Prolonged Complete Remission After Induction Chemotherapy Followed by Chemoradiation with Tomotherapy in Metastatic Nasopharyngeal Cancer

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Abstract. *Background: Nasopharyngeal carcinoma (NPC) is uncommon in the Western hemisphere and in Europe. The undifferentiated subtype has a relevant propensity to metastasize systemically, mostly in the skeleton. In patients with distant metastasis at presentation there is no consensus on the most appropriate approach. Case Report: Evaluation of a young patient with initially bony metastatic nasopharyngeal cancer treated with platinum-based induction chemotherapy followed by radiotherapy (performed with Tomotherapy) combined to chemotherapy on primary region with curative intent, and subsequent focal irradiation of the bone metastasis. Conclusion: After 27 months from the end of the planned treatment the patient has not shown any late toxicity or complications in the treated areas and is without any evidence of progression. It seems appropriate to treat selected metastatic patients with a radical intent, using induction chemotherapy followed by radical chemoradiotherapy on the primary region and high dose radiation on the metastasis. Moreover, Tomotherapy demonstrated a tolerable grade of acute toxicity without any relevant late complications.*

Nasopharyngeal carcinoma (NPC) is quite uncommon in the Western hemisphere and in Europe, but is an endemic disease in Southeast Asia, China and certain regions of Africa. The undifferentiated subtype (type 2b; WHO 2005) has a relevant propensity to metastasize systemically, mostly in the skeleton (1, 2). The chemo-radiation treatment constitutes the basis in the locally-advanced stage (3); however, in patients with distant metastasis at presentation there is no consensus on the most appropriate approach and there is a risk, by considering palliative therapy, to reduce the radical cure for the primary cancer site and worsen the prognosis. However, with the introduction of intensity modulated-radiotherapy (IMRT), it is possible to treat different sites minimizing the radio-correlated toxicities (4) justifying the use of such treatment for the benefit of disease improvement. In this report we present a case of a young patient who presented to our Institute (IST-IRCCS San Martino, Genoa, Italy) with initially bony-metastatic NPC. He was treated with platinum-based induction chemotherapy followed by concomitant chemoradiotherapy (performed with Tomotherapy) on primary region with curative intent and subsequent irradiation of the bone metastasis.

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Key Words: Nasopharyngeal cancer, tomotherapy, synchronous metastasis, chemoradiation.

Case Report

A 19-year old man complained of nasal voice, occasional headache and epistaxis three months prior to being diagnosed. On clinical examination, he was found to have a right laterocervical mass. Ultrasound examination (US) confirmed bilateral neck lymphadenopathy and excisional biopsy of the mass revealed an undifferentiated non-keratinizing carcinoma suggestive of a head and neck primary tumor. Endoscopic examination performed at the Department of Otorhinolaryngology of our Institute, revealed a mass in nasopharynx. Computed tomography (CT) and magnetic resonance imaging (MRI) showed pathological tissue localized in the left side of nasopharynx (Figure 1), exceeding the median line, with invasion of pterigopalatine fissure and beyond the skull close the anterior part of trigeminal ganglio-cisternae and bilateral laterocervical lymphnodes right levels IIA-IB-IIB-III-VA-VB with maximum diameter of 21 mm; left levels IIA-IIB-III-VA with maximum diameter of 42 mm). The patient was referred

to out Institute for a chemo-radiation treatment. To complete the staging and plan the radiation treatment, a 18 fluoro-deoxyglucose positron emission tomography (18F-FDG PET/CT) scan was organized which revealed metabolic avidity in nasopharynx (SUV 20.6) in several bilateral laterocervical lymphnodes (SUV 5.8 on right side, 14.8 on left side) and a focal FDG activity in the right anterior-inferior iliac spine (SUV 5.75) (Figure 2). Subsequent analysis of CT planning images confirmed the presence of a bone metastasis; the patient was thus staged as cT4-N2-M1 (stage IVc).

