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Impact of early radiological response evaluation on radiotherapeutic outcomes in the patients with nasal cavity and paranasal sinus malignancies

Hidehiro HOJO[1,2,*], Sadamoto ZENDA[2], Tetsuo AKIMOTO[2], Ryosuke KOHNO[2], Mitsuhiko KAWASHIMA[2], Satoko ARAHIRA[2], Teiji NISHIO[2], Makoto TAHARA[3], Ryuichi HAYASHI[4] and Keisuke SASAI[1]

[1]Graduate School of Medicine Department of Radiology, Juntendo University, 2-1-1, Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan
[2]Department of Radiation Oncology, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba, 277-8577, Japan
[3]Department of Gastrointestinal Oncology, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba, 277-8577, Japan
[4]Department of Head and Neck Surgery, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba, 277-8577, Japan
*Corresponding author. Graduate School of Medicine Department of Radiology, Juntendo University, 2-1-1, Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan. Tel: +81-3-3813-3111; Fax: +81-3-3816-0958; Email: hojo-h@juntendo.ac.jp

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We analyzed the correlation between primary tumor response within 6 months after radiation therapy (RT) including proton beam therapy (PBT) and progression free survival rate (PFS) in patients with nasal cavity and paranasal sinus malignancies to clarify the impact of early radiological evaluation of treatment response on prognosis. Sixty-five patients treated between January 1998 and December 2008, and whose follow-up duration was more than 2 years were included. The *Response Evaluation Criteria in Solid Tumors* (version 1.1) was used for the evaluation of treatment. Median age was 59 years (range 21–83 years). Olfactory neuroblastoma ($n = 20$, 30%) and squamous cell carcinoma ($n = 15$, 23%) were the major pathological tumor types. The median follow-up duration was 51.6 months. Radiological response evaluation within 6 months after treatment demonstrated that 15% of the patients achieved complete response (CR), and 3-year progression free survival rates of all patients was 49.2%. The 3-year PFS rates according to response for the treatment were 55.6% in the patients with CR and 46.4% in those with non-CR, respectively ($P = 0.643$). However, the 3-year PFS rates were 80.% in the patients with CR and 10.% in those with non-CR ($P = 0.051$) in the patients with squamous cell carcinoma (SCC) histology. Radiological response evaluation within 6 months did not have a significant impact on prognosis when analysis included all histology, although early radiological response within 6 months after RT had a borderline significant impact on treatment outcomes for the patients with nasal and paranasal SCC.

Keywords: response evaluation; nasal cavity; paranasal sinuses; radiation therapy; proton beam therapy

INTRODUCTION

Malignancies of the nasal cavity and paranasal sinuses are extremely rare, representing only 3–5% of all head and neck cancer and less than 1% of all malignancies [1–5]. Most cases are curatively treated by craniofacial surgery and postoperative radiation therapy, either alone or in combination [1–4, 6]. However, several problems with these treatment strategies remain. In cases where the disease has spread deeply into the intracranial region, surgical approaches are often complicated by the risk of serious functional deformity and a lack of satisfactory surgical clearance [7, 8]. Therefore, definitive radiation therapies (RTs) including 3D-conformal radiation therapy (3DCRT) or intensity modulated radiation

therapy (IMRT) and proton beam therapy (PBT) are often performed as an alternative treatment [2, 4, 9].

Generally, total tumor eradication is a fundamental efficacy measure for treatments and is often considered a surrogate for overall survival in the case of non-surgical approaches [10, 11]. However, Zenda *et al.* reported that patients with nasal or paranasal malignancies occasionally survive for long periods without complete response at the primary tumor site [9]. To our knowledge, however, there have been few reports that have examined response evaluation for nasal or paranasal sinus malignancies after non-surgical approaches. Here, we conducted a retrospective analysis examining the correlation between radiological tumor response and prognosis in patients with malignancies of the nasal cavity and paranasal sinuses to clarify the impact of early radiological evaluation of treatment response on prognosis.

