The Post-SIR-Spheres Surgery Study (P4S): retrospective analysis of safety following hepatic resection or transplantation in patients previously treated with selective internal radiation therapy (SIRT) with yttrium-90 resin microspheres

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Conflicts of interest and source of funding

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Synopsis

A retrospective study assessed safety of liver resection or transplantation following selective internal radiation therapy (SIRT) with yttrium-90 resin microspheres. This is the largest cohort to date in which post-surgical mortality and complication rates are reported.

Abstract

Background

Reports show that selective internal radiation therapy (SIRT) may downsize inoperable liver tumors to resection or transplantation, or enable a bridge-to-transplant. A small-cohort study found that long-term survival in patients undergoing resection following SIRT appears possible but no robust studies on post-surgical safety outcomes exist. The Post-SIR-Spheres Surgery Study (P4S) was an international, multicenter, retrospective study to assess safety outcomes of liver resection or transplantation following SIRT with yttrium-90 (Y-90) resin microspheres (SIR-Spheres®; Sirtex).

Methods

Data were captured retrospectively at participating centers on SIRT with Y-90 resin microspheres, surgery (resection or transplantation) and follow-up for all eligible patients. Primary endpoints were peri-operative and 90-day post-operative morbidity and mortality. Standard statistical methods were used.

Results

The study included 100 patients (hepatocellular carcinoma: 49; metastatic colorectal cancer [mCRC]: 30; cholangiocarcinoma, metastatic neuroendocrine tumor, other: 7 each); 36% of patients had ≥ 1 line of chemotherapy pre-SIRT. Sixty-three percent of patients had co-morbidities, including hypertension (44%), diabetes (26%) and cardiopathy (16%). Post-SIRT, 71 patients were resected and 29 received a liver transplant. Grade 3+ peri/post-operative complications and any grade of liver failure were experienced by 24% and 7% of patients, respectively. Four patients died <90 days post-surgery; all were trisectionectomies

(mCRC: 3; cholangiocarcinoma: 1) and typically had ≥ 1 previous chemotherapy line and pre-surgical co-morbidities.

Conclusions

In 100 patients undergoing liver surgery after receiving SIRT, mortality and complication rates appeared acceptable given the risk profile of the recruited patients.

Introduction

Selective internal radiation therapy (SIRT) with yttrium (Y)-90 labelled resin microspheres, enables targeted delivery of radiation to hepatic tumors, while largely sparing the surrounding liver parenchyma. SIRT is primarily used to treat inoperable primary or metastatic liver tumors,¹⁻⁶ and since 2009, recognized to have a role in downsizing tumors to allow resection.⁷⁻¹¹ Additionally, SIRT produces concomitant hypertrophy in the contralateral lobe.¹² This can enable patients who previously had insufficient future liver remnant (FLR) to become appropriate patients for surgery. Likewise, SIRT is used as a bridge to liver transplantation and for down-staging hepatocellular carcinoma (HCC) prior to transplantation.¹³⁻¹⁶

A recent, small-cohort study of nine patients found that long-term survival in patients undergoing resection following SIRT appears possible, but more information is needed on the pre-surgical use of SIRT and the risk of subsequent complications.¹⁷ To address the gap in the literature on post-surgical safety outcomes when SIRT has been used, the retrospective Post-SIR-Spheres Surgery Study (P4S) was initiated. P4S is the first study of this scale to assess safety outcomes of liver resection or transplantation following SIRT with Y-90 resin microspheres.

Methods

This was an international, multicenter, non-interventional, retrospective study on the safety of liver resection or transplantation following SIRT using Y-90 resin microspheres (SIR-Spheres: Sirtex Medical Limited, North Sydney, Australia). The study objectives were to assess peri-operative and post-operative morbidity and mortality associated with liver resection or transplantation in patients who had received SIRT with Y-90 resin microspheres.

All necessary approvals were obtained from the relevant Independent Ethics Committees and Institutional Review Boards.

