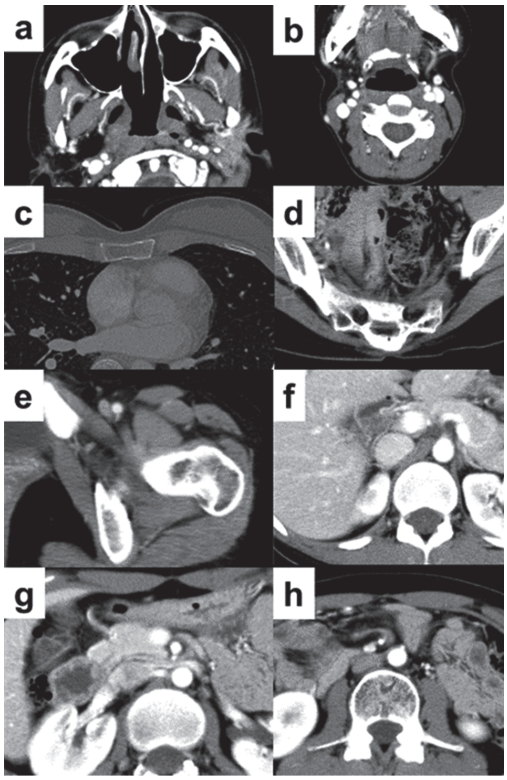

Fig. 4 CT images at 10-year after the last radiotherapy
The patient maintained complete responses in the primary nasopharyngeal tumor (a) and cervical lymph node metastases (b), the bone metastases of the sternum (c), sacrum (d) and left femur (e), liver metastasis (f), and paraaortic lymphnode metastases at the revel of right renal hilus (g) and lower pole of the right kidney (h) on CT images at 10-year after the last radiotherapy.

NPC follow guidelines established for adults.[13] Several studies have analyzed the treatment outcomes of NPC in pediatric patients; chemoradiotherapy resulted in survival rates of 60% to 91%.[14,15] Retrospective cohort study using the National Cancer Data Base of the Unites States indicated that pediatric patients with NPC had a decreased mortality risk relative to adults.[16] Cheuk et al reported that the outcome of children with NPC improved over the past 4 decades with the use of cisplatin-based chemotherapy and higher radiotherapy doses.[13] However, clinical reports for pediatric patients with stage IVc NPC was rarely reported. Retrospective study for 59 pediatric patients with NPC only included 2 patients with stage IVc.[13]

Complete response rate after platinum based chemotherapy in patients with metastatic NPC was ranged from 8 to 17%, median progression-free survival time was ranged from 6 to 9 months, and median overall survival time was ranged from 11 to 28 months.[17] More than and equal to 5 chemotherapy cycles was associated with better overall survival times in patients with metastatic NPC.[12] As mentioned in the introduction, local therapy to the metastatic lesions and radiotherapy to the nasopharynx could be selected in the patients with initially diagnosed stage IV NPC with oligometastases, and long term survival is expected in such patients.

In the current case, initial chemotherapy was insufficient as only one cycle. Two sites of painful bone metastases were recognized only 4 months after the completion of the concurrent

chemoradiotherapy for the primary region and the solitary bone metastasis. Therefore, palliative radiotherapy dose fractionation was selected. After that, three-time of repeated solitary metastasis appeared and were treated with salvage radiotherapy dose fraction as they arose, because neither recurrence of the radiated lesions nor occurrence of multiple metastases was recognized. Total 5 sites of repeated oligometastases had appeared for 2 years after initial treatments (Fig. 5). However, for ten-year follow up, surprisingly, neither recurrence nor metastasis has occurred since last radiotherapy.

This extremely rare case with multiple-organ metastases can be cured after radiotherapy. As factors to be considered, firstly, non-keratinizing squamous cell carcinoma and undifferentiated carcinoma, which pathogeneses are closely associated with Epstein-Barr virus infection, are known as higher radiosensitive tumor in comparison with keratinizing squamous cell carcinoma.[18] In previous reports in NPC patients, primary tumor control rates after radiotherapy were 29% in patients with keratinizing squamous cell cancers and 79% in those with non-keratinizing squamous cell carcinoma and undifferentiated carcinoma.[19] In the current case, the histology of the undifferentiated carcinoma could contribute to achieve good local control of the tumor. Previous review articles indicated that local control of oligometastatic lesions may slow or prevent further metastatic progression.[20,21] Secondly, we speculate that radiotherapy-induced immunogenic effects may play a role in the suppression of metastases. Recent reports demonstrated that ionizing radiation induces an immunogenic tumor cell death to distant, non-irradiated lesions, through tumor-specific cytotoxic T lymphocyte responses.[22,23] In the current case, repeated radiotherapy to the metastases might suppress the clinical expression of micrometastasis. The response to treatment and the host immune status may be key factors to the clinical relevance of micrometastases. Further accumulations of the cases with oligometastatic disease who achieved cure are needed to explore these factors.

In summary, we reported a very rare case of nasopharyngeal cancer with repeated oligometastases in longitudinal course who achieved more than ten year of disease-free survival time after radiotherapy to all the metastases. The current rare case is very significant not only from a clinical perspective, bringing attention to the importance of radiotherapy for repeated oligometastases in pediatric stage IVc NPC, but also in fostering discussion of the possibility of cure.

