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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 with Yttrium-90 Resin Microspheres

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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 postsurgical safety outcomes exist. The Post-SIR-Spheres Surgery Study 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 SIRT centers, with Y-90 resin microspheres, surgery (resection or transplantation), and follow-up for all eligible patients. Primary endpoints were perioperative and 90-day

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postoperative 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 one or more lines of chemotherapy pre-SIRT. Sixty-three percent of patients had comorbidities, including hypertension (44%), diabetes (26%), and cardiopathy (16%). Post-SIRT, 71 patients were resected and 29 received a liver transplant. Grade 3+ peri/postoperative complications and any grade of liver failure were experienced by 24 and 7% of patients, respectively. Four patients died <90 days postsurgery; all were trisectionectomies (mCRC: 3; cholangiocarcinoma: 1) and typically had one or more previous chemotherapy lines and presurgical comorbidities.

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-90 (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, has been recognized to have a role in downsizing tumors to allow resection.[7–11] Additionally, SIRT produces concomitant hypertrophy in the contralateral lobe,[12] which 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 downstaging 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 presurgical use of SIRT and the risk of subsequent complications.[17] To address the gap in the literature on postsurgical 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, NSW, Australia). The study objectives were to assess perioperative and postoperative 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 US on all consecutive patients who had received SIRT (± other treatments) for primary or secondary liver tumors before resection or transplantation, when data were available for at least 90 days postsurgery 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. Patients did not have to be treated with the intent to downsize 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 one or two segments), major but not extended (three to four segments resected), extended (removal of five or more 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 perioperative and 90-day postoperative morbidity (complications with a Clavien–Dindo classification[18] score of ≥3) and mortality. A secondary endpoint was postoperative hospital stay.

Anonymized information was collected on patient characteristics; tumor characteristics; tumor staging pre-

SIRT; details on the SIRT administered; whether FLR received SIRT; other treatments (such as previous liver-directed procedures or systemic chemotherapy before or after SIRT); presurgery profile, including an estimation of FLR; the surgical procedure; postoperative date of discharge and any readmissions, and postoperative complications (according to the Clavien–Dindo classification system[18]); posthepatectomy liver failure was assessed according to the 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, ≥80% of mandatory data needed to be available.

Statistical Analysis

Standard descriptive statistical methods were used. Summary statistics included the mean, standard deviation (SD), interquartile range (IQR), median, minimum and maximum values for continuous variables, and frequencies for categorical variables. Hazard ratios (95% confidence intervals [CIs]) 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, therefore 100 patients were included in this retrospective analysis (electronic 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 associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) technique. Additional tumorectomies were performed in 10 patients (accompanying resections classified as minor: 2; major/not extended: 6; extended: 2) and tumor ablation was performed 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 2 (2.8%) patients. Disease characteristics, pre- and post-SIRT chemotherapy, and other liver-directed therapies were similar among patients undergoing R0, and R1 or R2 resection.

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

Selective Internal Radiation Therapy Characteristics

Presurgical 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 an SIRT administration that spared the FLR (no SIRT to FLR 78.3% vs. SIRT to FLR 21.7%; $p = 0.118$) compared with 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 only conducted 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 grade 3+ complications of any type (12/20; 63.2%) occurred in patients undergoing extended resection of five or more segments. Eight 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 [five metastatic colorectal cancers (mCRCs); two cholangiocarcinomas] were in patients

TABLE 1 Patient and disease characteristics at the time of liver surgery

Variable	Population		
	Whole cohort (n = 100)	All resected (n = 71)	All transplant (n = 29)
Mean age (SD), 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	26 (26.0)	18 (25.4)	8 (27.6)
Race			
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			
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	44 (44.0)	31 (43.7)	13 (44.8)
Extrahepatic metastases	7 (7.0)	7 (9.9)	0
Primary tumor in place (non-hepatic)	18 (18.0)[a]	15(21.1)[a]	3 (10.3)
Important comorbidities	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	41 (41.0)	16 (22.5)	25 (86.2)
Total bilirubin grade ≥1	28 (28.3)[b]	11 (15.5)	17 (60.7)[b]
ASA physical status			
Median score (IQR)	3.0 (1.0)	3.0 (1.0)	3.0 (1.0)
Score ≥3	61 (61.0)	39 (57.4)	22 (78.6)

Data are expressed as n (%) unless otherwise specified

ASA American Society of Anesthesiologists, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *SD* standard deviation, *HCC* hepatocellular carcinoma, *IQR* interquartile range