Patients

Data were collected from centers in Asia-Pacific, Europe and the USA on all consecutive patients who had received SIRT ($\pm$ other treatments) for primary or secondary liver tumors before resection or transplantation, when data were available for at least 90 days post-surgery or until death. Centers with extensive experience in the use of SIRT within a multidisciplinary team, including hepato-pancreato-biliary (HPB) surgery, were volunteered during an advisory board of HPB surgeons in July 2012 or separately invited to participate by the study sponsor. Centers willing to participate were required to gain local ethics committee approval or waiver. All eligible patients from these centers were included if they were initially considered unsuitable for resection by the relevant personnel at the participating center, received SIRT using Y-90 resin microspheres, and subsequently had surgery for resection or transplantation before April 2014. Patients who underwent liver resection accompanied by ablation or two-stage surgical resection were included. The patients did not have to be treated with the intent to down-size or bridge to transplant.

The decision to operate was independent of inclusion in the study and was at the discretion of the relevant personnel at the participating center. The extent of hepatic resection was defined as minor (involving removal of 1 or 2 segments), major but not extended (3–4 segments resected), extended (removal of ≥ 5 segments), or total removal in the case of transplantation. Patients who only received ablation, or were enrolled in ongoing or unreported prospective clinical studies were excluded.

Outcome measures and endpoints

The safety endpoints of primary interest were: peri-operative and 90-day post-operative morbidity (complications with a Clavien-Dindo classification¹⁸ score of ≥ 3) and mortality. A secondary endpoint was post-operative hospital stay.

Anonymised information was collected on: patient characteristics; tumor characteristics; tumor staging pre-SIRT; details on the SIRT given; if FLR received SIRT; other treatments (such as previous liver-directed procedures or systemic chemotherapy before or after SIRT); pre-surgery profile including an estimation of FLR; the surgical procedure; post-operative date of discharge and any re-admissions, and post-operative complications (according to the Clavien-Dindo classification system¹⁸); post-hepatectomy liver failure was assessed according to International Study Group of Liver Surgery (ISGLS) grade;¹⁹ pathology report; and follow-up (including date of last visit, survival, and date and cause of death). To be eligible for inclusion $\geq 80\%$ of mandatory data needed to be available.

Statistical analysis

Standard descriptive statistical methods were used. Summary statistics include the mean, standard deviation (SD), interquartile range (IQR), median, minimum and maximum values for continuous variables and frequencies for categorical variables. Hazard ratios (and 95% CI) were derived from proportional hazards models. Standard statistical tests were used for categorical and continuous data.

Results

Patient characteristics

Sixteen centers participated in the study. From an initial 113 registered consecutive patients considered, 13 had insufficient data, and therefore 100 patients were included in this retrospective analysis (Supplementary Table 1). These patients received SIRT between January 1998 and March 2014, and were subsequently surgically resected or transplanted between August 1998 and March 2014. Patient and disease characteristics for the 100 patients included are shown in Table 1.

Surgical characteristics

Seventy-one patients underwent hepatic resection following SIRT and 29 received a liver transplant post-SIRT.

The extent of resection was minor in 20 (28.2%) patients, major but not extended in 32 (45.0%) patients, and extended in 19 (26.8%) patients. Two-stage resections were performed in 10 patients undergoing major resection, including seven by the ALPPS technique. Additional tumorectomies were performed in 10 patients (accompanying resections classified as, minor: 2; major/not extended: 6; extended: 2) and tumor ablation in nine patients (in resections classified as minor: 5; major/not extended: 4). Among the 71 patients undergoing liver resection, complete resection (R0) was achieved in 54 (76.1%) patients, R1 in 15 (21.1%) patients, and R2 in two (2.8%) patients. Disease characteristics, pre-SIRT and post-SIRT chemotherapy and other liver-directed therapies were similar among the patients undergoing R0, and R1 or R2.

Cadaveric organ donation was used in 24 (82.8%) of the transplants and the remaining 5 (17.2%) were living-related donors.

SIRT characteristics

Pre-surgical treatments are listed in Table 2.

The median total SIRT activity delivered was slightly higher among resected patients than transplanted patients (Table 2). Twenty-five (35.2%) resected patients had exposure of the FLR to SIRT; 22 (31.0%) patients received SIRT to the whole liver, and three patients had partial exposure of the FLR to SIRT. HCC patients were slightly more likely to have received a SIRT administration that spared the FLR (no SIRT to FLR 78.3% vs. SIRT to FLR 21.7%; $p=0.118$), compared to other tumor types. Sparing of the FLR was more frequent after March

2010, the median date of surgery, than before this date (no SIRT to FLR: 82% vs. 48%, respectively; $p<0.001$).

