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# Selective Internal Radiation Therapy: Distribution of Radiation in the Liver

MARK A. BURTON,* BRUCE N. GRAY,* PETER F. KLEMP,† DEBRA K. KELLEHER* and NATALIE HARDY*

**University of Western Australia, Department of Surgery and †Department of Medical Physics, Royal Perth Hospital, Perth, Western Australia*, 6000

**Abstract**—*Selective internal radiation therapy for primary and secondary liver cancer involves the intra-hepatic arterial injection of microspheres containing yttrium-90. The microspheres become entrapped primarily in, and thus preferentially irradiate, tumour tissue. During a clinical trial with this therapy it has been possible to take tumour and normal liver tissue samples, after microsphere injection, and measure their specific activity. Absorbed tissue radiation doses were then calculated for tumour and normal tissue samples from a total of nine patients. The mean tumour to normal tissue ratio for radiation dose for the nine patients was approximately* 6:1 *with a range of* 0.4:1–45:1. *Injection of similar amounts of activity in different patients resulted in markedly differing tissue doses depending on liver size and tumour burden. Normal liver tissue doses of between* 9 *and* 75 Gy *were measured while corresponding tumour tissue doses ranged from* 34 *to* 147 Gy. *Selective internal radiation therapy, combined with the blood flow changes resulting from angiotensin II administration, can provide preferentially high radiation doses to tumour tissue within the liver whilst relatively sparing the surrounding normal liver tissue.*

## INTRODUCTION

PRIMARY and secondary liver cancers are leading causes of cancer related deaths world-wide. In Western countries hepatic metastases outnumber primary tumours by about 50:1 [1] with the liver being involved in about 40% of patients with primary extrahepatic malignant disease [2]. Only 7% of patients with untreated hepatic metastases survive 1 year [3] and neither chemotherapy nor conventional radiotherapy significantly prolong patient survival [4]. The use of intrahepatic arterially introduced radioactive microspheres has recently been suggested as a potentially effective treatment modality for both primary and secondary liver cancer [5–7].

Selective internal radiation therapy (SIR therapy) has been implemented in a Phase II clinical trial at Royal Perth Hospital since early 1987. The therapy involves the intra-hepatic arterial injection of large numbers of resin microspheres incorporated with yttrium-90 (SIR spheres). The microsphere injection is preceded by the infusion of angiotensin II into the hepatic artery which constricts the normal liver vasculature and results in a blood flow favouring tumour tissue [8, 9]. The enhanced tumour blood flow transports the microspheres preferentially to the resident tumour where they become trapped and provide extensive radiation exposure. Yttrium-90 is a pure beta emitter of high mean energy (0.93 MeV), a mean penetration in tissue of 0.45 cm and a half life of 64.2 h making it highly attractive for this form of treatment.

The treatment has initially been provided during laparotomy to enable the measurement of individual radiation doses using an intraoperative radiation detection probe [10]. This has also allowed the retrieval of tissue samples from the liver of patients after the injection of microspheres to determine the patterns of distribution of radiation empirically.

## MATERIALS AND METHODS

### *SIR spheres*

The yttrium-90 SIR spheres were developed in the University Department of Surgery and are now manufactured in conjunction with the Australian Nuclear Science and Technology Organisation. Yttrium-90 is bound to resin microspheres of either 17.5 ± 2.5 or 32.5 ± 2.5 μm diameter. The microspheres have a specific gravity of approximately 1.6 g/ml and contain yttrium-90 at an activity

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Address correspondence to: Dr. M.A. Burton, University Department of Surgery, Royal Perth Hospital, Perth, Western Australia, 6000.

adjustable between 5 and 30 Bq/microsphere depending on their size (the larger microspheres being more active). The number of SIR spheres introduced into each patient varied between $49 \times 10^6$ and $118 \times 10^6$ depending on the size of the microspheres and the final tissue radiation dose achieved.

*SIR therapy*

The protocol for SIR therapy proceeds from a laparotomy [6]. The gastroduodenal artery is catheterized and perfusion of both lobes of the liver ensured. Initially 1 GBq of SIR spheres are suspended in a 5 ml syringe which is secured to a purpose built delivery system. This system includes facility for the injection of a bolus dose of 50 μg of angiotensin II pulsed into the main hepatic artery over 10 s. Approximately 30 s after the angiotensin II has been introduced a predetermined fraction of the suspended SIR spheres is pulsed into the hepatic artery. The normal liver tissue is then scanned with a solid state beta detection probe to obtain a mean count rate of the radiation being emitted from the surface of the liver. The procedure is then repeated until the desired normal tissue radiation dose is reached.

The beta probe was previously calibrated to enable calculation of the estimated radiation dose being delivered to the normal liver tissue [10]. The calibration procedure was performed in the normal livers of 10 sheep injected intra-hepatic arterially with SIR spheres. A linear relationship was found between detector recordings and the radiation dose as calculated from the activity of the livers after scintillation counting.

