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Research Article

Selective use of 99ᵐ Tc-Mebrofenin Hepatobiliary Scintigraphy Improves Outcomes: Experience in a Single Tertiary Referral Centre in Western Australia

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Abstract

Background: Major liver resections, performed for malignant and symptomatic benign tumours, carries a risk of post Hepatectomy Liver Failure (PHLF). Computed tomography and biochemical tests provide information on volumes and global function, however mebrofenin Hepatobiliary Scintigraphy (HBS) has the added benefit of assessing regional function. A remnant function $2.7\%/min/m^2$ has been suggested to prevent PHLF, and those with insufficient remnant function are able to undergo augmentation to facilitate surgery. We aim to review the outcomes on our selective use of HBS within a single tertiary referral centre.

Methods: All patients referred for major hemihepatectomy between February 2016 to December 2021 were reviewed at the multidisciplinary meeting. High risk patients were required to undergo HBS, and treatment tailored accordingly. Demographics and outcomes were reviewed from electronic medical records.

Results: 99 patients were included in the study, where 63 were considered high-risk due to larger resection volumes or pre-operative chemotherapy. Patients with sufficient function were able to undergo surgery. Conversely, patients identified to have insufficient remnant function despite sufficient volume had their treatments modified by performing a smaller resection with no complications, or augmentation performed where sufficient hypertrophy was achieved. 5 high-risk cohort patients developed PHLF, as compared to 8 patients from the low-risk cohort.

Conclusion: HBS is a useful pre-operative tool for risk assessment, allowing us to tailor treatments and improve patient outcomes. Patients who require larger resections, or have chronic liver disease should undergo HBS.

Introduction

Major liver resections are performed for a variety of indications including primary or secondary liver malignancy, and symptomatic benign liver tumours [1]. When evaluating a patient, factors including proximity of the lesion to vital hepatic inflow and outflow structures, projected future liver remnant volume (FL-remnant vol) and likelihood of Post Hepatectomy Liver Failure (PHLF) determine technical resectability [1]. Insufficient FLR-remnant vol is found to be an important predictor of PHLF which carries a mortality of between 1.2% to 32% [2,3].

Traditionally, Computed Tomography (CT) volumetric studies have been performed alongside biochemical blood tests and indocyanine green clearance to assess for FL-remnant vol and global liver function [1,4,5]. This is useful for patients with normal liver parenchyma, where there is homogenous liver function that correlates well with liver volume [2,4,6]. However, major liver resections are commonly performed in patients with underlying liver parenchymal disease such as Chemotherapy Associated Liver Injury (CALI), cirrhosis, hemochromatosis, steatohepatitis or obstructive jaundice [2]. Compromised liver parenchyma causes both global impairment and non-uniformity of liver function,

affecting the correlation between function and volume. In patients with normal liver parenchyma, a standardised future liver remnant (std-remnant vol) of 20%, where the total liver volume (TL-tot vol) is calculated from body surface area (BSA), is considered sufficient. However, a minimum of 30% std-remnant vol is required for those with mild liver disease and up to 40% or greater std-remnant vol may be required in established cirrhosis [7-9].

Tc99m mebrofenin Hepatobiliary Scintigraphy (HBS) is a dynamic study that measures hepatic uptake and excretion of a tracer. When combined with Single Photon Emission Computed Tomography (SPECT), it allows for further quantitative evaluation of regional hepatic function [4,6,7]. The anatomical FLR can then be defined on CT, and the function of the remnant sections (FL-remnant func) can then be measured. A common FL-remnant func cut off of $2.7\%/min/m^2$ has been suggested to avoid PHLF in patients with normal or compromised liver [4,10]. In addition, HBS may also be used to monitor compensatory increase in FL-remnant func in patients who undergo liver augmentation for insufficient FLR-func. An increase in both FL-remnant vol and FL-remnant func to safe levels may be achieved by a variety of techniques including contralateral Portal Vein Embolization (PVE) and Selective Internal Radiation Therapy (SIRT) with Yttrium 90 (^{90}Y) microspheres [8,11-14].