MATERIALS AND METHODS

Patients

Patients fulfilling the following criteria were included: (i) malignancies of the nasal cavity or paranasal sinuses, (ii) received RT including PBT as a curative setting at the National Cancer Center Hospital East (NCCHE) between January 1998 and December 2008 and (iii) had sufficient radiographic information, such as that obtained by magnetic resonance imaging (MRI) and computed tomography (CT) for response evaluation.

Pretreatment evaluation

Pretreatment evaluation included a physical examination, a direct flexible fiberoptic endoscopic examination, MRI and CT.

Tumor staging in the present study was based on sections of the nasal cavity and paranasal sinuses in the TNM classification of the Union for International Cancer Control (UICC; 7th edition), regardless of histology type. For olfactory neuroblastoma (ONB), a system devised by Kadish *et al.* [12], which is based on anatomic extension, was used. During the preparation of this article, Kadish A, B, and C ONB were reclassified as T1, T2 and T4. Radiologists, head and neck surgeons, and medical oncologists at our institution reviewed radiological evaluation for tumor staging.

Radiation therapy

Proton beam therapy (PBT)

We used a 3D CT planning system to prepare the treatment planning. In this system, the proton beam was generated with a Cyclotron C235 (Sumitomo Heavy Industries, Ltd, Tokyo, Japan) with an energy of 235 MeV. Based on our preclinical experiments, relative biological effectiveness was defined as 1.1. Dose distribution was optimized using the spread-out Bragg peak method and obtained using a broad-beam algorithm.

Conventional radiation therapy

All photon beam RT was delivered using 6-MV X-rays and either 3D conformal techniques or IMRT, depending on the year of treatment and adjacent organs at risk.

Irradiation field

In general, primary tumors and metastatic lymph nodes were included in the irradiated field. Elective nodal irradiation was not performed. Gross tumor volume (GTV) was determined by pretreatment assessment with any or all of CT, MRI and Positron Emission Tomography-CT (PET-CT). Clinical target volume (CTV) was defined as the GTV plus a 5-mm margin and the sinuses adjacent to the GTV. In cases involving brain invasion, the area of T2 prolongation on MRI was also included in the CTV. Planning target volume (PTV) was basically defined as the CTV plus a 3-mm margin for PBT and a 5–7-mm margin for RT, but was finely adjusted where necessary in consideration of organs at risk.

Imaging analysis

Response to treatment at the primary site was evaluated using the *Response Evaluation Criteria in Solid Tumors* (RECIST 1.1) [13]. Radiological response evaluation was carried out using CT/MRI performed within 6 months after treatment. At least two radiologists determined radiological evaluations for treatment response. In response evaluations within 6 months, patients who had achieved complete disappearance of all target lesions were defined as CR, while the remaining patients were classified as non-CR patients. Overall survival (OS) was calculated from the start of treatment to the date of death or last confirmed date of survival. Survival time was censored at the last confirmation date if the patient was alive. Progression-free survival (PFS) was defined as from the day of initiation of treatment to the first day of confirmation of progressive disease or death by any cause.

Statistical analysis

The close-out date for survival analysis was 31 December 2010. Data were analyzed using StatView statistical software (Version 5.0, SAS Institute, Cary, NC, USA). Cumulative survival and tumor control rates were calculated using the Kaplan–Meier product-limit method. Survival curves were estimated using the Kaplan–Meier product-limits method with the log-rank test. P values of <0.05 were considered statistically significant.

RESULTS

Patient and treatment characteristics

A total of 75 patients with malignancies of nasal or paranasal sinuses were treated with RT including PBT at the

NCCHE between January 1998 and December 2008. Sixty-five patients met the inclusion criteria and were retrospectively analyzed in our study. Patient characteristics are listed in Table 1. The median age was 59 years (range, 21–83 years), with 39 male and 26 female patients. Most of the patients had T4 tumors ($n = 53$), and the majority of patients presented with a tumor of the nasal cavity ($n = 43$). Six patients presented with cervical lymph node metastasis at the time of diagnosis.