*Biopsy samples*

Of the first 35 patients treated in the SIR therapy trial, nine had biopsy samples of both tumour and normal tissue taken after the SIR spheres had been delivered. All nine patients presented with primary adenocarcinoma arising from the large bowel and proven liver metastases. Informed consent was obtained from all patients prior to treatment.

The size of the biopsies varied from 0.62 to 10.1 g and in four patients (Nos. 5, 6, 8, 9) more than one biopsy was taken. Each biopsy was sectioned into 0.1–0.2 g samples for determination of radiation activity in a 3-channel liquid scintillation counter (Packard). Account was taken of quench and the geometry of counting as microspheres settle in sample vials. The activity was determined against a strontium-90/yttrium-90 standard. The mean specific activity was then calculated for each biopsy specimen.

*Dose determination*

The dosimetry was based on the specific activity of the biopsy samples assuming the SIR spheres and isotope were distributed homogeneously within the tissue. However, in reality the radiation activity is actually deposited in the tissue as a number of discrete point sources resulting in a very complex pattern of dose distribution. The absorbed dose for each kilogram of tissue has been calculated as 1.82 Gy for every 37 MBq of isotope [11, 12]. Thus the following equation was used:

$$\text{Activity (0.037 MBq)} = \frac{\text{desired dose (Gy)} \times \text{organ weight (g)}}{1.82}$$

This calculation provided an estimate of the absorbed tissue doses in both tumour and normal liver tissue compartments of the nine patients. Tumour radiation doses were estimated from sections of the growing edge of the tumour rather than from areas of central necrosis.

## RESULTS

Table 1 describes the mean radiation doses associated with the activity injected and the tumour to normal tissue radiation dose ratio (T/N ratio) for each patient. In all but one instance (patient 8) the radiation dose delivered to the tumour far exceeded that deposited in the associated normal parenchyma. The total injected activity for the patients varied from 755 to 2300 MBq and these activities resulted in measured normal liver tissue doses of between 9 and 75 Gy. The tissue doses measured in tumour tissue varied from 34 to 1474 Gy and the resultant T/N ratios ranged from 0.4:1 up to 45:1.

Samples from some biopsies demonstrated a high degree of variability and there was also a demonstrated variability amongst patients and between tumours in the one patient. This has been described by the percentage coefficient of variation (COV%) of multiple samples. However, the majority of samples showed good reproducibility. Where only two samples could be taken from any single biopsy the COV% has not been expressed.

No significant extra-hepatic distribution of either microspheres or free yttrium-90 was encountered after the introduction of the SIR spheres. No pulmonary, marrow or gastrointestinal toxicity was detected in any of the patients. All patients are pre-screened to test for hepatic breakthrough of technetium-99m labelled macro-aggregated albumin particles into the lungs. If significant breakthrough is recorded then SIR therapy is not performed. During the injection of the SIR spheres, small numbers of microspheres have occasionally been shown to shunt into vessels of the duodenum but with no evidence of radiation damage. Transient free isotope measured in urine or blood following injection is less than 50 kBq/l while contamination of other body fluids is also negligible.

*Table 1. Tumour and normal tissue radiation doses associated with the amount of activity injected for each patient. The percentage coefficient of variation (COV%) is provided for the number of samples of tissue from each biopsy specimen* (n). *T/N ratio is the ratio of radiation doses in tumour tissue compared to normal hepatic tissue for each biopsy*

| No. | Injected activity (MBq) | Tumour tissue Dose (Gy) | *n* | COV% | Normal tissue Dose (Gy) | *n* | COV% | T/N ratio |
|---|---|---|---|---|---|---|---|---|
| 1 | 1191 | 81 | 6 | 47 | 41 | 6 | 43 | 2:1 |
| | | 81 | 6 | 47 | 25 | 6 | 28 | 3:1 |
| 2 | 1923 | 133 | 7 | 32 | 62 | 13 | 34 | 2:1 |
| 3 | 1878 | 34 | 90 | 94 | 9 | 50 | 99 | 4:1 |
| 4 | 755 | 292 | 3 | 34 | 58 | 9 | 65 | 5:1 |
| 5 | 1110 | 174 | 2 | — | 28 | 6 | 22 | 6:1 |
| | | 174 | 2 | — | 26 | 2 | — | 7:1 |
| 6 | 1116 | 66 | 5 | 24 | 40 | 51 | 39 | 2:1 |
| | | 85 | 2 | — | 40 | 51 | 39 | 2:1 |
| | | 79 | 2 | — | 40 | 51 | 39 | 2:1 |
| 7 | 2300 | 229 | 7 | 31 | 36 | 24 | 31 | 6:1 |
| 8 | 1680 | 540 | 2 | — | 75 | 30 | 50 | 7:1 |
| | | 31 | 2 | — | 75 | 30 | 50 | 0.4:1 |
| | | 1474 | 12 | 19 | 33 | 12 | 65 | 45:1 |
| | | 1008 | 10 | 29 | 33 | 12 | 65 | 31:1 |
| | | 765 | 9 | 40 | 33 | 12 | 65 | 23:1 |
| | | 586 | 2 | — | 33 | 12 | 65 | 18:1 |
| | | 603 | 2 | — | 33 | 12 | 65 | 18:1 |
| 9 | 2284 | 197 | 4 | 86 | 27 | 11 | 138 | 7:1 |
| | | 153 | 2 | — | 10 | 7 | 160 | 25:1 |
| | | 63 | 4 | 34 | 13 | 11 | 87 | 5:1 |
| | | 100 | 8 | 50 | 24 | 6 | 43 | 4:1 |
| | | 114 | 18 | 98 | 58 | 40 | 60 | 2:1 |

