Original Article

The Role of Technetium-99m Methoxyisobutyl Isonitrile Scintigraphy in Predicting the Therapeutic Effect of Chemotherapy Against Nasopharyngeal Carcinoma

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BACKGROUND: The authors prospectively evaluated the correlation between technetium-99m methoxyisobutyl isonitrile (^{99m}Tc-MIBI) accumulation in tumors and response to induction chemotherapy in patients with nasopharyngeal carcinoma (NPC). **METHODS:** Eighty-six patients with locally advanced NPC underwent single-photon emission computed tomography 15 minutes after an intravenous injection of 740 megabecquerels (20 mCi) ^{99m}Tc-MIBI before chemotherapy. The tumor uptake ratio (TUR) was calculated. Two weeks after the second cycle of combined chemotherapy with 5-fluorouracil (5-FU) and cisplatin (DDP), the tumor response rate was evaluated. The correlation between ^{99m}Tc-MIBI accumulation in tumors and response to chemotherapy with 5-FU/DDP was examined. **RESULTS:** Positive accumulation of ^{99m}Tc-MIBI in tumors was observed in 76 patients (88.4%). The tumor response was a complete response (CR) in 8 patients, a partial response (PR) in 68 patients, stable disease (SD) in 9 patients, and progressive disease (PD) in 1 patient. The response rate (CR and PR) to 5-FU/DDP chemotherapy in patients who had positive ^{99m}Tc-MIBI accumulation (tumor uptake ratio [TUR] >1.1) was higher than that in patients who had negative ^{99m}Tc-MIBI accumulation (TUR ≤1.1; 98.7% vs 10%; $P < .001$). **CONCLUSIONS:** Patients with negative ^{99m}Tc-MIBI accumulation were resistant to 5-FU/DDP chemotherapy. ^{99m}Tc-MIBI imaging in patients with NPC was capable of predicting tumor response to chemotherapy with 5-FU/DDP and can help in the selection of patients for induction chemotherapy. *Cancer* 2011;117:2435–41. *© 2010 American Cancer Society.*

KEYWORDS: nasopharyngeal carcinoma, induction chemotherapy, chemosensitivity, technetium-99m methoxyisobutyl isonitrile.

Radiation therapy (RT) traditionally has been the standard treatment for patients with nasopharyngeal carcinoma (NPC). Although NPC is radiosensitive, the long-term survival of patients with advanced disease remains poor, and they have a high incidence of locoregional and distant failure.[1-4] To improve the prognosis, a variety of treatment regimens have been tested combining chemotherapy and RT in different schemes over the past decade, including induction chemotherapy, concurrent chemotherapy, and adjuvant chemotherapy. However, to date, the best sequence has not been established.

The main potential advantage of induction chemotherapy is that it may eradicate distant micrometastasis and decrease the tumor volume before radiation. It facilitates the delivery of chemotherapy at dose intensities that are not usually tolerated when chemotherapy is given in the concurrent or adjuvant setting. According to meta-analyses, the addition of cisplatin-based induction chemotherapy to RT in NPC was associated with a decrease in recurrence rates by 14.3% and in cancer-related deaths by 12.9% at 5 years.[5] However, a disadvantage of induction chemotherapy is the delay of definitive RT or the possibility of tumor progression while receiving chemotherapy in multidrug-resistant patients. Combined

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cisplatin (DDP) and 5-fluorouracil (5-FU) is the most commonly used regimen in NPC, with reported response rates that average 73% to 93%.[6-9] If patients with chemotherapy-resistant NPC were screened out before treatment, then they would be spared from ineffective induction chemotherapy.

Multidrug resistance may be the major barrier to efficient chemotherapy for cancer. One of the important mechanisms that leads to multidrug resistance is the increased expression of 170-kDa P-glycoprotein (P-gp), which acts as an adenosine triphosphate (ATP)-dependent efflux pump for several cytotoxic drugs.[10] Technetium-99m methoxyisobutyl isonitrile (^{99m}Tc-MIBI), a lipophilic cation that originally was developed for scintigraphic evaluation of coronary blood flow,[11,12] has been used to predict chemotherapy sensitivity and to detect functional P-gp expression in some types of cancers.[13-19] ^{99m}Tc-MIBI is taken up passively into the mitochondria in metabolically active cancer cells and then exported from cells by P-gp.[20,21] Thus, tumors that have low levels of ^{99m}Tc-MIBI accumulation likely have high P-gp activity. Significant correlations have been reported between ^{99m}Tc-MIBI scintigraphy and P-gp immunohistochemistry, response to chemotherapy, and/or patient outcomes in several types of malignancies.[13-19]

To our knowledge, the correlation between the extent of ^{99m}Tc-MIBI accumulation and response to chemotherapy has not been addressed previously in patients with head and neck cancer. Therefore, we used ^{99m}Tc-MIBI scintigraphy in patients with locally advanced NPC who were receiving induction chemotherapy. In this study, we evaluated whether the results from ^{99m}Tc-MIBI scintigraphy were correlated with chemotherapeutic effects and whether they can be used to provide useful information for the selection of chemotherapy-sensitive patients with NPC.