Within our centre, selected high-risk patients are required to undergo HBS, and their treatment tailored accordingly to improve outcomes. This study aims to evaluate whether the selective use of HBS has improved outcomes.

Patients and Methods

We performed a retrospective study that included all patients who were considered for major hepatectomy (3 or more segments) from 1ˢᵗ February 2016 until 31ˢᵗ December 2021. Treatment plans for patients were agreed upon during the Hepaticopancreaticobiliary (HPB) Multidisciplinary (MDT) team review which included HPB surgeons, radiologists, gastroenterologists, and medical and radiation oncologists. Treatment recommendations were made based on patients clinicopathological background and imaging. Patients identified to be at significant risk of PHLF were required to undergo HBS workup prior to being considered for major hepatectomy. Patients were considered high-risk if std-remnant vol was measured at <20% with presumed normal liver parenchymal function, or std-remnant vol of < 30% in the presence of steatohepatitis, fibrosis, previous chemotherapy, autoimmune liver disease, or other chronic liver disease causing underlying liver injury. Patients without liver injury but with <20% std-remnant vol were also required to undergo pre-operative HBS. Patients demographics, clinicopathological background, surgery, and radiological scans of were collected from electronic medical records. Outcomes including PHLF rate, surgical complications, and HBS results were recorded.

Total liver volume based on body surface area (TL-BSA vol) (was calculated using the formula $TLV^{BSA} = -794.41 + (1267.28 \times BSA)$ [15]. Standardised future liver remnant is expressed as a percentage of the FL-remnant vol based on the TL-BSA vol using

the formula $std - remnant\ vol = \frac{FLR}{TLV-BSA} \times 100\%$ [1,4].

PHLF is defined as per ISGLS definition listed in Table 1 [16]. This study protocol was approved by governance, evidence, knowledge, outcomes committee.

Grade	Clinical description	Treatment	Diagnosis	Clinical symptoms	Location for care
A	Deterioration in liver function	None	• UOP >0.5ml/kg/h • BUN <150mg/dL • >90% O_2 saturation • INR <1.5	None	Surgical ward
B	Deviation from expected post-operative course without requirement for invasive procedures	FFP; albumin; diuretics; NIV; abdo USS; CT scan	• UOP ≤0.5ml/kg/h • BUN <150mg/dL • <90% O_2 saturation despite oxygen supplementation • INR ≥1.5, <2	• Ascites • Weight gain • Mild respiratory insufficiency • Confusion • encephalopathy	Intermediate unit or ICU

| C | Multi-system failure requiring invasive treatment | Haemodialysis; intubation, extracorporeal liver support, salvage hepatectomy, vasopressor, ICP monitor, IV glucose for hypoglycaemia | • UOP ≤0.5ml/kg/h
• BUN ≥150mg/dL
• ≤85% O_2 sat despite high fraction of inspired oxygen support
• INR ≥2 | • Renal failure
• Haemodynamic instability
• Respiratory failure
• Large volume ascites
• encephalopathy | ICU |

Table 1: ISGLS grading of PHLF.

Statistics

Comparison of patient characteristics were performed using Chi Square test, and continuous data was tested using independent sample t-test. Paired data for a single population was performed with paired t-test, and correlation between variables was tested using Pearson correlation coefficient. Values were expressed as mean +/- Standard Deviation (SD). All statistical tests were 2-tailed, and differences are significant if P value was ≤ 0.05.