## DISCUSSION

The substantially higher radiation doses found in the tumour tissue compared to the normal tissue are likely in response to two factors. Firstly, there is a natural preferential blood delivery to hepatic tumours from the hepatic artery. Normal hepatic parenchyma derives its blood supply primarily from the portal vein but the reverse is true for hepatic tumours [13, 14]. Microspheres injected into that hepatic arterial blood flow will thus embolize tumour vasculature to a greater extent than normal vasculature. Secondly vasoconstrictors have been shown to restrict blood flow in the normal liver vessels but have little or no effect on the physiologically inert neovasculature of tumour tissue [15, 16]. Thus, administration of angiotensin II will shunt blood, and therefore microspheres, into tumour tissue rather than into normal tissue [8, 9].

It is not possible without a controlled study in man to determine quantitatively the effect of the use of angiotensin II on the distribution of SIR spheres and thus radiation in tumour and normal tissue. Observations from this and other laboratories [17, 18] indicate a probable T/N ratio in humans of about 2:1 or 3:1 without the use of angiotensin II. From the 23 tumour and normal tissue sample combinations the mean T/N ratio was approximately 10:1, while from the nine patients the mean T/N ratio was approximately 6:1. These figures correspond well to reported T/N ratios in animal tumour models [8, 19] of approximately 5–6:1 following the administration of angiotensin II and of reports in the order of 3–4:1 in humans [17, 20].

Comparison of the total injected activity for each patient and the resultant tumour and normal tissue radiation doses demonstrates the need for individualizing the amount of activity injected. For instance, patients 2 and 3 had similar amounts of activity administered but their normal liver tissue received markedly different radiation doses. In patients 6, 7 and 8 the normal tissue radiation doses were maintained around 40 Gy. However, the activity required to provide this radiation dose was substantially different for each patient. This results from both variation in the total size of the patients' livers and in the relative tumour burden. Observations made from the intra-operative dose measurements with the beta detection probe indicate that the smaller the tumour burden the less the amount of activity required for a given normal liver tissue dose. This will be the subject of a later communication.

It is common to find in the literature reports of the maximum tolerable dose for total or partial liver irradiation at levels of 3–40 Gy [21, 22]. In no patient within the present SIR therapy trial has evidence of acute or chronic hepatic radiation dam-

age been observed. This is despite a number of instances where large areas of normal liver have received doses in excess of 60 Gy.

There are several published reports of the hepatic administration of yttrium-90 containing microspheres in both animals and humans [7, 12, 23, 24]. Most of these reports cite the use of activities to produce total liver radiation doses in excess of 50 Gy as calculated by the same methodology as used in this study. No explanation has been provided for the discrepancy in the reported tolerable liver doses between external beam megavoltage radiation and internal radiation therapy with microspheres. Wollner *et al.* [24] described liver doses as high as 300 Gy as being compatible with survival in dogs. In line with the present study they have also advocated the use of hepatic exposures to humans of 50–100 Gy using yttrium-90 carrying microspheres.

A possible explanation for the different degree of tolerance to the exposure to SIR therapy is related to the point sourced radiation effect obtained using microspheres. Very high levels of radiation are encountered in tissue in close contact with microspheres, but this diminishes rapidly with distance away from the microsphere. Thus there will be areas of high cell kill close to microspheres while areas distant from the microspheres will be spared. This contrasts with the delivery of radiation to a tumour by external beam therapy where the prescribed dose is delivered evenly to every element of the target volume.

Coupled with the concept of point-sourced radiation effect is the anatomical area of microsphere trapping. Microspheres are trapped in and near the hepatic arterioles which are 1–2 mm distance from the central labular veins [25]. The central lobular veins are generally regarded as the main site of hepatic damage during exposure to external radiation [22, 26]. However, it is conceivable that during SIR therapy these areas of normal tissue are relatively spared by their distance from the microspheres. The same would not occur in the unstructured vasculature of the tumour tissue where microspheres accumulate in a relatively random fashion and in larger numbers.

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