The patient was submitted to three courses of induction chemotherapy with cisplatin 40 mg/mq, q21; days 1-2, and epidoxorubicin 90 mg/mq, q21; day1, and was re-staged after the treatment with another 18F-FDG PET/CT. The examination showed a strong reduction of active disease on nasopharynx and neck (residual SUV 2) and a complete bone response. The neck MRI confirmed the primary tumor and the nodal reduction. Combined chemoradiotherapy started four weeks after the last induction course with an alternated regimen (5). The patient was given cisplatin, 20 mg/m^2/day, days 1-4 and fluorouracil, 200 mg/m^2 day 1-4 weeks 1, 4, 7) alternated to three splits of radiation (week 2-3, 5-6, 8-9) up to 66 Gy. Radiation was delivered with Helical Tomotherapy using 6 MV photons. A simulation CT scan was performed in the supine position with a thermoplastic mask from head to shoulders. The head and neck volumes were defined in accordance with the International Commission on Radiation Units and Measurements Report 62 (ICRU62). The nasopharynx gross target volume (GTV) and the positive neck lymph node were determined according to diagnostic CT/MRI and FDG-PET/CT; to support counter GTV, a FDG-PET/CT fusion was performed. Three clinical target volumes (CTV) were delineated for head and neck site: CTV1, CTV2 and CTV3; CTV1 was defined as primary tumor and pathologic nodes plus 5 mm margin, CTV2 was defined as high-risk sites that typically include the tissues around the gross tumor volume and/or the neck nodal stations that have high risk of cancer involvement and/or lymph nodes that look suspicious on imaging, and CTV3 defined as low risk sub-clinical disease sites. Planning target volumes (PTV1-PTV2-PTV3) were defined as CTV1-CTV2-CTV3 plus 5 mm margin. CTV1 encompassed the pre-chemotherapy volume of the primary tumour and involved lymph nodes. PTV overlap with critical organs at risk (OARs) was managed by reducing the margin to 1-3 mm or by using overlap structures to limit dose to tolerated values. Treatment planning was performed using Tomotherapy Hi-Art planning station v.4 (Tomo Therapy, Madison, WI, USA). The prescribed dose was 66 Gy, in 2.20 Gy/fraction to PTV1, 60 Gy in 2.0 Gy/fraction to PTV2 and 54 Gy in 1.8 Gy/fraction to PTV3, all in 30 fractions. The daily simultaneous integrated boost dose was 20 cGy/fraction on GTV.

After completion of the therapy, the right spine bony metastasis received 45 Gy in 15 fractions, 4 fractions/weekly. IMRT optimization was carried-out pursuing Quantitative analyses of normal tissue effects in the clinic (QUANTEC) (6) for OARs dose/volume objectives in particular for spinal cord, brain stem, parotid glands, chiasm, optical nerves, larynx and oral cavity. If needed directional or complete blocking was used for lenses and eyes. Dose normalization was hard constrained to make median target dose equal to the prescribed dose. Before each treatment a megavoltage computed tomography (MVCT) scan was performed for patient positioning. Image matching was executed using automatic bone algorithm supervised by experienced medical staff.

At the end of the treatment, the patient showed dysgeusia and grade 2 dysphagia as well as mucositis, dermatitis and pain grade 1; after 12 and 24 months he did not complain any subacute or late toxicity. No xerostomia was reported.

The patient has now 27 months of follow-up with endoscopic examination, MRI and 18F-FDG PET/CT confirming no evidence of disease recurrence.

Discussion

To the best of our knowledge, there are few reports describing NPC with distant metastasis at presentation. Results suggest a poor prognosis in synchronous metastatic patients with median OS of 23.3 months (median OS is 33.8 *vs*. 21.3 months in single *vs*. multiple metastasis, respectively) significantly lower than metachronous metastatic patients where median OS is 36.7 months (7).

Among head and neck cancers, NPC has the highest propensity to distant metastases (about 5 to 7%); with the skeletal system being the most common site. Other typical sites of metastatic disease include lung and liver (8).

18F-FDG PET/CT has become a routine approach in oncology, because it provides important information about metabolic characteristics of malignancy, tumor stage and therapeutic response, and also provides higher sensitivity in detecting distant metastases than conventional work-up such as chest X-ray, liver ultrasound and bone scan (9-10). A recent meta-analysis points out the role of FDG PET and PET CT in the detection of bone metastasis in HNC patients (11).

