# Leakage Monitoring during Isolated Limb Perfusion: Comparison of Two Radioisotopic Techniques in a Patient with Malignant Melanoma.

Sapienza MT, Campos-Neto GC, Oliveira MAC, Akaishi E, Watanabe T, Ono CR, Costa PLA, Rodrigues CJ, Rodrigues Jr. AJ, Buchpiguel CA

Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil

**Abstract**

*The aim of this study was to compare two radioisotopic methods used to quantify systemic leakage during an isolated limb perfusion (ILP). A patient with recurrent lower limb melanoma was procedure submitted to high-dose cytostatic therapy during ILP. Leakage was monitored after administration of I-131 human serum-albumin (I-131 HSA), using a conventional scintillation probe over the heart. The same procedure was simultaneously performed using Tc-99m red blood cells (Tc-99m RBC) and a hand-held probe. Systemic leakage was quantified based on precordial count-rate variation. Both techniques showed similar curve patterns, with a slightly higher leakage value calculated with the hand-held probe than with the conventional probe (mean ratio=1.36). No systemic toxicity was observed and regression of the lesion was noted after one week. Leakage monitoring is a critical step for the implementation of ILP in the management of melanoma patients, and it can be easily performed using radioisotopic techniques.*

*Keywords: Melanoma, Chemotherapy, Radioisotope, Isolated Perfusion*

## Introduction

Treatment of malignant melanoma usually consists of lesion removal with a safety border. However, complementary treatment modalities may be required when there is local dissemination of melanoma. Isolated limb perfusion (ILP) allows the infusion of high concentration of cytostatic drugs in the limb. The most common used drug is melphalan, with complete response rates greater than 50%, although TNF-alpha has also been increasingly recommended (1).

Systemic leakage of the drugs used during ILP may occur as a consequence of communication between the systemic vasculature and the isolated limb. Toxicity is directly related to leakage rates, thus emphasizing the importance of leakage monitoring (1, 2, 3). In this case report we describe the use of two different quantitative radioisotopic techniques for leakage monitoring, comparing a hand-held probe with that of conventional gamma probe.

**World J Nuc Med 2005;4:108-110**

*Corresponence:*
*Marcelo Tatit Sapienza*
*Rua Barão do Melgaço 230/24, Real Parque*
*São Paulo SP Brazil*
*CEP 05684-030*
*E-mail: mtsapienza@hotmail.com*

## A Case Report

An 85 year-old female patient was submitted to isolated limb perfusion therapy for recurrent melanoma on the left leg. Isolation of the limb was achieved by clamping the femoral artery and vein and by applying a tourniquet in the groin. Femoral vessels were cannulated, and an extracorporeal bypass circuit containing a pump oxygenator and a heat exchanger was used to provide circulation to the isolated limb.

Isolated limb perfusion was performed for 70 minutes, but no cytostatic drugs were added to the circuitry during the first 30 minutes, while the temperature (40.5°C) and flow rates (200ml/min) were being stabilized. The limb was then selectively perfused for a period of 40 minutes under hyperthermic conditions, with a solution containing 75 mg of melphalan. Systemic leakage from the perfused limb was monitored by the two techniques described below.

### 1. Leakage Monitoring by the Conventional Probe using I-131 HSA as tracer

After the limb circuit was established, the patient was administered intravenously with 0.6MBq (16ìCi) of Iodine-131 labeled Human Serum-Albumin (I-131 HSA). A scintillation probe (model ZX, AlfaNuclear, Buenos Aires) with a 2-inches thick NaI(Tl) detector was set to a 20% window over 364 keV and placed laterally to the thorax, at 20 cm from the patient. Initial count rate was measured and registered three minutes after the systemic injection, followed by the injection of a tenfold higher dose of I-131 HSA into the perfusion circuit.

Thoracic count rate was monitored during the entire ILP procedure, with readings at every 5-minute interval or after changes in extracorporeal flow rates. An increase in count rate, indicating a leak from the perfusion circuit into the systemic circulation was calculated by the following equation:

**Lcp = (Ct / C0) x IR** **(Equation 1)**
Where:
*Lcp = Leakage percentage detected with the conventional probe*
*Ct = thoracic count rate at time t*
*C0= initial thoracic count rate*
*IR= Ratio between injected activity in the patient and in the circuit.*