[a] Excludes patients with HCC and cholangiocarcinoma

[b] Missing data on one patient

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 five or more 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 body mass index (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

TABLE 2 Presurgical treatment

Variable	Population		
	Whole cohort (n = 100)	All resected (n = 71)	All transplant (n = 29)
Pre-SIRT chemotherapy[a]			
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			
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	27 (27.0)	27 (38.0)	0
Liver-directed procedure	31 (31.0)	22 (31.0)	9 (31.0)
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			
Bridge to transplantation	9 (9.0)	1 (1.4)	8 (27.6)
Downsizing or palliative	84 (84.0)	63 (74.6)	21 (72.4)
Not available	7 (7.0)	7 (9.9)	0
Number of SIRT procedures			
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	32 (32.0)	22 (31.0)	10 (34.5)
SIRT to FLR	25 (25.0)	25 (35.2)	NA
Median (IQR) time from:			
First SIRT to surgery, months	6.6 (7.8)	5.7 (6.2)[b]	10.1 (7.8)
Last SIRT to surgery, months	5.8 (5.9)	4.7 (6.0)[b]	8.3 (7.6)

Data are expressed as n (%) unless otherwise specified

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, *ALPPS* associated liver partition and portal vein ligation for staged hepatectomy

[a] Data missing for one patient

[b] 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

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 multiorgan failure.

The other three deceased patients had mCRC. A 75-year-old patient died 26 days postsurgery due to sepsis. This patient had not received chemotherapy, or had FLR exposure to SIRT, but had comorbidities (cardiopathy and hypertension), an ASA score of 4 (severe systemic disease that is a constant threat to life) and an FLR <30%. The remaining two patients with mCRC had received more than one line of chemotherapy presurgery. One of these patients had hypertension presurgery, no exposure of FLR to SIRT, and died due to sepsis 2.6 months after surgery. The remaining 74-year-old patient died from anastomotic bleeding from a reconstructed portal vein 50 days post-

TABLE 3 Peri- and postoperative 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	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	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	24 (24.0)	15 (21.1)	9 (31.0)
Death from any cause within 90 days	4 (4.0)	4 (5.6)	0

Data are expressed as n (%) unless otherwise specified

IQR interquartile range

surgery. The patient had no comorbidities presurgery, 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 $\geq$3 in 61% of patients). Furthermore, a large proportion of patients had comorbidities 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 extrahepatic 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 (12.5–23% of patients had grade 3+ complications).[24–33] ALPPS was used in 7 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 downstaged using other methods are similar in P4S to overall complication rates reported after liver transplantation in the absence of previous SIRT.[35–37] However, it should be stressed that the aim of the current study was an assessment of safety, therefore assessing whether patients were downstaged 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- to 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, at the time of death, the treating physician considered these to be unrelated to SIRT. Three of these patients had severe comorbidities, and all four deaths were in patients who had

undergone extended resection of six 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 mechanisms 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. Furthermore, the eligibility of patients for surgery and the intent of SIRT depends on the clinical judgment 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.

CONCLUSIONS

This study reports mortality rates, complication rates, and liver failure rates in patients undergoing liver resection or receiving liver transplants after receiving SIRT. To date, this is the largest cohort of this type 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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REFERENCES

1. Ahmadzadehfar H, Biersack HJ, Ezziddin S. Radioembolization of liver tumors with yttrium-90 microspheres. *Semin Nucl Med*. 2010;40:105–121.
2. Bester L, Meteling B, Pocock N, et al. Radioembolization versus standard care of hepatic metastases: comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. *J Vasc Interv Radiol*. 2012;23:96–105.
3. Mulcahy MF, Lewandowski RJ, Ibrahim SM, et al. Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres. *Cancer*. 2009;115:1849–1858.
4. Rhee TK, Lewandowski RJ, Liu DM, et al. 90Y Radioembolization for metastatic neuroendocrine liver tumors: preliminary results from a multi-institutional experience. *Ann Surg*. 2008;247:1029–1035.
5. Sangro B, Carpanese L, Cianni R, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology*. 2011;54:868–878.
6. Seidensticker R, Denecke T, Kraus P, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. *Cardiovasc Intervent Radiol*. 2012;35:1066–1073.
7. Ahmadzadehfar H, Meyer C, Ezziddin S, et al. Hepatic volume changes induced by radioembolization with 90Y resin