MATERIALS AND METHODS

Eligibility Criteria

Patients who fulfilled all of the following criteria were eligible for this study: biopsy-proven, World Health Organization Type II or Type III NPC; stage T3 or T4 disease according to the 2002 American Joint Committee on Cancer (AJCC) staging system (the smallest dimension of the primary tumor had to be $\geq$20 mm with no gross evidence of distant metastasis and adequate hematologic function, including a total leukocyte count [white blood cells] $\geq$4000/µL and platelets $\geq$100,000/µL); adequate renal function (creatinine clearance $\geq$60 mL/minute); and a satisfactory Karnofsky performance status ($\geq$80). Exclusion criteria included age $\geq$70 years or <18 years, pregnancy or lactation, a history of previous treatment, or a previous malignancy.

^{99m}Tc-MIBI Scintigraphy

Anterior and posterior planar views were obtained before chemotherapy, and a 360° single-photon emission computed tomography (SPECT) nasopharyngeal image was obtained 15 minutes after an intravenous injection of 740 megabecquerels (20 mCi) ^{99m}Tc-MIBI. The equipment consisted of a rotating and large field-of-view gamma camera (General Electric Company, Waukesha, Wis) fitted with a low-energy, high-resolution collimator (collection energy, 140 KeV; window width, 20%). Sixty images were acquired, each from a 20-second exposure, during a 360-degree camera rotation. Transverse, coronal, and sagittal sections were reconstructed with attenuation correction using Hann filters (cutoff frequency = 10) to produce SPECT images. The findings from ^{99m}Tc-MIBI nasopharyngeal images were evaluated both qualitatively and quantitatively. SPECT images were interpreted visually by 2 independent nuclear medicine physicians before chemotherapy, and a consensus was reached regarding the findings. Images were defined as positive (focal abnormal accumulation at the tumor site) (Fig. 1A,B) or negative (no abnormal focus of activity at the tumor site) (Fig. 2A,B).[13,17] The tumor uptake ratio (TUR) was obtained from a coronal nasopharyngeal image. A region of interest (ROI) was carefully drawn over the tumor. Then, another ROI of the same size was drawn over the lateral pterygoid muscle. The TUR was calculated using the following formula[18]: TUR = (total counts in the ROI over the tumor)/(total counts in the same size ROI over the lateral pterygoid muscle).

Neoadjuvant Chemotherapy

The chemotherapy regimen consisted of 2 cycles of DDP 100 mg/m^2 as a rapid intravenous infusion on Day 1 and 5-FU 750 mg/m^2 daily as a continuous intravenous infusion on Days 1 through 5 repeated every 21 days. All patients received an antiemetic prophylaxis consisting of 5-hydroxy-tryptamine-3 receptor antagonists plus 20 mg of dexamethasone.

Evaluation of Chemotherapy Response

All patients had magnetic resonance (MR) images obtained before treatment and 2 weeks after the second

