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Elective hepatic resection is feasible and safe in a regional centre

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Abstract

Background: Hepatic resectional surgery remains a highly specialized area of general surgery usually reserved for completion at tertiary metropolitan referral centres. Port Macquarie, on the Mid North Coast of New South Wales, is the only regionally based hospital offering surgery of this nature in mainland Australia. The purpose of this study is to review the data for patients undergoing hepatic resectional surgery in this non-metropolitan centre in order to illustrate that these operations can be carried out safely in a regional setting with comparable results to tertiary-level centres.
Methods: A retrospective review of consecutive patients undergoing elective hepatic resections at Port Macquarie from February 2008 to 31 October 2015 was completed. Pre-morbid patient clinical and demographic factors, histopathological details, post-operative complications, survival and mortality data were all noted.
Results: A total of 66 consecutive elective liver resections were performed during the study period. Metastatic colorectal cancer was the most commonly observed pathology (n = 33, 50.0%). The 90-day mortality was 4.5% (n = 3) whilst 17 patients (n = 17, 25.8%) experienced major complications (Clavien–Dindo grade 3 or 4). The median overall survival following hepatectomy for colorectal metastases was 48 months (95% confidence interval 37–59 months).
Conclusion: Our study shows excellent morbidity, mortality and survival for hepatic resectional surgery performed in a regional centre and is comparable data to major metropolitan centres. Our study confirms that major hepatic resectional surgery in this setting is safe and effective.

Introduction

Hepatic resectional surgery has traditionally been the domain of tertiary-level hospitals. In Australia, and the world, it is currently debated whether certain complex upper gastrointestinal surgeries, including liver resections, are safely performed in lower-volume centres, with evidence in the literature available to support both sides of the argument.[1–3] Regardless of this, the field of hepatobiliary surgery is expanding, with a growing ability to remove colorectal cancer (CRC) metastases in increasing numbers and locations, and surgery being offered to larger numbers of elderly patients.[4] The liver is the most common site for CRC metastatic disease, and resection of hepatic metastases prolongs survival and achieves cure in selected patients.[5–7] Moreover, although there is no randomized study to compare liver resection with non-surgical treatment, surgical resection remains the gold standard and only potentially curative treatment for hepatic metastases from CRC.[8,9]

Mortality from liver resections has decreased over the years, despite surgical intervention becoming more aggressive,[10] with high-volume centres quoting post-operative mortality <5% in current literature.[11–13] Regardless of the improvement in mortality, morbidity rates remain elevated with overall rates up to 57% reported in large volume centres[14] and major morbidity figures (Clavien–Dindo classification ≥3) listed in the vicinity of 30%.[15]

Hepatic resectional surgery has been available in Port Macquarie, a regional centre on the Mid North Coast of New South Wales, Australia since early 2008. It is the only regionally based centre undertaking these types of resections in mainland Australia. This study is a retrospective review of elective hepatic resections carried out in Port Macquarie since its inception in 2008. We aim to show

that hepatic resections can be performed safely in this regional setting, with low mortality and morbidity levels comparable to those seen in tertiary-level centres.

Methods

Patient selection and demographics

Following the ethics approval of the study for quality assurance purposes, a retrospective review of all patients who underwent major elective hepatic resections in Port Macquarie was undertaken. All resections were performed by a single surgeon and were undertaken in both the public and private sectors. The vast majority of resections were completed at Port Macquarie Base Hospital, a 195-bed facility in a rural coastal setting with intensive care unit (ICU) support. A single resection was undertaken at Port Macquarie Private Hospital, a 77-bed facility with high-dependency supports only. Patient data were collected from the prospective database of the surgeon, with in-hospital post-operative data collated retrospectively from hospital records.

