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BNCT for advanced or recurrent head and neck cancer

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HIGHLIGHTS

- This study is clinical trials of BNCT for head and neck cancers.
- BNCT was performed in 20 advanced/recurrent head and neck cancer patients.
- The effective rate [(CR+PR)/total cases] was 90%.
- BNCT is effective the patients with radio resistance head and neck cancer.
- BNCT is a potential curative therapy for patients with head and neck cancer.

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ABSTRACT

The therapeutic effect of surgery and/or combination of conventional chemoradiotherapy is limited in the patients with recurrent squamous cell carcinoma (SCC) and locally advanced non-squamous cell carcinoma without malignant melanoma (non-SCC) of the head and neck. Currently, clinical trials of BNCT for head and neck cancers are being conducted in some institutes to verify its the effectiveness. BNCT was performed in 10 patients with recurrent SCC, 7 patients with recurrent non-SCC and 3 patients with newly diagnosed non-SCC in our university between October 2003 and September 2007. Eleven patients showed complete remission and 7 patients showed partial remission of irradiated site. The effective rate [(CR+PR)/total cases] was 90%. No severe acute or chronic normal-tissue reactions were observed in any patients. BNCT is effective and safe in the patients with recurrent SCC and locally advanced non-SCC.

1. Introduction

Head and neck cancers (HNCs) account for approximately 10% of all cancers, and about 90% of them are squamous cell carcinoma (SCC). Surgery represents the mainstay of treatment for resectable primary site. However, the main drawback of surgery, especially for advanced T-stage (primary tumor) cancer, is deterioration of patients' quality of life (QOL) because the head and neck have many important physiological and cosmetic functions. On the other hand, the patients with unresectable cancer are candidates for radiation therapy or chemoradiotherapy. Although these therapies are effective for SCC, it is difficult to perform re-radiation therapy for SCCs that recur after these therapies, because of intolerable of surrounding normal-tissue against re-radiation therapy. In addition, these SCCs might show radio resistance. T3–T4 advanced non-SCCs, such as adenocarcinoma, mucoepidermoid carcinoma and adenoid cystic carcinoma, also show radio- and chemoresistant. BNCT is high linear energy transfer (LET) radiation and tumor-selective radiation without serious damage of surrounding normal-tissue. BNCT might be effective and safe in the patients with inoperable, locally advanced HNCs even if that recur at previously irradiated sites. This paper is intended to present our preliminary experience of treating patients with HNC (recurrent SCC, locally advanced non-SCC) at the Kyoto University Reactor (KUR) and Japan Research Reactor 4 (JRR4) of the Japan Atomic Energy Agency.

2. Material and method

2.1. ^{18}F-BPA-PET study

The accumulations of BPA (para-boronophenylalanine) in the tumor and surrounding normal-tissue were imaged and quantified by an ^{18}F-BPA-PET (fluorine-18-labeled BPA positron emission

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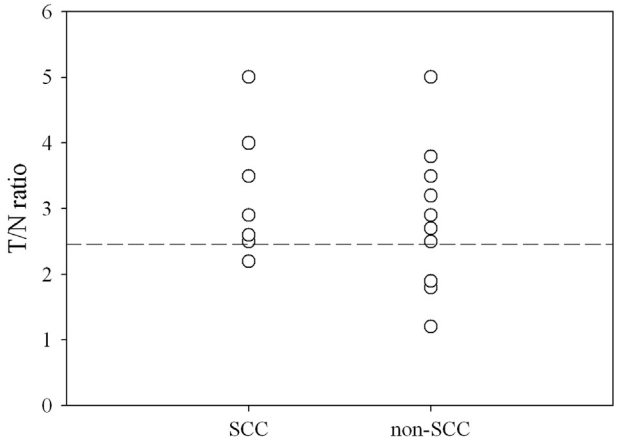

Fig. 1. Kawasaki Medical School (KMS) group data of ^{18}F-BPA-PET. Eleven patients with recurrent SCC and 8 patients with non-SCC were registered in ^{18}F-BPA-PET study from October 2003 to September 2007. There was no difference in the T/N ratio between SCC and non-SCC group. Ten of 11 patients with SCC and 10 of 13 patients with non-SCC showed T/N ratio of 2.5 and over, and underwent BNCT.

tomography) study before BNCT in all patients. Imahori et al. (1998)

The tumor/blood, normal-tissue/blood, and tumor/normal-tissue (T/N) ratios of ^{18}F-BPA intensity was estimated 40 min after ^{18}FBPA i.v. administration. T/N ratios of SCC and non-SCC patients are shown in Fig. 1.