Medical records and pathological reports were reviewed to assess the histological examination results. ONB was the major histological type ($n = 20$), followed by squamous cell carcinoma (SCC, $n = 15$), melanoma ($n = 9$), adenoid cystic carcinoma (ACC, $n = 9$), undifferentiated carcinoma ($n = 6$), and others ($n = 6$) (Table 1).

RT was given to 13 patients. Three of the 13 patients received IMRT and the remaining 10 patients were administered 3DCRT. Median doses were 66 Gy (range, 66–70 Gy). Fifty-two patients received PBT, with median doses of 65 GyE (range, 60–70 GyE). A total of six patients had clinically positive cervical lymph nodes at the beginning of treatment. Three of six patients underwent a neck dissection and the remaining three patients received complete neck irradiation in the definitive setting.

Systemic chemotherapy

As the present data was compiled over a 10-year period, several treatment methods were used in our study. A total of 31 patients received chemotherapy in addition to radiation therapy. The chemotherapy regimens are listed in Table 2.

Treatment outcomes

Median interval between the end of treatment and radiological response evaluation was 9.5 weeks (range, 2–27 weeks). In the radiological response evaluation within 6 months, CR was achieved in 10 (15%) of the 65 patients. With a median follow-up period of 51.6 months (range, 25–125 months), the 3-year PFS and OS rates of all patients were 44.2% and 72.1%, respectively (Fig. 1). Loco-regional

Table 1. Patient characteristics (N = 65)

Characteristic		N
Age (range)		59 yrs (21-83 yrs)
Gender (male/female)		39/26
Primary site	Nasal cavity	43
	Ethmoidal sinus	11
	Maxillary sinus	5
	Sphenoid sinus	4
	Other site	2
Tumor type	ONB	20
	SCC	15
	ACC	9
	Melanoma	9
	Undifferentiated	6
	Others	6
T stage	T1 (Kadish A)	1
	T2 (Kadish B)	7
	T3	4
	T4 (Kadish C)	53
N stage	N0	59
	N1	3
	N2	3

Abbreviations: ACC, adenoid cystic carcinoma; ONB, olfactory neuroblastoma; SCC, squamous cell carcinoma; Undif, undifferentiated carcinoma

Table 2. Treatment methods and radiation schedules

Treatment			N
Chemotherapy	IC regimen	DOC + CDDP + TS-1	12
		CDDP + 5-FU	1
		CDDP + VP-16(+ADM)	2
		DOC + CPT-11	6
		none	44
	CRT regimen	CDDP	15
		CDDP + 5-FU	4
		5-FU	1
		DOC + CPT-11	1
		none	44
Radiotherapy	Modality	Proton	52
		Photon	12
		Electron	1
	RT dose schedule	60 GyE/15 fr	7
		65GyE/26fr	41
		66 GyE/33 fr	8
		70 GyE/28 fr	1
		70 Gy/33 fr	1
		70 GyE/35 fr	7

Abbreviations: ADM, doxorubicin; CPT-11, irinotecan; CRT, chemoradiotherapy; CDDP, cisplatin; DOC, docetaxel; 5-FU, 5-fluorouracil; IC, induction chemotherapy; TS-1, tegafur-gimeracil-oteracil; VP-16, etoposide

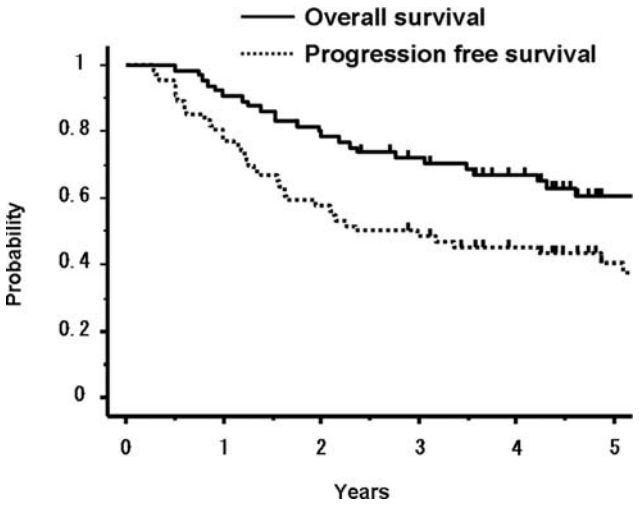

Fig. 1. PFS and OS curves of all patients. With a median follow-up period of 51.6 months, the 3-year PFS and OS rates of all patients were 44.2% and 72.1%, respectively.