The median (95% CI) follow-up time from first SIRT was 40.5 (26.5–48.3) months (median for resection and transplant: 38.3 and 48.3 months, respectively) and from surgery was 30.7 (20.6–41.2) months (median for resection and transplant: 30.7 and 40.2 months, respectively).

At the time of surgery, more patients had comorbidities in the cohort that had received SIRT sparing the FLR compared with those with FLR exposed to SIRT (67.4% vs. 40.0%, respectively; $p=0.043$). Additional tumor ablation was more likely to be performed in patients with SIRT to FLR (32.0% vs. 2.2%; $p<0.001$), and ALPPS was conducted only in patients with no SIRT to the FLR (15.2% vs. 0; $p=0.555$).

Safety outcomes

Outcomes 90 days after surgery are summarized in Table 3. In the liver resection group, most (12/20; 63.2%) grade 3+ complications of any type occurred in patients undergoing extended resection of ≥ 5 segments. Eight out of 10 liver failure complications occurred in patients undergoing extended resection: both remaining liver failure cases were grade 1 and occurred in patients undergoing major but not extended resection). All seven grade 3+ liver failures were in patients (5 metastatic colorectal cancer [mCRC]; 2 cholangiocarcinoma) undergoing extended resection. The only liver failure complication among those receiving a liver transplant was grade 2.

Any grade 3+ complications occurred in 24.0% of resected patients with FLR exposed to SIRT, compared with 30.4% in those whose FLR did not receive SIRT ($p=0.783$). Any grade and grade 3+ liver failure complications were reported in 16.0% and 12.0% of patients with

FLR exposed to SIRT, respectively, compared with 13.0% and 8.7%, respectively, in those whose FLR did not receive SIRT ($p=0.733$ and $p=0.691$, respectively, for the comparisons).

Four deaths occurred within 90 days of surgery, all in the cohort that underwent extended resection of ≥ 5 segments. The treating physician did not consider SIRT to be the cause of death in any of these four cases. One 66-year-old patient with cholangiocarcinoma died within 30 days of surgery; the patient had a BMI of 35, an American Society of Anesthesiologists (ASA) score of 3 (severe systemic disease), and cardiopathy, diabetes and hypertension pre-SIRT. This patient had received one line of chemotherapy pre-SIRT and further chemotherapy between SIRT and surgery, and had FLR partially exposed to prior SIRT. The patient underwent an extended right hepatectomy and subsequently developed grade 5 liver and renal failure. The patient died after lapsing into an irreversible coma due to multi-organ failure.

The other three deceased patients had mCRC. A 75-year-old patient died 26 days post-surgery due to sepsis. This patient had not received chemotherapy or had FLR exposure to SIRT, but had co-morbidities (cardiopathy and hypertension), an ASA score of 4 (severe systemic disease that is a constant threat to life) and an FLR $<30\%$. The other two patients with mCRC had received >1 line of chemotherapy pre-surgery. One of these patients had hypertension pre-surgery, no exposure of FLR to SIRT, and died due to sepsis 2.6 months after surgery. The other 74-year-old patient died 50 days post-surgery from anastomotic bleeding from a reconstructed portal vein. The patient had no co-morbidities pre-surgery, an ASA score of 3, and an FLR of 20% which had been exposed to SIRT.

Discussion

Retrospectively collected data from this heterogeneous cohort of 100 patients show that mortality rates, complication rates and liver failure rates in patients receiving liver transplants or undergoing liver resection after receiving SIRT are similar to the expected rates in this

population. These results are encouraging because the population analyzed in P4S was at a high risk of complications or death (i.e. the ASA score was ≥ 3 in 61% of patients).

Furthermore, a large proportion of the patients had co-morbidities known to complicate major surgery.²⁰⁻²³ Previous chemotherapy use and previous liver-directed procedures were also frequent in this cohort. Most resections (71.8%) were either major or extended.