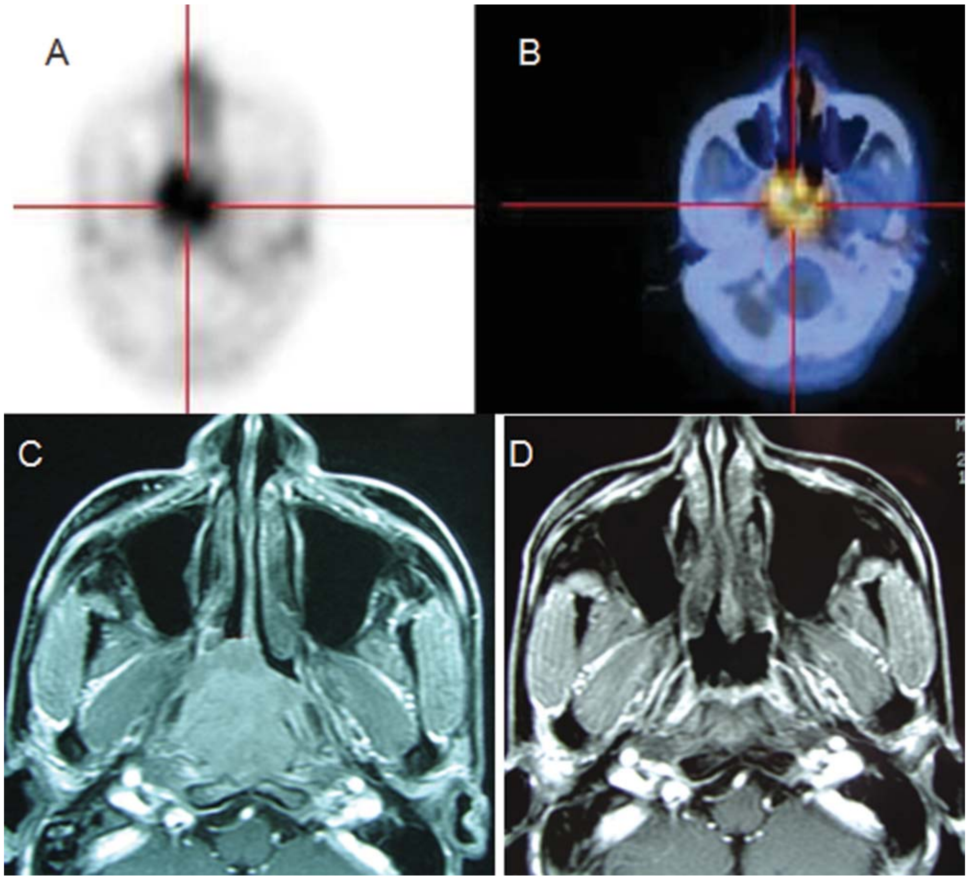

Figure 1. These are images from a man aged 49 years with nasopharyngeal carcinoma (NPC). (A) A technetium-99m methoxyisobutyl isonitrile (^{99m}Tc-MIBI) single-photon emission computed tomography (SPECT) scan shows positive uptake of 99mTc-MIBI in tumor (tumor uptake ratio = 5.28). (B) This is a ^{99m}Tc-MIBI SPECT/computed tomography fusion image. (C) This magnetic resonance (MR) image was obtained before chemotherapy. (D) This MR image was obtained after 2 cycles of 5-fluorouracil/cisplatin chemotherapy.

cycle of 5-FU/DDP chemotherapy. MR images were acquired with a General Electric 1.5-Tesla unit using a head and neck coil. T1-weighted, fast spin-echo images in the axial and sagittal planes (repetition time [TR], 400-500 msec; echo time [TE], 10-15 msec) and T2-weighted, fast spin echo images in the axial plane (TR, 4000-5000 msec; TE, 80-100 msec) were obtained before the injection of contrast material. After intravenous injection of gadolinium-complexed diethylene triamine pentaacetic acid at a dose of 0.1 mmol/kg of body weight, T1-weighted, fast spoiled gradient echo (FSPGR), fat-suppressed axial and coronal sequences were acquired (TR, 150-250 msec; TE, 2-10 msec). Section thickness was 6 mm with a 1-mm interslice gap for the axial plane and 4 mm without an interslice gap for the coronal and sagittal planes. Response to chemotherapy was evaluated on T1-weighted, FSPGR, fat-suppressed MR images according to the Response Evaluation Criterion In Solid Tumors[22] by diagnostic radiologists who were blinded to the results from ^{99m}Tc-MIBI SPECT imaging.

Statistical Analysis

All statistical analyses were performed using the SPSS software package (version 10.0; SPSS Inc., Chicago, Ill). The chi-square test was used to analyze correlations between ^{99m}Tc-MIBI tumor accumulation and primary tumor response. A 2-tailed *P* value $<.05$ was considered statistically significant in all analyses.

RESULTS

Patient Characteristics

From June 2005 to July 2007, 86 eligible patients participated in this study. The clinical characteristics of those patients are provided in Table 1.

