Applicability of radiocolloids, blue dye and fluorescent indocyanine green to sentinel node biopsy in melanoma

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Abstract

The patients with primary cutaneous melanoma underwent sentinel node (SN) mapping and biopsy at 25 facilities in Japan by the combination of radiocolloid with gamma probe and dye. Tc^{99m}-tin colloid, Tc^{99m} -phytate, 2% patent blue violet (PBV) and 0.4% indigocarmine were used as tracers. In some hospitals, 0.5% fluorescent indocyanine green, which allows visualization of the SN with an infrared camera, was concomitantly used and examined. A total of 673 patients were enrolled, and 562 cases were eligible. The detection rates of SN were 95.5% (147/154) with the combination of tin colloid and PBV, 98.9% (368/372) with the combination of phytate and PBV and 97.2% (35/36) with the combination of tin colloid or phytate and indigocarmine. SN was not detected in 12 cases by the combination method, and the primary tumor was in the head and neck in 6 of those 12 cases. In 8 of 526 cases (1.5%), SN was detected by PBV but not by radiocolloid. There were 13 cases (2.5%) in which SN was detected by radiocolloid but not by PBV. In 18 of 36 cases (50%), SN was detected by radiocolloid but not by indigocarmine. Concomitantly used fluorescent indocyanine green detected SN in all of 67 cases. Interference with transcutaneous oximetry by PVB was observed in some cases, although it caused no clinical trouble. Allergic reactions were not reported with any of the tracers. Tc^{99m}-tin colloid, Tc^{99m} -phytate, PBV and indocyanine green are useful tracers for SN mapping.

Key words: Sentinel lymph node biopsy, Melanoma, Tin colloid, Phytate, Patent blue violet, Indigocarmine, Indocyanine green, Japan

Introduction

Intraoperative lymphatic mapping and selected lymphadenectomy have made it possible to determine the lymphatic flow from a primary tumor and to identify its sentinel lymph node(s) (SN) in the regional basin[1-3]. Since its sixth edition, the AJCC/UICC melanoma staging system has incorporated the pathological evaluation in SN into the new staging criteria for melanoma [4]. In Japan, sentinel node biopsy (SNB) has been verified for over a decade and is now widely performed in melanoma staging[5, 6]. However, prior to the completion of the present study, SNB had been performed only in the context of clinical trials and had not been covered by public health insurance in Japan. In order to gain approval for clinical use and to gain insurance coverage, we planned a multicenter clinical trial under the unified methods.

Materials & Methods

The multicenter study was performed from January 2007 to October 2009. Patients underwent cutaneous lymphoscintigraphy with radiopharmaceuticals, either one day before or on the day of the operative procedure. Tc^{99m}-tin colloid and Tc^{99m} -phytate, which have particle sizes ranging from 400 to 5000 nm and from 200 to 1000 nm, respectively, were used as radiocolloid. Using the lymphoscintigraphic images, the skin site corresponding to the highest accumulation of radioparticles was identified and marked. At the time of surgery, 2% patent blue violet or 0.4% indigocarmine was injected intradermally at the primary tumor site. Furthermore, in some hospitals, 0.5% fluorescent indocyanine green, which allows visualization of the SN with an infrared camera,

was concomitantly used in the combination of radiocolloid and blue dye. An incision was made on the skin site that was the most radioactive by the gamma probe.

Candidates for the study were patients with primary invasive cutaneous melanoma without any clinical evidence of metastatic disease. Exclusion criteria were as follows: patients with distant metastasis, patients with severe liver dysfunction, patients who were nursing infants or who were pregnant or might be pregnant, patients who did not provide informed consent and patients regarded as not suitable for this study by their physicians. Before this study, the protocol of SNB was approved by a ethics committee of each institution and was registered in UMIN Clinical Trials Registry (UMIN-CTR: http://www.umin.ac.jp/ctr/index-j.htm)