**2. Leakage Monitoring using a Hand-Held Probe using Tc-99m RBC as tracer**

This technique was performed simultaneously with the I-131 HSA measurements. A hand-held probe with a cadmium-zinc-telluride crystal, model Neo2000 (Neoprobe Corp., Dublin-Ohio) was placed at 5 cm above the heart. Patient was intravenously administered with 185MBq (5 mCi) of technetium-99m labeled red-blood-cells (Tc-99m RBC) (UltraTag-Mallinckrodt), followed by the administration of a tenfold higher dose of Tc-99m RBC in the perfusion circuit. Injections of Tc-99m RBC were performed almost simultaneously with those of I-131 HSA. Count rate over the heart was monitored during the entire ILP procedure, with 5-minute interval readings. Due to the shorter half-life of technetium-99m, count rates were decay corrected, before leakage was calculated by the following equation:

**Lhp = (Ct / C0) x IR** **(Equation 2)**
Where:
*Lhp = Leakage percentage detected with the hand-held probe.*
*Ct = pre-cordial count rate on time t (decay corrected)*
*C0= initial count rate over the heart*
*IR= Ratio between injected activity in the patient and in the circuit.*

A sudden increase at systemic leakage was clearly associated with an attempt to increase the perfusion flow-rate by 10%, at the beginning of Melphalan infusion (Figure 1). Although a similar curve pattern was observed by both methods, the percent of leakage calculated with the hand-held probe (Lhp) was slightly greater than the one estimated with the conventional scintillation probe (Lcp). Mean ratio between Lhp and Lcp after the first 30 minutes of isolated limb perfusion was 1.36 (standard deviation = 0.07), reaching a maximum Lcp of 4.1% and Lhp of 2.8% at the end of the perfusion.
After a period of 70-minute perfusion, the extremity was washed out and flow was reestablished. No systemic toxicity was observed during or after the procedure. Patient had significant regression of the lesion in the first week after the procedure.

## Discussion

Isolated limb perfusion allows the infusion of high concentrations of cytostatic drugs during hyperthermic perfusion of the limb, and it is used for the complementary treatment of advanced or recurrent melanoma confined to a limb. Radioisotopic leakage monitoring is recommended to assure the safety of the procedure, but there is no clear standardization of this procedure in literature.
Monitoring can be performed by repeated venous blood sampling after injection of radiolabeled albumin or red-blood-cells in the perfusion system. Although leakage can be quantified by *in vitro* methods, quantifying procedures may be technically difficult to perform. Another limitation is that a well-counter must be available close to the patient in the surgical center.
A more practical way of detecting systemic leakage is a continuous precordial monitoring with a probe. Due to its increasing availability in most surgical centers, the use of a