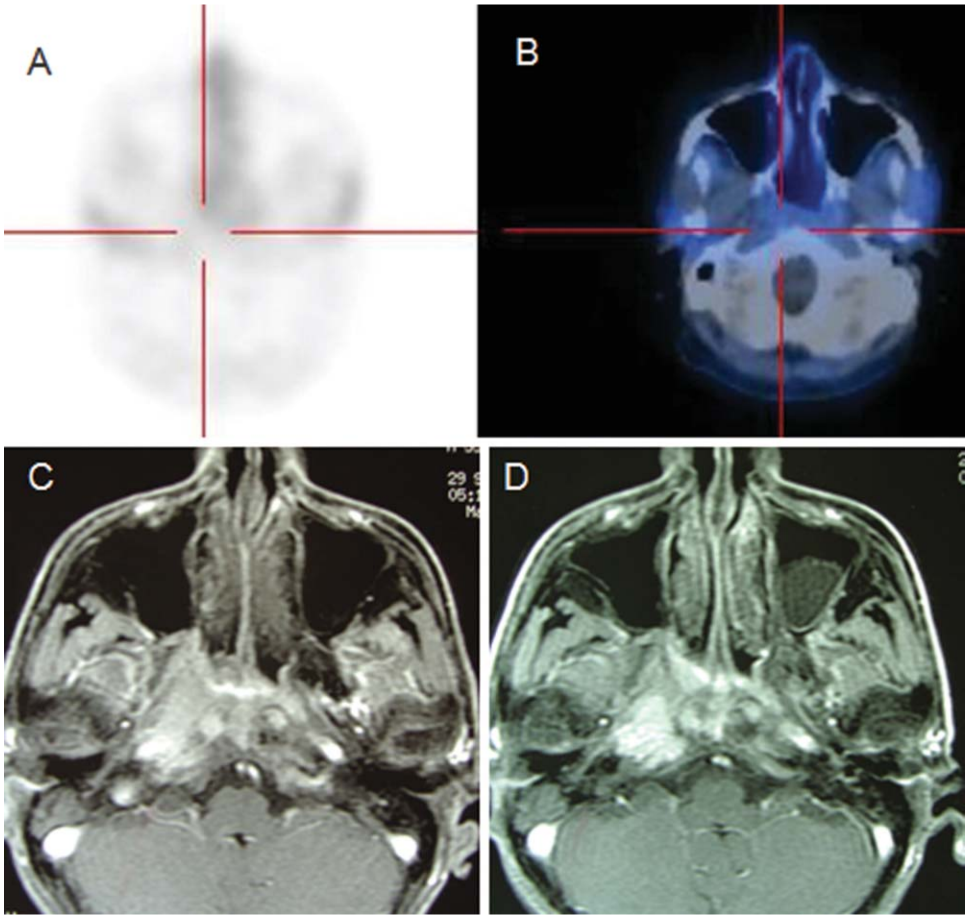

Figure 2. These are images from a man aged 46 years with nasopharyngeal carcinoma (NPC). (A) A technetium-99m methoxyisobutyl isonitrile (^{99m}Tc-MIBI) single-photon emission computed tomography (SPECT) scan shows negative uptake of 99mTc-MIBI in tumor (tumor uptake ratio = 0.97). (B) This is a ^{99m}Tc-MIBI SPECT/computed tomography fusion image. (C) This magnetic resonance (MR) image was obtained before chemotherapy. (D) This MR image was obtained after 2 cycles of 5-fluorouracil/cisplatin chemotherapy.

^{99m}Tc-MIBI Accumulation in NPC

According to the quantitative evaluation, positive accumulation of ^{99m}Tc-MIBI in tumors was observed in 76 of 86 patients (88.4%), and negative accumulation was observed in 10 of 86 patients (11.6%), as interpreted by the nuclear physicians. Further analysis indicated that the overall TUR was $\leq$1.1 (range, 0.9-1.1) in the 10 negative patients and >1.1 (range, 1.1-5.4) in the 76 positive patients. The correlation between ^{99m}Tc-MIBI accumulation and tumor classification is detailed in Table 2.

Tumor Response Rate

Two weeks after the second cycle of chemotherapy with 5-FU/DDP, the responses were as follows: a complete response (CR) was attained in 8 patients, a partial response (PR) was attained in 68 patients, 9 patients had stable disease (SD), and 1 patient had progressive disease (PD) according to evaluations by diagnostic radiologists.

5-FU/DDP Chemotherapy Was Effective in Patients With Positive ^{99m}Tc-MIBI Accumulation

The results from ^{99m}Tc-MIBI imaging interpreted by the nuclear physicians and the tumor response results interpreted by the diagnostic radiologists finally were sent to the clinicians, who established the correlation between ^{99m}Tc-MIBI tumor accumulation and response to DDP/5-FU induction chemotherapy. Table 3 indicates that the response rate (combined CRs and PRs) to 5-FU/DDP chemotherapy in patients who had positive ^{99m}Tc-MIBI accumulation was much higher than that in patients who

Table 1. Patient Characteristics

Characteristic	No. of Patients
Age, y	
Range	24-67
Median	48
Sex	
Men	63
Women	23
Tumor classification	
T3	49
T4	37
Lymph node status	
N0	9
N1	18
N2	50
N3	9
Pathologic type	
WHO type II	9
WHO type III	77

WHO indicates World Health Organization.

had negative ^{99m}Tc-MIBI accumulation (98.7% vs 10%; $P < .001$).