An earlier retrospective chart review in 9 of 106 patients who underwent hepatic resection after SIRT treatment reported 90-day grade 3+ complications and mortality rates of 78% and 33%, respectively.¹⁷ The lack of attention to predetermining patient characteristics (e.g. eligibility criteria, previous ablation and comorbidities were not specified in the study) and the inclusion of patients undergoing simultaneous resection at extra-hepatic sites may have elevated the risk of complications and may be partly responsible for the observed high rate of morbidity and mortality following resection. Indeed, the authors highlighted the importance of careful patient selection when determining eligibility for resection.¹⁷

While comparisons with reports of complication rates following liver transplantation or resection in patients who have not received SIRT is problematic, in general it appears that the rates reported in the P4S cohort are not different to previous reports in similar patient cohorts (12.5% to 23% of patients had grade 3+ complications).²⁴⁻³³ ALPPS was used in seven of 10 patients undergoing two-stage major resection in this study. Studies show a high rate of complications with ALPPS, as noted by a systematic review of 13 publications that reported grade 3a+ complications in 44% of 295 patients undergoing the procedure.³⁴

Complications following liver transplantation in HCC down-staged using other methods are similar in P4S to overall complication rates reported after liver transplantation in the absence of previous SIRT.³⁵⁻³⁷ It should be stressed, however, that the aim of the current study was an assessment of safety, and therefore, assessing whether patients were down-staged to within acceptable transplantation criteria is outside the scope of this manuscript.

Furthermore, comparing the P4S results with the findings from previous studies is, of course, unreliable.

The median time between SIRT and resection in this cohort was 4.7 months. While these data do not allow a firm recommendation, it may be reasonable to propose a 2–3-month minimum time between last SIRT and resection. In patients who underwent hepatic resection or liver transplantation in P4S, median time from surgery to hospital discharge was 10 or 11 days, respectively. This observed length of hospitalization compares favorably with studies in the published literature of patients who had not received SIRT, but again, such comparisons are illustrative only.^{26, 28, 36, 38-42}

While the overall mortality rates, complication rates and liver failure rates are encouraging, the negative or positive impact of SIRT on individual patients is more difficult to assess. Four deaths were reported during this study, and these were considered unrelated to SIRT by the treating physician at the time of death. Three of these patients had severe co-morbidities, and all four deaths were in patients who had undergone extended resection of 6 segments. It is apparent that the more liver segments removed through surgery, the greater the risk for patients of liver failure and other life-threatening complications, particularly if the FLR has previously been insulted by systemic chemotherapy, or there is an underlying disease such as cirrhosis.^{27, 32, 43-46} However, it is impossible to completely exclude a relationship with SIRT. There is no known pathogenic mechanism to explain how SIRT could have contributed to death in these four patients. Likewise, it is also impossible to exclude the other factors described above that may have contributed to the death of these patients.

Although the impact of FLR exposure to SIRT on complications is not obvious from these results, it would be prudent in treatment planning strategies to spare segments of the liver that do not require SIRT, and maximize the potential for contralateral hypertrophy and subsequent resection.^{8, 9, 13, 14, 47, 48} In P4S, sparing FLR from exposure to SIRT was improved

in patients treated most recently, which may relate to the publication of key studies that suggested such an approach was beneficial.^{10, 11}

Several limitations associated with such retrospective analyses should be acknowledged. The impact of selection bias is unknown; it is possible that centers that participated were those with the most positive past experience with SIRT. Interpretation of the results also relies on accurate record-keeping, for example, the possible link between complications and treatments is difficult to ascertain when data are collected retrospectively and the impact of SIRT doses cannot be assessed from these data – however, the relationship between SIRT activity and potential subclinical liver damage is poorly understood anyway. Furthermore, the eligibility of patients for surgery and the intent of SIRT depends upon the clinical judgement of the healthcare teams at each center, which may not be consistent. As surgery following SIRT is rare, gathering information on a large cohort required the inclusion of a wide range of patients treated over a long period of time: this heterogeneous population makes drawing global conclusions problematic, and changes in practice over time may have influenced safety outcomes. However, the study represents outcomes in routine clinical practice, which is of direct relevance to clinicians.