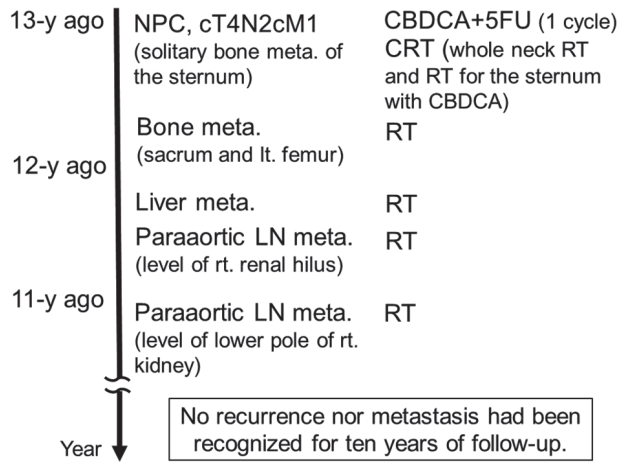

Fig. 5 Overview of the disease time course and treatment
NPC: nasopharyngeal carcinoma, CBDCA: carboplatin, CRT: chemoradiotherapy, LN: lymph node, RT: radiotherapy.

DISCLOSURE

The authors declare no conflicts of interest associated with this manuscript.

REFERENCES

1) Chua ML, Wee JT, Hui EP, Chan AT. Nasopharyngeal carcinoma. *Lancet*. 2016;387(10022):1012–1024.
2) Hui EP, Leung SF, Au JS, et al. Lung metastasis alone in nasopharyngeal carcinoma: a relatively favorable prognostic group. A study by the Hong Kong Nasopharyngeal Carcinoma Study Group. *Cancer*. 2004;101(2):300–306.
3) Pan CC, Lu J, Yu JR, et al. Challenges in the modification of the M1 stage of the TNM staging system for nasopharyngeal carcinoma: a study of 1027 cases and review of the literature. *Exp Ther Med*. 2012;4(2):334–338.
4) Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. 1995;13(1):8–10.
5) Rades D, Dziggel L, Janssen S, Blanck O, Hornung D, Schild SE. A survival score for patients receiving stereotactic radiosurgery alone for brain metastases from breast cancer. *Anticancer Res*. 2016;36(3):1073–1076.
6) Janssen S, Rades D. Primary breast cancer with synchronous metastatic disease: indications for local radiotherapy to the breast and chest wall. *Anticancer Res*. 2015;35(11):5807–5812.
7) Pasqualetti F, Montrone S, Vivaldi C, et al. Stereotactic body radiotherapy in patients with lung oligometastases from colorectal cancer. *Anticancer Res*. 2017;37(1):315–319.
8) Niibe Y, Yamashita H, Sekiguchi K, et al. Stereotactic body radiotherapy results for pulmonary oligometastases: a two-institution collaborative investigation. *Anticancer Res*. 2015;35(9):4903–4908.
9) Palma DA, Louie AV, Rodrigues GB. New strategies in stereotactic radiotherapy for oligometastases. *Clin Cancer Res*. 2015;21(23):5198–5204.
10) Planchard D, Soria JC, Michiels S, et al. Uncertain benefit from surgery in patients with lung metastases from breast carcinoma. *Cancer*. 2004;100(1):28–35.
11) McDonald ML, Deschamps C, Ilstrup DM, Allen MS, Trastek VF, Pairolero PC. Pulmonary resection for metastatic breast cancer. *Ann Thorac Surg*. 1994;58(6):1599–1602.
12) Tian YH, Zou WH, Xiao WW, et al. Oligometastases in AJCC stage IVc nasopharyngeal carcinoma: a subset with better overall survival. *Head Neck*. 2016;38(8):1152–1157.
13) Cheuk DK, Billups CA, Martin MG, et al. Prognostic factors and long-term outcomes of childhood nasopharyngeal carcinoma. *Cancer*. 2011;117(1):197–206.
14) Mertens R, Granzen B, Lassay L, Gademann G, Hess CF, Heimann G. Nasopharyngeal carcinoma in childhood and adolescence: concept and preliminary results of the cooperative GPOH study NPC-91. Gesellschaft fur Padiatrische Onkologie und Hamatologie. *Cancer*. 1997;80(5):951–959.
15) Zubizarreta PA, D'Antonio G, Raslawski E, et al. Nasopharyngeal carcinoma in childhood and adolescence: a single-institution experience with combined therapy. *Cancer*. 2000;89(3):690–695.
16) Richards MK, Dahl JP, Gow K, et al. Factors Associated with mortality in pediatric vs adult nasopharyngeal carcinoma. *JAMA Otolaryngol Head Neck Surg*. 2016;142(3):217–222.
17) Chan OS, Ngan RK. Individualized treatment in stage IVC nasopharyngeal carcinoma. *Oral Oncol*. 2014;50(9):791–797.
18) Ou SH, Zell JA, Ziogas A, Anton-Culver H. Epidemiology of nasopharyngeal carcinoma in the United States: improved survival of Chinese patients within the keratinizing squamous cell carcinoma histology. *Ann Oncol*. 2007;18(1):29–35.
19) Reddy SP, Raslan WF, Gooneratne S, Kathuria S, Marks JE. Prognostic significance of keratinization in nasopharyngeal carcinoma. *Am J Otolaryngol*. 1995;16(2):103–108.
20) Onishi H, Ozaki M, Kuriyama K, et al. Stereotactic body radiotherapy for metachronous multisite oligorecurrence: a long-surviving case with sequential oligo-recurrence in four different organs treated using locally radical radiotherapy and a review of the literature. *Pulm Med*. 2012;2012:713073.
21) Withers HR, Lee SP. Modeling growth kinetics and statistical distribution of oligometastases. *Semin Radiat Oncol*. 2006;16(2):111–119.
22) Formenti SC, Demaria S. Systemic effects of local radiotherapy. *Lancet Oncol*. 2009;10(7):718–726.
23) Ahmed MM, Guha C, Hodge JW, Jaffee E. Immunobiology of radiotherapy: new paradigms. *Radiat Res*. 2014;182(2):123–125.