TC⁹⁹m Mebrofenin HBS

HBS is performed on a SPECT/CT using either Siemens Symbia T16 or GE Discovery 670. Patients are fasted for at least 4 hours before the procedure. A dose of 200 MBq of Tc-99m mebrofenin is administered intravenously. Dynamic imaging was acquired from 36 frames at a rate of 10sec/frame, for the first 6 minutes during the uptake sequence. Next, SPECT/CT imaging was acquired from 60 projections at a rate of 8sec/projection at peak hepatic activity. This is followed by a delayed dynamic excretion sequence of 15 frames at 60sec/frame [17]. Data were processed on the symbia.net workstation. Regions of interest delineating the heart and whole liver were drawn to estimate blood pool activity to obtain geometric mean datasets, as well as the time activity curve and normalised curve. Calculation of dynamic and SPECT parameters to obtain hepatic uptake rate and FLR function were as described by W. de Graaf [5]. Guided by the planned surgical resection areas, liver remnants were plotted based on anatomical landmarks in order to obtain FLRᶠ.

Portal Vein Embolization (PVE)

PVE was performed by interventional radiologists. All PVE was performed on the right lobe. An ipsilateral approach was undertaken on all patients. A mixture of histoacryl and lipiodol with varying ratios of between 1:3-1:6 was used as the embolic material. In patients who also underwent HVE, Amplatz type 2 plug was applied to the right hepatic vein.

SIRT

SIRT was performed by interventional radiologists. All patients underwent SIRT simulation and planning 1 week prior. 10 patients received treatment to the right lobe, and 1 patient to the left. An average of 2.709 +/-0.814 - 4.52 GBq of Y-90 resin SIR-spheres was administered during each procedure. 90Y PET CT is performed after the procedure to verify deposition of SIRT microspheres.

Results

206 patients were referred for hepatectomy. 99 patients were considered for major resection and were included in the study. 2 patients were excluded from analysis due to death from separate pathologies. Upon MDT review, 64 of 99 candidates for major resection were identified to be high risk and underwent HBS as part of their surgical work up. 1 patient was excluded due to failure to achieve proper contrast opacification of hepatic structures and resultant failure to provide reliable calculations. 35 of 98 patients were considered low risk and proceeded directly with surgery.

Patients demographics and planned resections are presented in Table 2. Patients within our high-risk cohort were planned for larger resections including right or extended right hemihepatectomy, had colorectal cancer or hepatocellular carcinoma, and had previously received chemotherapy.

Patient characteristics	All (n = 98)	HBS (n=52)	No HBS (n=34)	P value
Male: Female	63:35	45:18	18:17	0.078
Age	60.1±14.82	61.5 ± 13.9	57.6 ± 16.2	0.22
Comorbidities				
Hypertension	22	16	6	0.45
Hypercholesterolaemia	17	10	7	0.59
T2DM	16	11	5	0.78
IHD	13	9	4	0.76
Respiratory issues	9	6	3	1
Other Malignancy	10	7	3	1
Other PMHx	32	18	14	0.27
Indication				
Colorectal Mets	46	34	12	
Hepatocellular Ca	19	16	3	
Cholangio Ca	17	9	8	.00095
Other Malignancy	7	3	4	
Benign	9	1	8	
Liver Injury				
Chemotherapy	46	36	10	0.011
Hepatitis B/C	10	9	1	0.09
ETOH cirrhosis	1	1	0	1
Biliary stasis	4	2	2	0.62
Steatohepatitis	2	2	0	0.54
Other Liver Injury	5	3	2	1
Planned Resection				
Right / Extended right (RH / ERH)	66	48	18	
Left / Extended Left (LH / ELH)	24	8	16	0.0012
Central resection (CR)	2	1	1	
3 / 4 segmentectomy	6	6	0	