microspheres. A single-centre study. *Eur J Nucl Med Mol Imaging*. 2013;40:80–90.
8. Chua TC, Bester L, Akther J, Morris DL. Successful right hepatectomy after four treatments of yttrium-90 microspheres (SIR-Spheres) and concomitant FOLFOX as bridging therapy to resection of colorectal liver metastases. *Anticancer Res*. 2010;30:3005–3007.
9. 9. Fernandez-Ros N, Silva N, Bilbao JI, et al. Partial liver volume radioembolization induces hypertrophy in the spared hemiliver and no major signs of portal hypertension. *HPB (Oxford)*. 2014;16:243–249.
10. Gaba RC, Lewandowski RJ, Kulik LM, et al. Radiation lobectomy: preliminary findings of hepatic volumetric response to lobar yttrium-90 radioembolization. *Ann Surg Oncol*. 2009;16:1587–1596.
11. Gulec SA, Pennington K, Hall M, Fong Y. Preoperative Y-90 microsphere selective internal radiation treatment for tumor downsizing and future liver remnant recruitment: a novel approach to improving the safety of major hepatic resections. *World J Surg Oncol*. 2009;7:6.
12. 12. Teo JY, Allen JC Jr, Ng DC, et al. A systematic review of contralateral liver lobe hypertrophy after unilobar selective internal radiation therapy with Y90. *HPB (Oxford)*. 2016;18:7–12.
13. 13. Inarrairaegui M, Pardo F, Bilbao JI, et al. Response to radioembolization with yttrium-90 resin microspheres may allow surgical treatment with curative intent and prolonged survival in previously unresectable hepatocellular carcinoma. *Eur J Surg Oncol*. 2012;38:594–601.
14. Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. *Am J Transplant*. 2009;9:1920–1928.
15. Tohme S, Sukato D, Chen HW, et al. Yttrium-90 radioembolization as a bridge to liver transplantation: a single-institution experience. *J Vasc Interv Radiol*. 2013;24:1632–1638.
16. Radunz S, Treckmann J, Baba HA, et al. Long-term outcome after liver transplantation for hepatocellular carcinoma following yttrium-90 radioembolization bridging treatment. *Ann Transpl*. 2017;22:215–221.
17. Henry LR, Hostetter RB, Ressler B, et al. Liver resection for metastatic disease after Y90 radioembolization: a case series with long-term follow-up. *Ann Surg Oncol*. 2015;22:467–474.
18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
19. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery*. 2011;149:713–724.
20. Tzeng CW, Vauthey JN. Postoperative complications and oncologic outcomes after resection of colorectal liver metastases: the importance of staying on track. *Ann Surg Oncol*. 2013;20:2457–2459.
21. Langella S, Russolillo N, Forchino F, et al. Impact of obesity on postoperative outcome of hepatic resection for colorectal metastases. *Surgery*. 2015;158:1521–1529.
22. Amptoulach S, Gross G, Kalaitzakis E. Differential impact of obesity and diabetes mellitus on survival after liver resection for colorectal cancer metastases. *J Surg Res*. 2015;199:378–385.
23. Wang H, Yang J, Zhang X, Yan L. Liver resection in hepatitis B-related hepatocellular carcinoma: clinical outcomes and safety in overweight and obese patients. *PLoS ONE*. 2014;9:e99281.
24. Fuks D, Nomi T, Ogiso S, et al. Laparoscopic two-stage hepatectomy for bilobar colorectal liver metastases. *Br J Surg*. 2015;102:1684–1690.
25. Lodewick TM, de Jong MC, van Dam RM, et al. Effects of postoperative morbidity on long-term outcome following surgery for colorectal liver metastases. *World J Surg*. 2015;39:478–486.
26. Morris-Stiff G, Marangoni G, Hakeem A, et al. Redefining major hepatic resection for colorectal liver metastases: analysis of 1111 liver resections. *Int J Surg*. 2016;25:172–177.
27. Narita M, Oussoultzoglou E, Fuchshuber P, et al. What is a safe future liver remnant size in patients undergoing major hepatectomy for colorectal liver metastases and treated by intensive preoperative chemotherapy? *Ann Surg Oncol*. 2012;19:2526–2538.
28. Urbani L, Masi G, Puccini M, et al. Minor-but-complex liver resection: an alternative to major resections for colorectal liver metastases involving the hepato-caval confluence. *Medicine*. 2015;94:e1188.