Results

A total of 673 patients were enrolled. Each patient who had received SN mapping with a combination of blue dye and radiocolloid with a handheld gamma probe were eligible for analysis of the detection rate; 562 patients met that criterion. The detection rate of SN in those cases was 97.9% (550/562). The detection rates of SN were 95.5% (147/154) in patients given the combination of tin colloid and patent blue violet, 98.9% (368/372) in those given the combination of phytate and patent blue violet and 97.2% (35/36) in those given the combination of tin colloid or phytate and indigocarmine (Table 1). SN was not detected in 12 cases by the combination method. In 6 of those cases, the primary tumor was in the head and neck (Table 2). In 8 of 526 cases (1.5%), SN

was detected by patent blue violet but not by tin colloid (7 cases) or by phytate (1 case). There were 13 cases (2.5%) in which SN was detected by radiocolloid but not by patent blue violet. In 18 of 36 cases (50%), SN was detected by radiocolloid but not by indigocarmine. Concomitantly used fluorescent indocyanine green detected SN in all 67 cases. Toxicity was evaluated in 673 cases. Interference with transcutaneous oximetry by patent blue violet was observed in some cases, although it caused no clinical trouble. Allergic reactions were not reported in tin colloid (154 cases), phytate (372 cases), patent blue violet (527 cases), indigocarmine (36 cases) or indocyanine green (94 cases). No other problems related to the tracers were reported.

Discussion

Our results showed that both Tc^{99m}-tin colloid and Tc^{99m} –phytate detected SN with a high degree of accuracy. The SN detection rates were 95.5% with the combination of tin colloid and patent blue violet and 98.9% with the combination of patent blue violet and phytate. In 6 of 12 cases in which SN was not detected, the primary tumor was in the head and neck region, similar to the tendencies in previous reports[7]. In 8 cases, SN was detected by patent blue violet but not by tin colloid (7 cases) or by phytate (1 case). We supposed that halation may have caused the failure in 4 of 7 cases in which tin colloid was used, because of the closeness of the primary tumor and SN. In the 527 cases in which patent blue was used, there were 13 cases in which SN was detected by radiocolloid but not by patent blue violet. Technical factors may have influenced the phenomenon. Indigocarmine could not detect SN in half of the cases. The concentration might

be too low to detect SN, because the approved concentration of indigocarmine in Japan is now only 0.4%. These results indicate that the combination of radio colloid and dye is important for detecting SN without failure.

Concomitantly used fluorescent indocyanine green detected SN in all 67 cases. Because indocyanine green has a characteristic absorption peak of 800 nm in the near-infrared region, it can be used for real-time fluorescence navigation to detect SN[8]. This method might be useful as a complement to lymphoscintigraphy, the gamma probe technique and blue dye.

Reported adverse effects of isosulfan and patent blue dyes include allergic reactions such as urticaria, rash and, rarely, anaphylaxis, protracted blue discoloration, interference with transcutaneous oximetry and cutaneous necrosis[3]. In our study, interference with transcutaneous oximetry by patent blue violet was observed in some cases, although it caused no clinical trouble. No allergic reactions were observed.

In conclusion, radiocolloids, blue dyes and indocyanine green were useful tracers for SN mapping in this study. The concentration of indigocarmine might need to be substantially increased. These data were sent to the Ministry of Health, Labor and Welfare of Japan. In April 2010, SNB was approved by the Japanese public health insurance system.

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Table 1　Tracers and detection rates
(the combination of dye and radiocolloid with gamma probe)

Tracer	Detection rate	No. of cases
PB* & Phytate	98.9% (368/372)	372
PB+‡, Phytate+		366
PB+, Phytate-§		1
PB-, Phytate+		1
Not detected		4
PB & Tin-colloid	95.5% (147/154)	154
PB+, Tin-colloid+		127
PB+, Tin-colloid-		7
PB- , Tin-colloid+		13
Not detected		7
I† & Phytate/Tin-colloid	97.2% (35/36)	36
I+, Phytate or Tin-colloid +		17
I+, Phytate or Tin-colloid -		0
I-, Phytate or Tin-colloid +		18
Not detected		1

PB*: patent blue violet, I†: indigocarmine, +‡: detected, -§: not detected

Table 2 Profiles of the cases in which SN was not detected (n=12)

Location (No. of cases)	Radiocolloid	Dye
Head & neck (6)		
Cheek	T*	PB‡
Ear	P†	PB
Ear	T	I§
Eyelid	T	PB
Cheek	T	PB
Lip	T	PB
Trunk (2)		
Chest	T	PB
Back	T	PB
Upper extremity (2)		
Upper arm	T	PB
Finger	P	PB
Lower extremity (2)		
Sole	P	PB
Sole	P	PB

T*: Tin colloid, P†: Phytate, PB‡: Patent blue, I§: Indigocarmine