Table 2: Baseline characteristics of high and low risk cohort.
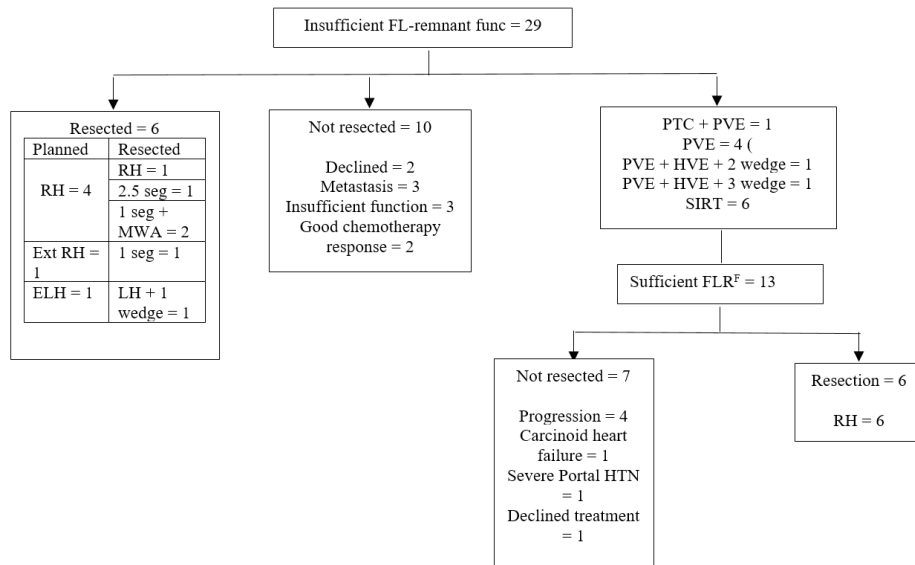
Patients with Sufficient FL-Remnant func

34 of 63 patients had sufficient FL-remnant func on HBS, and all 34 had sufficient std-remnant vol. Outcomes are summarised in Figure 1. 18 patients underwent their planned surgery, 1 patient underwent 5 wedge resections and 3 ablations instead of the planned right hemihepatectomy due to portal hypertension. 10 of 63 patients did not undergo surgery. This was due to progression of disease in 8 patients, and anatomical issues precluding resection in 2 patients. 4 SIRT and 1 PVE was performed despite adequate function. 2 SIRT and 1 PVE was done to improve borderline FL-remnant func of 2.8-2.9%/min/m², however 1 developed progression of disease during the interval period. Among the two other patients who underwent SIRT, one was to reduce bleeding risk by devascularising a large lesion, but developed disease progression; the other was performed to achieve tumour shrinkage and improve resectability due to proximity to the middle hepatic vein.
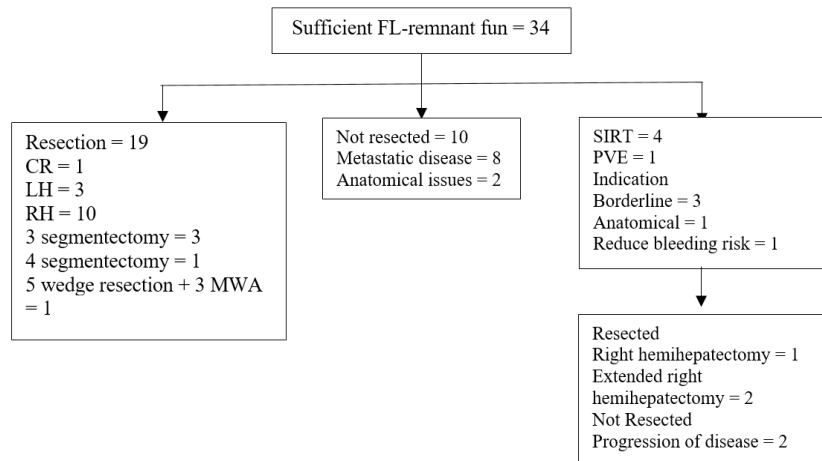
Figure 1: Outcomes for patients with sufficient FL-remnant func.

Patients with Insufficient FL-remnant func

29 of 63 patients had insufficient FL-remnant func, despite 14 patients with sufficient std-remnant vol of >30%. Outcomes are summarised in Figure 2. 5 patients underwent a smaller then planned resection, with no complications recorded. 1 patient with insufficient function underwent a planned right hemihepatectomy, on the basis of sufficient remnant volume of 38%, without complications. 10 patients did not undergo resection. 13 patients underwent augmentation with either SIRT or PVE. All patients achieved sufficient remnant hypertrophy, however only 6 patients were able to undergo their planned resections.