Patient selection, assessment and preoperative workup

Port Macquarie used a standard preoperative assessment from the commencement of the programme in 2008. All patients who were referred to the service were initially presented for discussion at the Mid North Coast Cancer Institute (MNCCI) gastrointestinal oncology multidisciplinary team (MDT) meeting. The suitability for *operative* intervention primarily depended upon patient factors and staging results from a (standard) triple-phase computed tomography (CT) scan of the abdomen/pelvis and high-resolution CT of the chest. *Primovist* liver-directed magnetic resonance imaging (MRI) was utilized routinely from its availability in Port Macquarie from July 2011. Positron emission tomography (PET) CT was reserved for staging patients with recurrent disease *following* previous liver resection. At this point, patients who were deemed *resectable* proceeded to elective hepatic resection locally (and are included in this review), and those who were deemed *inoperable* were referred for palliative therapies. All *resectable* patients with CRC metastatic disease received neoadjuvant chemotherapy as standard therapy.

A standard anaesthetic approach was used for all patients including initial clinic review preoperatively, and then routine use of a thoracic epidural, central venous catheter and arterial line intraoperatively. All patients were extubated immediately following resection.

Surgical technique and peri-operative management

Open resections were performed in a standard manner via either a right-sided ‘J-type’ or tri-radiate subcostal incision as determined by the surgeon. Routine intraoperative ultrasonography was used to confirm the location and numbers of tumours as well as margins for resections. Resections for CRC were completed using a remnant liver preservation approach, thereby leaving the option for re-do liver resection in the event of recurrent liver disease. Linear vascular staplers were used for ligation of major vascular and biliary pedicles. The liver edge was sealed with argon plasma coagulation and Tisseal© glue (Baxter Healthcare, Deerfield, IL, USA) and a 19-Fr passive suction drain left routinely. Laparoscopic resections were completed for small, peripheral tumours at the discretion of the surgeon. A standard five-port technique was used, with routine use of laparoscopic ultrasound, and a transhepatic approach made to the relevant vascular pedicles.

Post-operatively, patients were routinely admitted to ICU and were managed according to the principles of an enhanced recovery after surgery (ERAS) approach including early feeding and mobilization. Assuming an uncomplicated course, a planned discharge date was identified for day 6 post-operatively.

Follow-up

Patients were followed up in a standard fashion dependent on the underlying pathology leading to the resection. All patients were seen at an initial 6-week post-operative check. Those whose pathology was benign with no post-operative complications were discharged. Patients undergoing resections for malignant lesions were reviewed with 3-monthly tumour markers, assuming they had a secretory lesion, and imaging with CT scan during the first year. They then continued follow-up with 6-monthly reviews until the end of post-operative year 5, and then annual review after 5 years as per standard protocol.

Statistical analysis

Pre-morbid patient clinical and demographic factors, histopathological details, post-operative complications, 90-day mortality and survival for resections for CRC metastatic disease were all recorded. Data were analysed using SPSS Statistics (Version 22; IBM, Chicago, IL, USA). The study end date was defined as 31 October 2015. Survival data were calculated using the Kaplan–Meier method.

Results

Patient selection and demographics

From February 2008 to 31 October 2015, a total of 66 elective liver resections were performed in Port Macquarie on 61 patients with mean follow-up across the study period of 31 months (interquartile range 12–50). Baseline patient characteristics are shown in Table 1.

The types of resections performed over the study period are summarized in Table 2, with a varied complexity of cases represented in the series. In terms of the pathological indications for surgery, resection of CRC liver metastases (n = 33, 50.0%) was the most common, followed by resections for non-CRC malignant disease (n = 18, 27.3%). Resection margins amongst the cohort undergoing oncological surgery were satisfactory with R0 resections confirmed on histopathology in 92.2% (n = 47). Fifteen patients underwent surgery for benign disease (n = 15, 22.7%) with no deaths identified at the census date. Surgery was indicated in the majority of these patients (n = 9, 13.6%) as malignancy could not to be ruled-out on imaging alone. The remaining benign cases were all