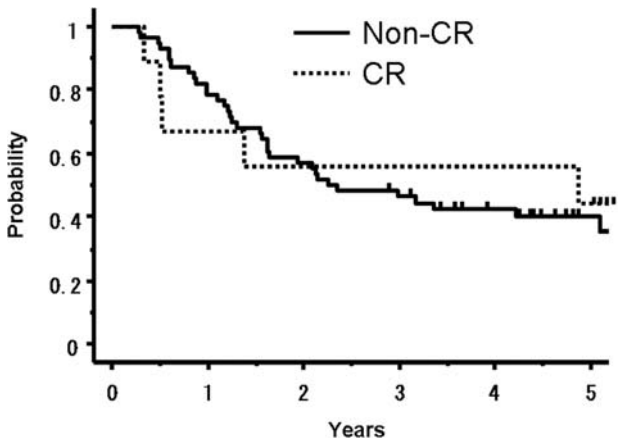

Fig. 2. PFS curves of all patients based on the results of radiological response evaluation within 6 months. The 3-year PFS rate was 55.6% in the patients whose response was CR and that of those whose response was non-CR was 46.4%, respectively ($P = 0.643$).

progression was observed in 52.3% of patients and distant metastasis was developed in 12.3% of patients. In the patients who achieved CR, the 3-year PFS rate was 55.6% and that of those whose responses were non-CR was 46.4%, respectively, which did not represent a statistically significant difference ($P = 0.643$) (Fig. 2).

In the patients whose histology was SCC, the 3-year PFS rate was 80.0% in the patients who achieved CR ($n = 6$) and 10.0% in those whose responses were non-CR ($n = 9$). The difference between patients with CR and those with non-CR was borderline significant ($n = 0.051$) (Fig. 3).

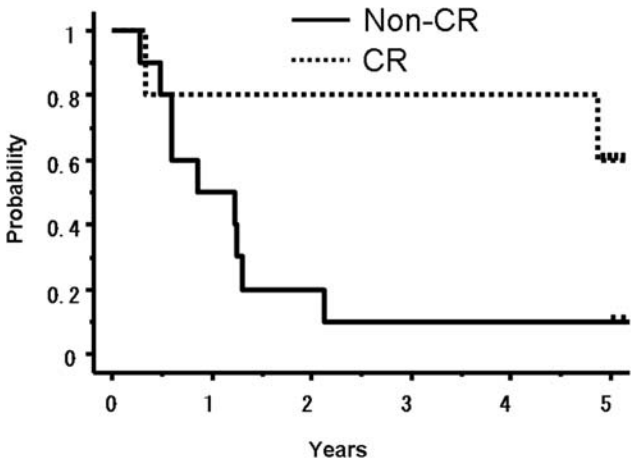

Fig. 3. PFS curves of the patients whose histology was SCC based on the results of radiological response evaluation within 6 months. The 3-year PFS rate was 80.0% in the patients who achieved CR and 10.0% in those whose responses were non-CR. The difference between patients with CR and those with non-CR was borderline significant ($P = 0.051$).

DISCUSSION

In the present retrospective study, we demonstrated that radiological response evaluation within 6 months after radiation therapy with or without chemotherapy in patients with malignancies of the nasal cavity or paranasal sinuses did not have a significant impact on prognosis such as PFS when we analyzed all patients included whose histologies were SCC and non-SCC. However, the results of this study demonstrated that the difference in the 3-year PFS of the SCC patients between those with CR and those with non-CR was borderline significant (80% vs 10%). This raised the possibility that early radiological response might serve as a surrogate for treatment outcomes (PFS) especially in patients with SCC histology.