Figure 2: Outcomes for patients with insufficient FL-remnant func.

Liver hypertrophy post Augmentation

8 patients underwent PVE. 1 had concurrent biliary decompression, and 2 patients underwent concurrent hepatic vein embolization (HVE) with wedge metastectomy on the remnant lobe. 1 patient did not have HBS prior to PVE and was excluded from analysis. Average time between PVE to repeat HBS was 44.43 +/- 11.52 days. There was no significant change in TL-vol (-82.57 +/- 256.97ml, t=-0.6, p=0.57) or TL-func (-0.6 +/- 1.68%/min/m², t=-1.77, p=0.13). Hypertrophy of FL-remnant vol was significant (234.43 +/- 136.11ml, t=7.07, p=0.0004). It should be noted that the 2 patients who underwent multiple wedge metastectomy would result in a smaller FLR hypertrophy on HBS, skewing the data. PVE resulted in significant increase in FL-remnant func (1.56 +/- 0.77%/min/m², t=6.62, p=0.00057). There is a weak correlation between increase in FL remnant volume and function (r= 0.464, p=0.294). 1 patient developed portal hypertension post PVE and underwent cyberknife, and 1 patient developed disease progression. 10 patients underwent SIRT, with 2 patients receiving two-staged treatments. 1 patient also underwent biliary decompression via ERCP.

Average time between SIRT and repeat HBS was 138.5 +/- 94.8 days. There was no significant change in TL-vol (mean= 263.8 +/- 483.85ml; t=1.72, p=0.119), however there was a significant decrease in TL-func (mean= -2.01 +/- 2.79%/min/m²; t=-3.44, p=0.007). SIRT resulted in significant hypertrophy of FL-remnant vol (mean = 402.7 +/- 365.96ml, t=3.48, p=0.007); and FL-remnant func of (mean =1.07 +/- 0.77%/min/m², t=4.26, p=0.0021). There is a significant correlation between increase in FL remnant hypertrophy and improvement of function (r=

0.78, p=0.0079). No patients developed complications, but 6 patients developed progression of disease and did not undergo resection. There is no statistically significant difference in the degree improvement of either FL remnant volume and function between the PVE and SIRT group (t=1.15, P= .27; t=-1.33, p=.20 respectively).

Post Hepatectomy Liver Failure

34 high-risk patients underwent major resection where 5 developed PHLF. 3 patients with both sufficient std-remnant vol and FL-remnant func, with a mean of 3.7%/min/m², developed grade A PHLF after undergoing right hemihepatectomy. 1 patient had borderline FL-remnant func of 2.8%/min/m² and underwent SIRT, achieving a FL-remnant func of 4.7%/min/m² but developed grade B PHLF after extended right hemihepatectomy. 1 patient had insufficient FL-remnant func of 2.2%/min/m² and underwent PVE, achieving a FLRᶠ of 4%/min/m², but developed grade A PHLF post right hemihepectomy. All patients with insufficient function who underwent a smaller than planned resection did not develop PHLF. 7 patients among the low-risk group developed grade A PHLF after undergoing right hemihepatectomy, and 1 patient with a history of primary sclerosing cholangitis developed grade B PHLF post left hemihepatectomy.

Liver Injury and Function

Within our high-risk cohort, there were significantly more patients who underwent chemotherapy, which places them at risk of CALI and impacting liver function. Our patients who received pre-operative chemotherapy had smaller TL-tot vol (1808 +/- 501.58ml; t=2.68, p=0.001; no chemo=2279.59 +/- 744.91ml)

but similar TL-tot func (7.96 +/- 2.39%/min/m^2; t=0.38, p=0.7; no chemo=8.22 +/- 2.02%/min/m^2). Similarly, 9 patients with chronic liver injury had smaller TL-tot vol (1482.5 +/- 494.86ml; t=-3.12, p=0.004) and smaller TL-tot func although this was not significant (7.28 +/- 2.85%/min/m^2; t=-1.02, p=0.32).