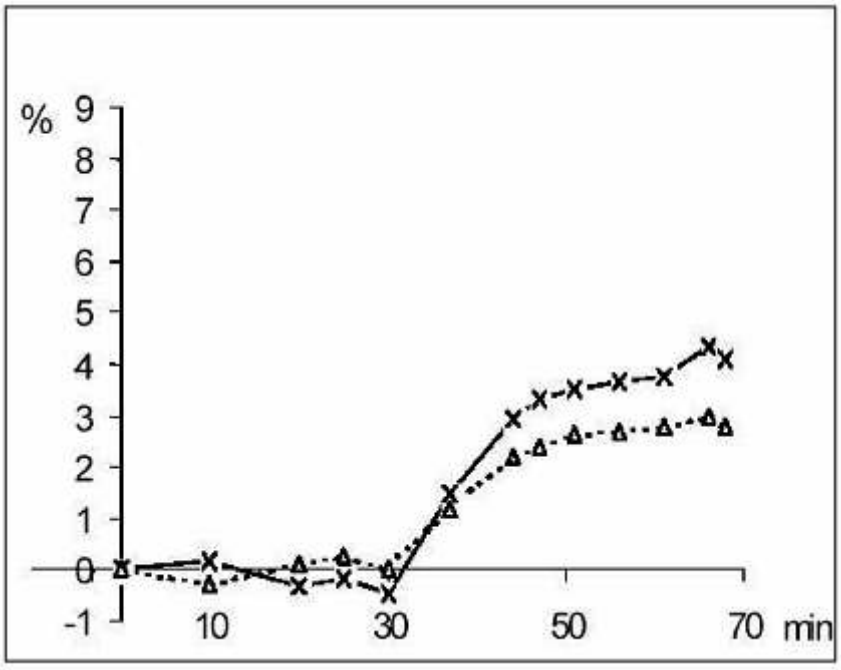


**Figure 1** Systemic leakage quantified during ILP with Tc-99m RBC using a hand-held

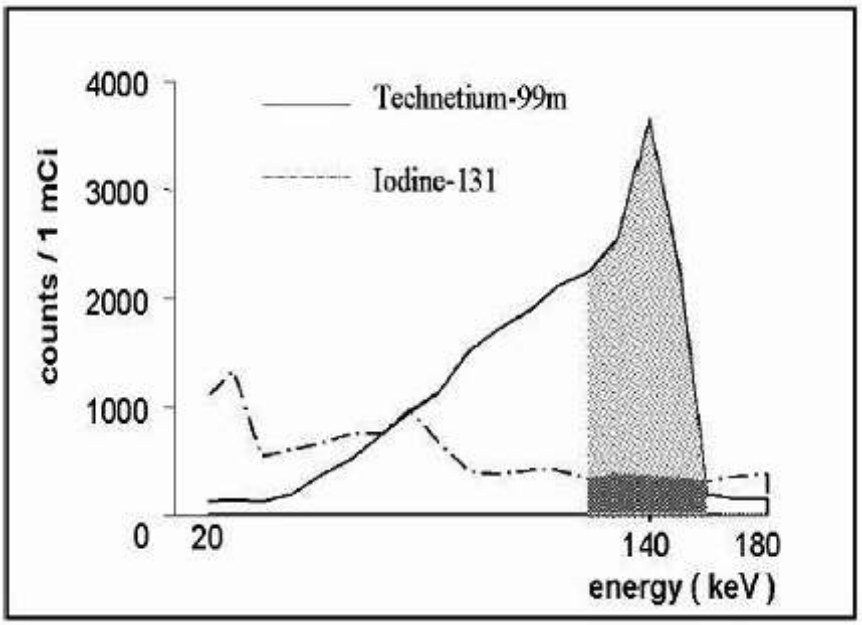


**Figure 2** Technetium-99m and Iodine-131 energy spectrum acquired with 37 MBq (1 mCi ) point-sources placed at 5 cm from the probe. Down-scatter from iodine-131 accounts for approximately 15% of the total counts in the Tc-99m energy window.

hand-held probe would be an excellent alternative. However, hand-held probes are designed for identification of small foci of uptake, and are particularly vulnerable to geometric errors that could lead to uncertainties in the determination of leakage. These concerns were minored by the observation of a high correlation between a portable probe count-rate and simultaneous *in vitro* measures performed during ILP (4). Unfortunately, the equations described cannot be reproduced in other institutions, since any change in probe sensitivity or positioning woul affect the results.

The use of a hand-held probe to evaluate systemic leakage was compared in this patient with a technique already established in literature, using I-131 HSA and a conventional scintillation probe (5). Both techniques are based upon the administration of the radiopharmaceutical into the systemic circulation and approximately tenfold higher dose of the same isotope into the isolated limb. Then, initial systemic activity is used as a correction factor that allows subsequent increases in count rates to be directly related to the percentage of blood arriving from the isolated limb.

The hand-held probe's lower sensitivity made it necessary to increase the activity administered to the patient and also the activity injected into the circuit. Instead of using a higher activity of I-131 HSA, we chose to use *in vitro* labeled Tc-99m RBC. If identical activities of both radiopharmaceuticals were used, the iodine-131 down-scatter contribution in the 140keV window would be about 15% (Figure 2). Considering that a 300-times smaller activity of I-131 HSA was injected, the influence of iodine-131 on Tc-99m RBC readings can be assumed to be minimal (0.05%).

Curve patterns using either the hand-held probe or the scintillation detector were similar in this patient. Differences in quantifications may be more related to the radiopharmaceutical used than to the detection device. The choice of radiopharmaceuticals was based on their retention in the vascular compartment, although a slow and progressive decrease in intravascular activity may be observed when using albumin, due to extra-vascular leak of the protein. Since the stability in the vascular compartment is essential for a successful procedure, we recommend *in vitro* labeled RBC as the radiopharmaceutical of choice. The use of hand-held probes can facilitate monitoring of isolated limb perfusion, as it is available in most surgical centers.

## References

1. Rossi CR, Foletto M, Pilati P, Mocellin S, Lise M. Isolated limb perfusion in locally advanced cutaneous melanoma. Semin Oncol 2002; 29:400-409.
2. Lejeune FJ, Kroon BB, Di Filippo F, et al. Isolated limb perfusion: the European experience. Surg Oncol Clin N Am 2001; 10:821-32.
3. Cattel L, Buffa E, De Simone M, et al. Melphalan monitoring during hyperthermic perfusion of isolated limb for melanoma: pharmacokinetic study and Tc-99m albumin microcolloid technique. Anticancer Res 2001; 21:2243-2248.
4. Sandrock D, Horst F, Gatzemeier W, et al. Leakage measurement during selective limb perfusion using a gamma probe. Eur J Nucl Med 1996; 23:534-538.
5 Eggermont AM, Schraffordt KH, Klausner JM, et al. Isolated limb perfusion with tumor necrosis factor and melphalan for limb salvage in 186 patients with locally advanced soft tissue extremity sarcomas. The cumulative multicenter European experience. Ann Surg 1996; 224:756-764