This study reports mortality rates, complication rates and liver failure rates in patients undergoing liver resection or receiving liver transplants after receiving SIRT. This is the largest cohort of this type to date, in which safety outcomes are reported. The data from P4S appear to offer reassurance that liver resection or transplantation is feasible in patients who have previously received Y-90 resin microspheres. We acknowledge the limitations of such a retrospective approach, and suggest that prospective data, possibly via the use of a prospective registry that gathers information on SIRT dosimetry and all complications, are needed to fully assess the safety of liver resection or transplantation after SIRT.

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Table 1. Patient and disease characteristics at the time of liver surgery.

Variable	Population		
	Whole cohort	All resected	All transplant
	(n=100)	(n=71)	(n=29)
Mean (SD) age, years	60.7 (11.0)	61.8 (10.9)	57.7 (10.8)
Male / female, %	73.0 / 27.0	70.4 / 29.6	79.3 / 20.7
BMI			
Mean (SD), kg/m ²	26.6 (4.6)	26.7 (4.3)	26.2 (5.4)
BMI >30, n (%)	26 (26.0)	18 (25.4)	8 (27.6)
Race, n (%)			
Asian	17 (17.0)	11 (15.5)	6 (20.7)
Black	2 (2.0)	1 (1.4)	1 (3.4)
White	81 (81.0)	59 (83.1)	22 (75.9)
Tumor type, n (%)			
HCC	49 (49.0)	23 (32.4)	26 (89.7)
Colorectal	30 (30.0)	30 (42.3)	0
Cholangiocarcinoma	7 (7.0)	7 (9.9)	0
Neuroendocrine	7 (7.0)	4 (5.6)	3 (10.3)
Other	7 (7.0)	7 (9.9)	0
Bilobar liver tumors, n (%)	44 (44.0)	31 (43.7)	13 (44.8)
Extra-hepatic metastases, n (%)	7 (7.0)	7 (9.9)	0
Primary tumor in place (non-hepatic), n (%)	18 (18.0) [‡]	15 (21.1) [‡]	3 (10.3)
Important co-morbidities, n (%)	63 (63.0)	41 (57.7)	22 (75.9)

Cardiopathy	16 (16.0)	11 (15.5)	5 (17.2)
Diabetes	26 (26.0)	15 (21.1)	11 (37.9)
Hypertension	44 (44.0)	31 (43.7)	13 (44.8)
COPD	3 (3.0)	2 (2.8)	1 (3.4)
Renal insufficiency	1 (1.0%)	1 (1.4%)	0
Other	21 (21.0)	11 (15.5)	10 (34.5)
Cirrhosis, n (%)	41 (41.0)	16 (22.5)	25 (86.2)
Total Bilirubin Grade ≥ 1 , n (%)	28 (28.3) [‡]	11 (15.5)	17 (60.7) [†]
ASA physical status			
Median (IQR) score	3.0 (1.0)	3.0 (1.0)	3.0 (1.0)
Score ≥ 3 , n (%)	61 (61.0%)	39 (57.4%)	22 (78.6%)

[‡] Excludes patients with HCC and cholangiocarcinoma.

[†] Missing data on 1 patient. ASA – American Society of Anesthesiologists. BMI – body mass index. COPD – chronic obstructive pulmonary disease.

Table 2. Pre-surgical treatment.

Variable	Population		
	Whole cohort	All resected	All transplant
	(n=100)	(n=71)	(n=29)
Pre-SIRT chemotherapy, n (%)			
None	63 (63.6)	35 (50.0)	28 (96.6)
1 line	20 (20.2)	20 (28.6)	0
>1 line	16 (16.2)	15 (21.4)	1 (3.4)
Post-SIRT chemotherapy, n (%)			
None	78 (78.0)	52 (73.2)	26 (89.7)
≥1 line	22 (22.0)	19 (26.8)	3 (10.3)
Pre- or post-SIRT use of oxaliplatin or irinotecan, n (%)	27 (27.0)	27 (38.0)	0
Liver-directed procedure, n (%)			
Resection	13 (13.0)	9 (12.7)	4 (13.8)
Ablation	16 (16.0)	9 (12.7)	7 (24.1)
Portal vein embolization	12 (12.0)	10 (14.1)	2 (6.9)
Arterial (TAE, TACE, HAI)	9 (9.0)	9 (12.7)	0
Radiation to abdomen	1 (1.0)	1 (1.4)	0
Intent of SIRT, n (%)			
Bridge to transplantation	9 (9.0)	1 (1.4)	8 (27.6)
Down-sizing or palliative	84 (84.0)	63 (74.6)	21 (72.4)
Not available	7 (7.0)	7 (9.9)	0