Discussion

HBS is a useful pre-operative tool to assess the remnant function to help reduce the risk of PHLF. Within our centre, the selective use of HBS for patients considered to be at high risk of PHLF has allowed individual treatment to be adjusted to ensure sufficient remnant function. Patients found to have insufficient FL-remnant func where able to undergo a smaller resection or augmentation, thereby reducing their risk of PHLF and improving outcomes.

One of the main modifiable predictors of PHLF is FL-remnant vol [1]. Estimation of FL-remnant vol can be difficult due to the volumetric variation between each Couinaud segment, and among individuals [1]. To account for each individual metabolic requirement, a FL-remnant vol based on CT volumetry, standardized to BSA was proposed [15]. Chun et al. found that the standardised future liver remnant (sFLR) cut off <20% is able to predict post-operative hepatic dysfunction in patients without chronic liver disease, with a positive predictive value of 80%, and negative predictive value of 86% [9]. In patients with liver injury, impact of the damaged parenchyma on the liver function cannot be assessed by standard CT imagery, and the remnant liver might not have the required function to meet an individual's metabolic needs. Studies have shown that patients with abnormal parenchyma have lower TL-tot func despite having a large non-tumoural TL-tot vol [6,7]. As a result, Vaughty et al. proposed a cut off of 30% std-remnant vol for injured livers, and 40% std-remnant vol for well compensated cirrhotic livers [2,18]. However, the FL-remnant func was found to be a better predictor, having better positive and negative predictive values as compared to std-remnant vol [7].

Within our high-risk cohort, pre-operative chemotherapy was the main factor placing patients at risk of liver injury (57.14 %). However, these patients who received pre-operative chemotherapy did not have statistical differences in total liver volume or function. CALI occurs in 30-50% of patients who receive chemotherapy; 5-Fluorouracil increases the risk of steatosis, irinotecan causes steatohepatitis, and oxaliplatin causes sinusoidal obstruction [2,19,20]. There has been contrasting reports on the impact of pre-operative chemotherapy on liver function and postoperative complications. Preoperative chemotherapy of less than 12 cycles was found to have no impact on liver function as assessed by HBS [19,21]. It was proposed that chemotherapy would cause transient impairment of liver function which is expected to improve following several weeks [18,22,23]. This is consistent with our findings of similar TLF, however it is beyond the scope of this study to review specific chemotherapy agents and duration on their impact on liver function.

Patients with insufficient FL-remnant func, PVE and SIRT are effective methods of inducing hypertrophy and increasing function, allowing surgery to proceed with reduced morbidity [8,11-14,23,24]. PVE induces FL-remnant vol hypertrophy of 25.2-50.4%, resulting in a larger increase in FL-remnant func of 55% [8,21]. This increase in FLR volume and function is not influenced by the underlying liver parenchyma or previous chemotherapy regime. However, in patients who received chemotherapy, a FL-remnant func of <1.92%/min/m2, or <1.72%/min/m2 in those without, is predictive of insufficient regeneration after PVE [8,23]. Sufficient increase in FL-remnant func of up to 50.3% is usually achieved within the first 3-4 weeks to allow surgery to proceed [1,8,11,25]. In our cohort, we had sufficient hypertrophy of the remnant volume and improvement in function with an average of 54.9 and 87.22% respectively. In addition, PVE is a safe procedure with a low morbidity rate of approximately 2.2%, even in patients with liver injuries [11,26]. Complications associated with PVE include portal hypertension, hepatic abscess, portal vein thrombosis, subcapsular haematoma, coil misplacement, oesophageal bleed, and septic necrosis11. However, despite its safety profile, various studies have demonstrated tumour progression and high rates of unresectable disease post PVE [8,12]. In this aspect, SIRT has the added advantage of local disease control, while producing comparable hypertrophy of FL-remnant vol [14,24]. SIRT does not cause macrovascular embolization, but hypertrophy of the FL-remnant vol is likely due to its radiation effects [13]. This translates to a slower rate of hypertrophy of 0.7%/week which declines over time, achieving a maximum of 40-45% at 9 months [24,27]. On the other hand, the resultant radiation fibrosis has been attributed to increased complications post hemihepatectomy [14]. In our study, we experienced similar improvement in both FL-remnant vol and FL-remnant func both in our PVE and SIRT cohorts. Interestingly, the increase in FL-remnant vol post SIRT was similar with other studies but within a shorter interval of an average of 138.5 days. Among our 7 patients who underwent PVE, 1 developed tumour progression along the common hepatic artery and was unresectable despite a moderate time interval of 46 days between PVE to planned resection. Comparatively, 6 of 10 of our SIRT patients did not proceed with liver resection due to metastatic progression of their disease despite having local control. The study by Wright et al suggested 6 months interval post SIRT to allow for disease observation and sufficient hypertrophy of untreated liver segments [13]. Given significant portion of our SIRT cohort developed disease progression within a shorter time interval, it raises the question optimal interval time between SIRT and resection given its slow kinetic growth rate and risk of disease progression.