The optimal treatment of malignancies in the nasal cavity and paranasal sinuses is controversial. Existence of risk organs such as brain nerves and extension to skull base often makes it difficult to remove tumors totally, indicating that RT would be an effective approach for nasal cavity and paranasal sinus malignancies. The 5-year OS rate after RT with or without surgery ranged from 15% to 55% [1–6]. Regarding the clinical outcomes after PBT, several studies including a study from our institution demonstrated that 5-year OS ranged from 70–80%, although the histological types of patients analyzed were not homogenous. These results indicated that clinical outcomes were slightly better than those after conventional radiation therapy [9, 14, 15, 16]. The main advantages of radiation therapy for nasal cavity and paranasal malignancies are to preserve organs and their functions by delivering enough total dose to the tumors while sparing excessive doses to the adjacent

critical normal structures such as the brain, brainstem and the optic structures. Among radiotherapeutic approaches, PBT can provide higher doses to tumors compared with 3DCRT or IMRT because of the unique physical properties of PBT. The physical properties of protons are rapid fall-off at the distal end of the Bragg peak and sharp lateral penumbra, depending on energy, depth and delivery [6, 15, 16].

The objective evaluation of tumor shrinkage is often considered a surrogate for survival [10, 17]. In esophageal cancer, endoscopic findings 4 or 6 weeks after concurrent chemoradiotherapy or RT alone have been used as a surrogate for survival [18, 19], while disease control rate and CR/partial response (PR) 8 weeks after registration are associated with longer survival in advanced non-small-cell lung cancer [17]. Initial loco-regional response is also important in radiotherapeutic outcomes of patients with head and neck SCC. However, the treatment response of nasal cavity or paranasal sinus malignancies, with the exception of SCC, appears to differ from those of other malignancies. The results of this study indicate that salvage treatment should be carefully considered in patients whose histologies are non-SCC, even if the patient does not achieve CR at the time of radiological response evaluation within 6 months. This raises the possibility that radiological response evaluation within 6 months after radiation therapy might not be optimal, especially in patients whose histologies are non-SCC, e.g. ONB, ACC or melanoma. However, early radiological response in patients whose histology was SCC would be important, similar to other SCCs of the head and neck cancer, such as hypopharyngeal cancer. There are a few reports regarding the optimal timing of radiological evaluation using CT or MRI after radiotherapy. Hermans *et al.* suggested using follow-up CT at 8–12 weeks after completion of radiotherapy with larynx and hypo pharynx [20]. In addition, response evaluation at eight weeks after the completion of treatment was often adopted in clinical trials for head and neck cancer [21, 22]. This might suggest that the optimal timing of radiological response evaluation in patients with nasal and paranasal sinus malignancies appears to be different according to the histological type, although the number of patients analyzed in this study is still not enough to draw a definite conclusion. There is a limit to the ability of morphological images, such as CT or MRI, to evaluate tumor shrinkage after radiotherapy of the nasal cavity or paranasal sinus malignancies without SCC; it is necessary to evaluate with dynamic images such as PET-CT.

Recently, there have been many studies that have demonstrated the clinical usefulness of new imaging modalities, particularly PET-CT in response evaluation for RT with or without chemotherapy [17, 23]. In our clinical practice, the changes in positivity of PET-CT before and after RT provided helpful information regarding the decisions for salvage treatment. In the present study, however, we could not evaluate local response using PET-CT in addition to CT and MRI, because PET-CT before and after treatment was only available in a limited number of patients. Hence, investigation regarding the clinical usefulness of PET-CT including other new imaging modalities in response evaluation for nasal and paranasal malignancies other than SCC is warranted in future prospective trials.

Limitations of our study are as follows. First, the number of patients according to histological type was small, resulting in insufficient statistical differences between each group, and second, the optimal response evaluation of lymph nodes metastases could not be sufficiently discussed.

In conclusion, the results of this study demonstrated that radiological response evaluation within 6 months did not provide significant impact on prognosis when analysis included all histology such as ONB, although early radiological response within 6 months after radiation therapy had a borderline significant impact on treatment outcomes (PFS) for nasal and paranasal malignancies in patients with SCC histology. Hence, further study is warranted to ensure the impact of histological type on the outcomes of early radiological response evaluation.

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