Table 1 Study population characteristics and outcomes data

Sex, male/female, *n* (%)	28/36 (42.4/57.6)
Age, years, mean ± SD	67 ± 14
ASA, *n* (%)	
1	9 (13.6)
2	48 (72.7)
3	9 (13.6)
Preoperative haemoglobin, median (IQR)	135 (125–146)
Post-operative haemoglobin, trough, median (IQR)	102 (91–116)
Intraoperative transfusion, *n* (%)	1 (1.5)
Post-operative transfusion, *n* (%)	1 (1.5)
Post-operative INR, peak, median (IQR)	1.2 (1.1-1.4)
Post-operative ALT, peak, median (IQR)	381 (180–717)
Post-operative bilirubin, peak, median (IQR)	18 (11–29)
Total LOS, days, median (IQR)	7 (6–11)
ICU LOS, days, median (IQR)	4 (2–6)
Follow-up, months, median (IQR)	31 (12–50)
90-day mortality, *n* (%)	3 (4.5)

ALT, alanine transaminase; ASA, American Society of Anesthesiologists score; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; LOS, length of stay; SD, standard deviation.

Table 2 Types of hepatic resection

Type of resection	*n* (%)
Minor†	26 (39.4)
Minor complex‡	9 (13.6)
Major§	31 (47.0)
Bilobar¶	14 (21.2)
Synchronous††	1 (1.5)
Laparoscopic	4 (6.1)

†Resection of <3 segments in accessible areas. ‡Resection of <3 segments from difficult posterior locations (segments 1, 6, 7 and 8). §Any resection involving ≥3 segments. ¶Resection involving *both functional lobes* of the liver. ††Simultaneous resection of primary and metastatic disease.

symptomatic including three patients with hepatic cysts (*n* = 3, 4.5%), and three patients with complications of intrahepatic biliary calculi (*n* = 3, 4.5%).

Overall mortality and morbidity

Overall 90-day mortality rate was low (*n* = 3, 4.5%). One patient died from acute hepatic failure in the context of cirrhosis following resection for primary intrahepatic cholangiocarcinoma. A second patient's death following resection for intrahepatic cholangiocarcinoma was attributable to a massive pulmonary embolus in the context of a recurrent bile leak. The third patient died from overwhelming sepsis due to an anastomotic leak following synchronous resection for primary and metastatic CRC. In total, there were 39 patients (*n* = 39, 59.1%) who had adverse events occur following liver resection. The majority of these (*n* = 22, 33.3%) were minor (Clavien–Dindo grade 1 or 2) whilst 17 (*n* = 17, 25.8%) experienced major complications (grade 3a, 3b or 4). Grade 3a complications were attributable to collections requiring radiologically guided percutaneous drainage (*n* = 12, 18.2%) and were caused by infection (*n* = 7, 10.6%), pleural effusion (*n* = 3, 4.5%) and bile leak (*n* = 2, 3.0%). One patient (*n* = 1, 1.5%) had a grade 3b complication requiring return to the operating room for washout of an infected wound collection. There were four cases (*n* = 4, 6.1%) with grade 4 life-threatening complications: two cases required inotropic support for sepsis from infected collections, and two required prolonged non-invasive ventilatory support for non-surgical complications (stress-induced cardiomyopathy and acute respiratory distress syndrome, respectively).

Table 3 CRC metastases resection outcomes (*n* = 33)

Intraoperative or post-operative transfusion, *n* (%)	1 (3.0)
ICU LOS, days, median (IQR)	3 (2–5)
Total LOS, days, median (IQR)	7 (6–12)
90-day mortality, *n* (%)	1 (3.0)
Kaplan–Meier disease-free survival, months, median (95%CI)	13 (10–17)
Kaplan–Meier overall survival, months, median (95%CI)	48 (37–59)
Kaplan–Meier 3-year overall survival, %	72

CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay.

Resection for metastatic CRC

Thirty-three (*n* = 33, 50.0%) patients underwent hepatic resection for metastatic CRC. The morbidity and mortality data for this subgroup of patients are outlined in Table 3, while the overall Kaplan–Meier survival is shown in Figure 1. At the close of the study, 15 of these patients were still alive and two of those were from the first year of the series. There was only one inpatient death as described above and all other patient deaths following resection for CRC metastases were from disease progression. Of these, three recurred solely in the liver, a further seven recurred in the liver and another extrahepatic site, and the rest had completely extrahepatic recurrence. Median disease-free survival (DFS) was 13 months with the two long-term survivors from the first year of the series both disease-free at the census date (Fig. 2).