Number of SIRT procedures, n (%)			
1	80 (80.0)	56 (78.9)	24 (82.8)
2	18 (18.0)	13 (18.3)	5 (17.2)
3	2 (2.0)	2 (2.8)	0
Median (IQR) total SIRT activity, GBq			
	1.5 (0.9)	1.5 (0.9)	1.3 (1.4)
SIRT to whole liver, n (%)			
	32 (32.0)	22 (31.0)	10 (34.5)
SIRT to FLR, n (%)			
	25 (25.0)	25 (35.2)	na
Median (IQR) time from:			
First SIRT to surgery, months	6.6 (7.8)	5.7 (6.2) [‡]	10.1 (7.8)
Last SIRT to surgery, months	5.8 (5.9)	4.7 (6.0) [‡]	8.3 (7.6)

* Data missing for one patient

FLR – future liver remnant. IQR – interquartile range. SIRT – selective internal radiation therapy. TAE – transarterial embolization. TACE – transarterial chemoembolization. HAI – hepatic arterial infusion of chemotherapy. na – not applicable.

[‡] 1.6 (0.6) months for first or last SIRT to ALPPS surgery; 6.2 (6.1) months for first SIRT to non-ALPPS surgery and 5.6 (5.7) months for last SIRT (prior to resection) to non-ALPPS surgery.

Table 3. Peri- and post-operative complications and other outcomes (in the first 90 days after surgery).

Variable	Population		
	Whole cohort (n=100)	All resected (n=71)	All transplant (n=29)
Any complication, n (%)	48 (48.0)	33 (46.5)	15 (51.7)
Grade 3+	24 (24.0)	20 (28.2)	4 (13.8)
Any grade of liver failure, n (%)	11 (11.0)	10 (14.1)	1 (3.4)
Grade 3+	7 (7.0)	7 (9.9)	0
Median (IQR) time from surgery to hospital discharge, days	9.0 (9.0)	10.0 (9.0)	11.0 (10.0)
Readmission within 90 days, n (%)	24 (24.0)	15 (21.1)	9 (31.0)
Death from any cause within 90 days, n (%)	4 (4.0)	4 (5.6)	0

IQR – interquartile range.

SUPPLEMENTARY APPENDIX

Supplementary Table 1. Patient distribution by center

Patient numbers by center, n (%)	Population		
	Whole cohort* (n=100)	All resected (n=71)	All transplant (n=29)
Clinical Universidad de Navarra, Pamploma	28 (28.0)	18 (25.4)	10 (34.5)
Klinikum Karlsruhe, Karlsruhe	11 (11.0)	11 (15.5)	0
University Hospitals Leuven, Leuven	5 (5.0)	5 (7.0)	0
Institut Jules Bordet, Brussels	6 (6.0)	4 (5.6)	2 (6.9)
Institute of Transplantation, Newcastle Upon Tyne	7 (7.0)	7 (9.9)	2 (6.9)
University of Bologna, Bologna	5 (5.0)	3 (4.2)	0
Ospedale Santa Chiara, Pisa	2 (2.0)	2 (2.8)	0
Saint Francis Hospital, Tulsa	2 (2.0)	2 (2.8)	0
Carolinas Medical Center, Charlotte	4 (4.0)	4 (5.6)	0

Methodist Dallas Medical Center, Dallas	7 (7.0)	1 (1.4)	6 (20.7)
National Cancer Center, Singapore	4 (4.0)	3 (4.2)	1 (3.4)
Taipei Veterans General Hospital, Taipei	8 (8.0)	5 (7.0)	3 (10.3)
Wakefield Clinic, Wellington	4 (4.0)	4 (5.6)	0
Austin Hospital, Heidelberg	2 (2.0)	0	2 (6.9)
St Vincent's Hospital/St George Hospital, Sydney	5 (5.0)	5 (7.0)	0)

* Another 13 patients were excluded from analysis: insufficient mandatory data, 9; no liver surgery, 2; no SIRT, 1; <90 days follow-up 1