29. Vibert E, Pittau G, Gelli M, et al. Actual incidence and long-term consequences of posthepatectomy liver failure after hepatectomy for colorectal liver metastases. *Surgery*. 2014;155:94–105.
30. Wolf PS, Park JO, Bao F, et al. Preoperative chemotherapy and the risk of hepatotoxicity and morbidity after liver resection for metastatic colorectal cancer: a single institution experience. *J Am Coll Surg*. 2013;216:41–49.
31. Zhou YM, Zhang XF, Li B, et al. Postoperative complications affect early recurrence of hepatocellular carcinoma after curative resection. *BMC Cancer*. 2015;15:689.
32. Li GZ, Speicher PJ, Lidsky ME, et al. Hepatic resection for hepatocellular carcinoma: do contemporary morbidity and mortality rates demand a transition to ablation as first-line treatment? *J Am Coll Surg*. 2014;218:827–834.
33. Wicherts DA, de Haas RJ, Andreani P, et al. Short- and long-term results of extended left hepatectomy for colorectal metastases. *HPB (Oxford)*. 2011;13:536–543.
34. Schadde E, Schnitzbauer AA, Tschuor C, et al. Systematic review and meta-analysis of feasibility, safety, and efficacy of a novel procedure: associating liver partition and portal vein ligation for staged hepatectomy. *Ann Surg Oncol*. 2015;22:3109–3120.
35. Dai WC, Chan SC, Chok KS, et al. Good long term survival after primary living donor liver transplantation for solitary hepatocellular carcinomas up to 8 cm in diameter. *HPB*. 2014;16:749–757.
36. Lei JY, Yan LN, Wang WT. Transplantation vs resection for hepatocellular carcinoma with compensated liver function after downstaging therapy. *World J Gastroenterol*. 2013;19:4400–4408.
37. Wan P, Zhang JJ, Li QG, et al. Living-donor or deceased-donor liver transplantation for hepatic carcinoma: a case-matched comparison. *World J Gastroenterol*. 2014;20:4393–4400.
38. Allard MA, Cunha AS, Gayet B, et al. Early and long-term oncological outcomes after laparoscopic resection for colorectal liver metastases: a propensity score-based analysis. *Ann Surg*. 2015;262:794–802.
39. Vigano L, Capussotti L, Majno P, et al. Liver resection in patients with eight or more colorectal liver metastases. *Br J Surg*. 2015;102:92–101.
40. Lee KK, Kim DG, Moon IS, et al. Liver transplantation versus liver resection for the treatment of hepatocellular carcinoma. *J Surg Oncol*. 2010;101:47–53.
41. Ito T, Tanaka S, Iwai S, et al. Outcomes of laparoscopic hepatic resection versus percutaneous radiofrequency ablation for hepatocellular carcinoma located at the liver surface: a case-control study with propensity score matching. *Hepatol Res*. 2016;46(6):565–74.
42. Yankol Y, Mecit N, Kanmaz T, et al. Lessons learned from review of a single center experience with 500 consecutive liver transplants in a region with insufficient deceased-donor support. Exp Clin Transpl 2016;14(2):191–200.

43. Narita M, Oussoultzoglou E, Bachellier P, et al. Post-hepatectomy liver failure in patients with colorectal liver metastases. *Surg Today*. 2015;45:1218–1226.
44. Wiggans MG, Fisher S, Adwan H, et al. Partial preservation of segment IV confers no benefit when performing extended right hepatectomy for colorectal liver metastases. *HPB Surg*. 2013;2013:458641.
45. Shindoh J, Tzeng CW, Aloia TA, et al. Safety and efficacy of portal vein embolization before planned major or extended hepatectomy: an institutional experience of 358 patients. *J Gastrointest Surg*. 2014;18:45–51.
46. Wong TC, Cheung TT, Chok KS, et al. Treatment strategy to improve long-term survival for hepatocellular carcinoma smaller than 5 cm: major hepatectomy vs minor hepatectomy. *World J Surg*. 2014;38:2386–2394.
47. Garlipp B, de Baere T, Damm R, et al. Left-liver hypertrophy after therapeutic right-liver radioembolization is substantial but less than after portal vein embolization. *Hepatology*. 2014;59:1864–1873.
48. Braat AJ, Huijbregts JE, Molenaar IQ, et al. Hepatic radioembolization as a bridge to liver surgery. *Front Oncol*. 2014;4:199.