Non-CRC malignant disease

Eighteen (*n* = 18, 27.3%) patients underwent resections for malignancy *other* than CRC. Five (*n* = 5, 7.6%) patients underwent resections for primary liver cancer, with three of these patients alive and recurrence-free at the census date. Both of the deaths in this group were due to disease progression and occurred at 8 and 10 months, respectively. Five (*n* = 5, 7.6%) patients underwent resection for primary intrahepatic cholangiocarcinoma, with no survivors beyond 8 months. The majority of the remaining patients were alive at the census date, but with either recurrence or residual disease including two highly selected patients who underwent initial and repeat resections for hepatic metastases from renal cell carcinoma and junctional gastric cancer, respectively. Also included were single patients with metastatic carcinoid tumour and gastrointestinal stromal tumour, and a single patient with locally invasive gallbladder cancer. The lone patient with metastatic disease of unknown primary died 11 months after their resection due to disease progression.

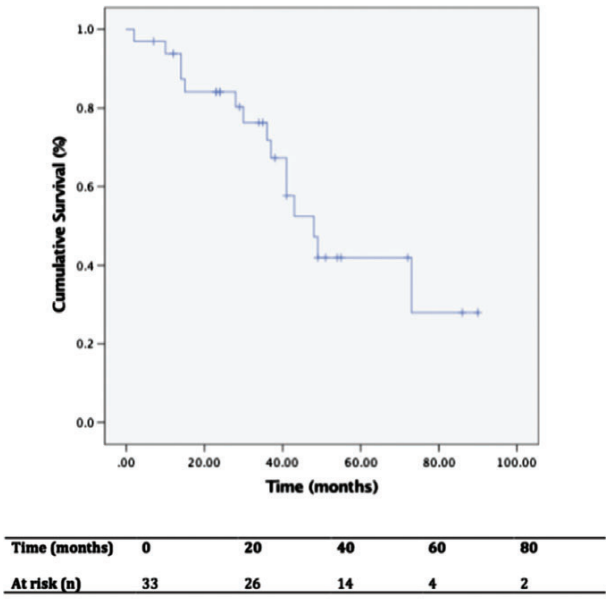

Fig. 1. Kaplan–Meier overall survival rates of patients with colorectal cancer liver metastases.

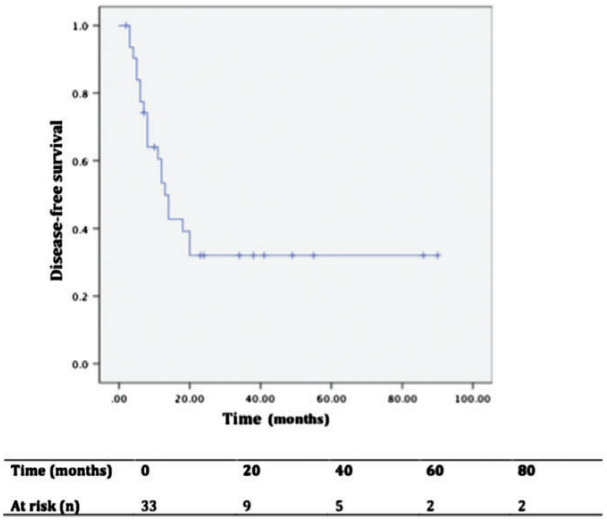

Fig. 2. Kaplan–Meier disease-free survival rates of patients with colorectal cancer liver metastases.

Discussion

Our study is the first review of hepatic resections in a regional centre in mainland Australia and we show that this surgery is safe with low mortality and comparable morbidity and survival data to high-volume tertiary centres carrying out similar procedures.