The use of HBS allowed us to identify 14 patients with std-remnant vol of >30% but had insufficient FL-remnant func.

Augmentation was performed on 7 patients, allowing 3 patients to undergo their planned right hemihepatectomy, and 1 patient to undergo a smaller resection. 1 patient underwent their planned right hemihepatectomy on the basis of sufficient std-remnant vol of 38%. In addition, while patients with adequate FL-remnant func also had sufficient std-remnant vol, 5 patients only had borderline remnant function and were able to undergo augmentation to further reduce their risk of PHLF. Within our high-risk cohort, 4 cases of PHLF occurred among patients who had sufficient FL-remnant func, where 3 underwent right hemihepatectomy, and 1 underwent an extended right hemihepatectomy. Among those with insufficient FL-remnant func, 1 episode occurred in a patient who underwent right hemihepatectomy post PVE, having achieved a FL-remnant func of 4%/min/m^2. The absence of PHLF in patients who underwent a smaller resection due to insufficient remnant function is reflective of the utility of HBS in planning and adaptive management. When compared to the low-risk cohort, the HBS group had lower rates of PHLF but the difference was insignificant. 7 patients in the low-risk had grade A PHLF after undergoing right hemihepatectomy, while 1 patient with grade B PHLF underwent a left hemihepatectomy, but had a history of primary sclerosing cholangitis. This would suggest that patients planned for large volume resections, or have chronic liver injury warrants further HBS workup.

Despite demonstrating the useful application of HBS in high risk patients, our study has its limitations. Firstly, this is a retrospective study which limits available outcomes. Formal volumetric studies were not performed on low risk of the patients. Conversely, patients who are at low-risk of PHLF did not undergo HBS either. As a result, formal comparison between CT liver volumes, standardised volumes, and function could not be performed, and their correlation could not be determined. The available data only allowed us to compare the functional volume and function in high risk patients, resulting in selection bias. Furthermore, some patients with significantly impaired function did not undergo surgery, and hence do not have histological information on their liver parenchyma, which likely to be significantly compromised. This lack of histological data limits our ability to gain meaningful information. A prospective study would provide more data and allow for better assessment of the above variables. Lastly, while majority of our patients were considered to be high risk due to their previous chemotherapy treatment, the impact on chemotherapy regime on liver function was not determined as it is beyond the scope of this study.

Conclusion

This study demonstrates the utility of HBS as part of the pre-operative risk assessment for high-risk patients. We were able to tailor treatments by augmentation or alteration of resection volumes for patients who would otherwise not have been surgical candidates due to insufficient remnant volumes, or who have been at risk of PHLF due to insufficient remnant function. Patients who should be selected for HBS include those requiring large resection volumes, abnormal liver parenchyma known from biopsies, or have a history of chronic liver injury. Patients who received a short course of adjuvant chemotherapy with normal liver biochemical tests may not need to be considered as at high risk. In those with insufficient remnant function, PVE and SIRT are safe procedures to augment and improve remnant function and resectability.

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