Table 2. Relation Between Technetium-99m Methoxyisobutyl Isonitrile Accumulation and Tumor Classification

	No. of Patients		
Tumor Classification	MIBI Negative	MIBI Positive	*P*
T3	4	45	.25
T4	6	31	
Total	10	76	

MIBI indicates methoxyisobutyl isonitrile.

Table 3. Relation Between Technetium-99m Methoxyisobutyl Isonitrile Accumulation in Tumors and Responses to Chemotherapy

	No. of Patients		
Tumor Response	MIBI Negative	MIBI Positive	*P*[a]
CR	0	8	.58
PR	1	67	.00
SD	8	1	.00
PD	1	0	.12
Total	10	76	

MIBI indicates methoxyisobutyl isonitrile; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
[a] Fisher exact test.

DISCUSSION

In the current study, we demonstrated a significant correlation between pretherapy ^{99m}Tc-MIBI accumulation in tumor and tumor response to chemotherapy. Patients who had negative ^{99m}Tc-MIBI accumulation had less sensitivity to 5-FU/DDP compared with patients who had positive ^{99m}Tc-MIBI accumulation, suggesting that ^{99m}Tc-MIBI can help to select patients for effective induction chemotherapy with 5-FU/DDP.

Regarding ^{99m}Tc-MIBI and P-gp, previous studies have demonstrated a significant correlation between ^{99m}Tc-MIBI accumulation and P-gp expression in several types of cancers.[13-19] To our knowledge, the current study is the first report of ^{99m}Tc-MIBI in patients with NPC. Piwnica-Worms et al.[23] reported that the uptake of ^{99m}Tc-MIBI was increased approximately 10 times in cells that had low expression of P-gp. In addition, after the application of drugs that can inhibit the activity of P-gp, such as verapamil and cyclosporine, the uptake of ^{99m}Tc-MIBI increased approximately 200 times in cells that had abundant P-gp expression. These findings strongly indicate that ^{99m}Tc-MIBI is a suitable substrate of P-gp.

Several methods, such as Northern or Western blot analyses and immunohistochemistry, have been used to evaluate P-gp expression in cancer tissues. However, these results may not fully represent all tumor characteristics, because most specimens were obtained from small parts of heterogeneous and large tumors and may not have accounted for the characteristics of the entire tumor. This is especially true in NPC, because radiation therapy is the standard treatment for NPC, and it is impossible to acquire large cancer specimens. In contrast, ^{99m}Tc-MIBI imaging can evaluate the entire tumor noninvasively, allowing for repeated assessments, and can serve as a surrogate for P-gp expression in the whole tumor.

Concerned with the correlation between the chemotherapeutic effect and ^{99m}Tc-MIBI accumulation, several other studies have demonstrated that chemotherapy with doxorubicin is more effective in patients who have greater ^{99m}Tc-MIBI accumulation with lung cancer,[14-16] breast cancer,[13] and bone and soft tissue tumors.[19] Our results indicate that patients with NPC who had intense ^{99m}Tc-MIBI accumulation had greater sensitivity to 5-FU/DDP chemotherapy, consistent with those previous reports. In addition to P-gp expression in tumor tissues, ^{99m}Tc-MIBI accumulation in tumors can be affected by many factors, such as blood flow, tissue viability, vascular permeability, tumor necrosis, metabolic demand, and mitochondrial activity of the tumor.[24] We believe that those factors may be responsible for poor responses to 5-FU/DDP chemotherapy even in patients with greater ^{99m}Tc-MIBI accumulation.

Recently, induction chemotherapy with a docetaxel, DDP, and 5-FU triple-combination regimen (TPF) has been widely investigated in head and neck cancer; and large-scale randomized trials have demonstrated the benefits of TPF compared with DDP/5-FU.[25,26] Induction chemotherapy with docetaxel-based or paclitaxel-based combination regimens followed by concurrent chemoradiation therapy also demonstrated promising results in patients with locally advanced NPC.[27,28] In vitro and in vivo studies also have demonstrated a correlation between P-gp expression and docetaxel/paclitaxel resistance.[29-31] It remains to be determined whether ^{99m}Tc-MIBI imaging can predict the therapeutic effect of chemotherapy with docetaxel-based or paclitaxel-based regimens.

In conclusion, ^{99m}Tc-MIBI imaging in NPC can predict tumor response to chemotherapy with DDP/5-FU. The current results have demonstrated that DDP/5-FU is less active in patients who have negative ^{99m}Tc-MIBI accumulation.

CONFLICT OF INTEREST DISCLOSURES

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