In addition, it is useful to complete the correct staging given by CT and MRI during the staging process, the treatment evaluation and the follow-up. The identification of distant metastases based on staging methods may indicate that a patient is not a candidate for curative approach and that a more palliative treatment may be used. However, it has been recognized that the clinical course of metastatic patients can vary with occasional long-term survivors (12). As in our case, some patients, presented with locoregionally-advanced disease, will be found to have asymptomatic low-volume

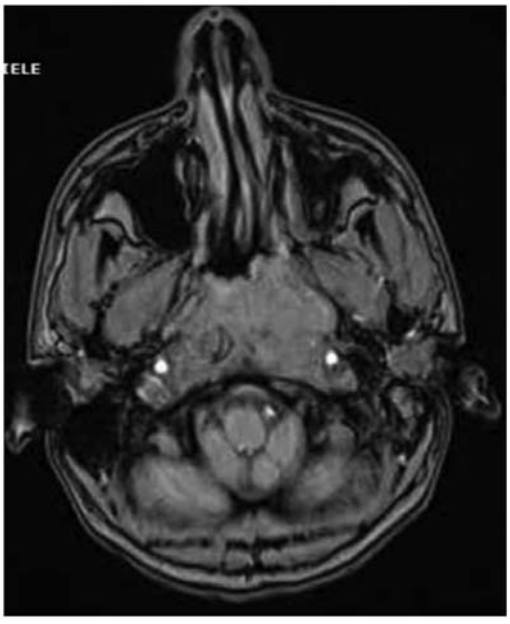

Figure 1. *Magnetic Resonance Imaging (MRI) showing pathological tissue in nasopharynx.*

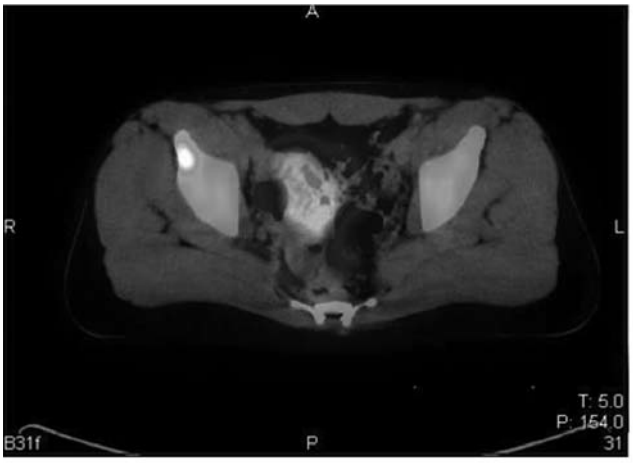

Figure 2. *^{18}Fluoro-deoxyglucose positron emission tomography (^{18}F-FDG PET/CT) scan detecting a focal FDG uptake.*

single or oligo-metastases. In these patients, treatment depends on the localization and the extent of the disease. Platinum-based induction chemotherapy followed by chemoradiation treatment belongs to category 3 according to the main guidelines, and can reduce the primary tumor and also control the distant disease, permitting thus a more radical approach in case of response to the induction therapy.

In our case, after a complete response on bone and a partial response on primary site and neck nodes due to chemotherapy, it has been reasonable to consider treating the patients in the locally advanced stage. Furthermore, Tomotherapy permits a high conformal dose distribution, with an improvement of normal tissue sparing, with consequent lower toxicity (13).

After completion of chemoradiation, we treated the aforementioned bone metabolic active site with 45 Gy in 15 fractions, biologically very similar to what the patient received to nasopharynx and nodal disease (14). More than two years after the end of the treatment, the patient has not shown any late toxicity or complications in the treated areas and does not present any evidence of local or distant progression.

Conclusion

Undoubtedly, a wide difference of prognosis in terms of OS exists in patients with initial metastatic disease, depending mostly on the number and the localization of lesions. However, after an accurate selection of the patients, with a complete staging performed with CT, MRI and PET/CT, it seems appropriate treating also, in addition to other cases, selected IVc stage (oligo-metastasis) patients with a radical intent, using chemoradiotherapy on the primary site and further high-dose radiation to the metastasis. PET/CT is demonstrated to be a method of choice for the detection of distant metastasis and the effective prognosis of treatment, mainly during the course of the disease than during follow-up. Moreover, Tomotherapy demonstrated a tolerable grade of acute toxicity without any relevant late complications.

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Received May 9, 2014
Revised June 25, 2014
Accepted June 27, 2014