Post-operative mortality has been well reported both in Australia and internationally, with large case series of available results consistently reporting inpatient and 90-day mortality rates of less than 5%.[11–13,15–18] Dokmak *et al.* published the largest case series of elective hepatectomy involving 2012 cases and showed an overall 90-day mortality of 5.2%[14] – our 90-day mortality was 4.5% which is comparable. Interestingly, two separate reviews examining the effect volume of cases has on operative mortality quoted rates of 3 and 4% in high-volume centres which is comparable to our rate at a low-volume centre.[19,20]

Importantly, the major morbidity rate at Port Macquarie was 25.8% (n = 17), a figure that is clearly comparable to larger international case series where rates of between 24 and 30% are reported.[12,14,15] Although the overall morbidity rate at Port Macquarie was 59.1% (n = 39), which does appear quite high, it is comparable with the rate reported from the largest international case series published in the literature (56.5%).[14] The majority of the identified morbidity cases were minor complications (n = 22, 33.3%) with all unexpected events including increased post-operative pain, urinary tract infection, and asymptomatic pleural effusion included for analysis.

From the outset, *identifiable* selection bias amongst our cohort was kept to a minimum as no patients were *referred on* whose disease was determined to be resectable. Although a tertiary-centre was *not utilized* for assistance in decision-making, each patient was vigorously discussed at the local MNCCI MDT meeting and all parties within that environment agreed upon an individual management plan prior to its implementation on a patient level. In addition, we believe that our reported morbidity rates further reflect an aggressive approach to oncological resection, as does the number of patients undergoing complex minor resections – a more difficult surgical approach specifically undertaken to preserve liver tissue for possible future resection.

Certain issues we identified can be attributable to unique difficulties brought about by operating in a regional setting. The lack of local liver-directed MRI services was certainly a concern up until July 2011 when *Primovist* MRI became widely available. As it would be, our benign resection rate is somewhat high, however, most of these (n = 9) occurred in the period *before* liver-directed MRI was available locally, meaning patients given the option *preferred* to remain within the local region for their workup, understanding that without MRI, malignancy was not *best* able to be ruled-out on imaging alone. Again, MDT discussion for each of these patients remained crucial to their individual treatment. We also acknowledge that our overall length of stay (LOS), especially ICU LOS (Table 1), was high in the age of ERAS. Again, the relative isolation of Port Macquarie meant that a cautious approach was upheld from the outset. Patients, especially those travelling, were preferably kept for a minimum of 6 days to ensure their proximity to the primary operator during the period in which complications were most likely to become apparent. In a similar vein, patients remained in ICU longer as it was felt that specialized post-operative management, especially that required for a thoracic epidural, was best completed in a higher-level care environment.

No other treatment, apart from surgical resection, offers a patient the chance of cure for hepatic CRC metastases, and thus in this high-risk surgical cohort, a certain level of morbidity must be accepted. In terms of CRC survival statistics, although a single Australian institution has reported median overall survival (OS) greater than 100 months,[18] these results have not been

replicated elsewhere in the literature where reported median OS rates range between 34 and 56 months.[3,12,16,17] Our rate is comparable at 48 months and although we have only reported a 3-year OS (72%), which again is comparable to other Australian institutions,[3,16–18] our dataset for 5-year survival statistics (n = 13) is too small from which to draw accurate conclusions. We do acknowledge that the initial part of our DFS curve (Fig. 2) is quite steep with 10 patients recurring within 6 months of their initial liver resection. It is *unlikely* that the lack of local liver-specific MRI would have impacted on this outcome, as all but one of those early recurrences was distant to the liver, however more accessible PET scanning, not currently available locally, may have made a difference. Importantly, patients with early recurrence were all offered further treatment with surgery, or chemotherapy, either in combination or alone, or treatment with another modality, such as SIR spheres (Sirtex, Sydney, NSW, Australia), *not available* in Port Macquarie.

Finally, although not within the scope of this study, we believe that there are numerous social and quality of life benefits of offering this surgery in certain regional centres. Further investigation is required into quantifying these perceived benefits but would include likely decreased overall costs, improved patient social supports and decreased psychological stress and anxiety related to the surgery itself.

Conclusion

Our study demonstrates for the first time that regional hepatic surgery in mainland Australia is safe, with comparable outcomes to those of tertiary-level Australian and international centres. Specifically, major morbidity, 90-day mortality and long-term survival data for CRC metastases is comparable to other larger series, at times when over 2000 patients were included.[14] We would argue that the above study highlights that the expanding field of hepatic resectional surgery warrants extension of regional services rather than their reduction or removal.

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