2.2. Indications for BNCT

(1) A newly diagnosed T3/T4 advanced and recurrent HNCs.
(2) The maximum depth of tumor is within 5 cm in depth from the skin surface to achieve a curative dose of the target by using an epithermal neutron beam.
(3) T/N ratio is more than 2.5. T/N ratio is calculated by the results of ^{18} F-BPA-PET.
(4) Consent to perform BNCT is obtained from the patient and their family.
(5) Approval for BNCT is given by our Medical Ethics Committee.

2.3. Treatment procedures

The patient undergo CT scan for treatment planning just prior to BNCT using a computer workstation equipped with the Japan Atomic Energy Research Institute Computational Dosimetry System: JCDS (JRR4) (Kumada et al., 2001) and SERA (KUR) (Nigg et al., 1999) dose planning software. The total dose of BPA (L-enantiomer, >95% ^{10}B enriched) is 500 mg/kg body weight (B.W.). Two hours before neutron irradiation, intravenous administration of 200 mg/kg B.W./h of BPA is started. To monitor the boron concentration in the blood, venous blood samples were obtained every 1 h from starting BPA administration to finishing neutron irradiation. The boron concentrations in the blood are measured by prompt γ-ray analysis and/or inductively coupled plasma-atomic emission spectrometry (ICP-AES). The blood boron concentration curves are plotted against time. The tumor and normal-tissue boron concentrations are estimated by the results of ^{18}F-BPA-PET.

Patients are positioned on the treatment table in the irradiation room of the reactor and attached the collimator to shield normal tissue, and then tumor site is irradiated with epithermal neutron with the BPA flow rate of 100 mg/kg B.W./h (Ono et al., 2006). All patients are placed in a sitting or supine position during irradiation. After final setting of the patients, thermo-luminescence dosimeters (TLDs) are attached to the skin surface involved in the irradiation field and gold wires are placed in the collimator for dosimetry. We placed a gelatin sheet, 5-mm thickness, on the skin of the radiation field to enhance the irradiation dose at the tumor surface. Neutron flux (n/cm^2/s) is measured using gold wires 15 min after the start of irradiation. The neutron irradiation time is decided using the JCDS based on the neutron flux measured at 15 min after the start of irradiation and the estimated blood boron concentration curves.

2.4. Radiation doses by BNCT

BNCT for the HNC is performed using epithermal neutron beam of the reactor with single fraction at a reactor power of 3.5 MW (JRR4) and 5 MW (KUR), in our group (2 fractions in Finland group (Kankaanranta et al., 2007)). The control dose to the tumor is planned to be more than 20 Gy-Eq (weighted dose) and the maximum dose to tumor-surrounding normal tissue is set not to exceed 15 Gy-Eq. These values were calculated by JCDS on the basis of the mean blood boron level during neutron irradiation and directly measuring the neutron flux at the tumor site using gold wires. These treatment doses are achieved by the indications of BNCT (2) and (3).

3. Results

Ten patients with recurrent SCC, 7 patients with recurrent non-SCC (adenoid cystic carcinoma, 2 cases; adenocarcinoma, 1; papillary adenocarcinoma, 2; mucoepidermoid carcinoma, 1; and undifferentiated cancer, 1) and 3 with newly diagnosed T4 advanced non-SCC (adenoid cystic carcinoma, 2 cases; and acinic cell carcinoma, 1) underwent BNCT between October 2003 and September 2007. The median follow up time was 15.9 months (range, 3–56 months). Local response of these 20 patients after BNCT was as follows: 11 showed complete remission (CR) clinically. Fig. 2 represents the images of CT and ^{18}F-BPA-PET before, and that of CT 5 months after treatment in recurrent SCC case which showed CR with BNCT. Seven patients showed partial remission (PR), and 2 did no change. The effective rate [(CR+PR)/total cases] was 90% (Aihara et al., 2006). No severe acute or chronic normal-tissue reactions (more than grade II of the RTOG/EORTC score) were experienced in any patients. Seventeen patients died 3–44 months (median 18.8 months) after BNCT and the main cause of death was distant metastasis.

In all patients, 1- and 2-year overall survival rates were 47.1% and 31.4%, respectively, and the 1- and 2-year disease free survival rates were 22.0% and 0%. However, the 1- and 2-year loco-regional progression-free survival rates were 55.9% and 22.4%, respectively (Fig. 3). All 3 patients with newly diagnosed T4 advanced non-SCC showed complete response of the primary site within 3 months after BNCT. The 1-year loco-regional progression-free survival rate was 100% and overall survival rate was 66.7% at 18 months in these 3 patients.

4. Discussion

The treatment of locally advanced and recurrent SCC were very difficult. The reported tumor effective rate and the median survival of 69 patients with advanced/recurrent head and neck SCC who received palliative chemotherapy and/or radiation therapy were approximately 30% and 6–10 months, respectively (Worden et al., 2006). The 2-year loco-regional progression-free survival and overall survival rates in 105 patients with recurrent HNC who underwent re-radiotherapy were 42% and 37%, respectively [82].