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Liver Transplantation for Non-resectable Colorectal Liver Metastases

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8. References

Abbreviations

ALPPS: Associated liver partition and portal ligation for staged hepatectomy

APOLT: Auxillary partial orthotopic LT

CLM: Colorectal liver metastases

CRC: Colorectal cancer

DBD: Donation after brain death

DCD: Donation after circulatory death

DDLT: Deceased donor liver transplantation

DFS: Disease free survival

ECD: Extended criteria donor

IOUS: Intraoperative ultrasound

LDLT: Live donor liver transplantation

LN: lymph nodes

LT: liver transplantation

LVP: Liver venous deprivation

MMR: Mismatch repair

MSI: Microsatellite instability

MTV: metabolic tumour volume

OS: Overall survival

PET: Positron Emission Tomography

PVE: Portal vein embolisation

PVL: Portal vein ligation

RAPID: Resection and partial segment II/III LT with delayed total hepatectomy

RCT: Randomised controlled trial

R0 resection: Complete resection with histologically negative margin

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1. Background

1.1. Liver resection for CLM

Colorectal cancer (CRC) is the second most common cause of cancer death in New Zealand, and the incidence is increasing in patients under age 50 (New Zealand Cancer Registry, Ministry of Health) and projected to increase further[1]. Nearly all deaths from CRC are due to metastatic spread. The route of dissemination from the bowel to the liver is via the portal circulation and the liver is the most common site of metastatic spread of CRC after locoregional lymph nodes. In a proportion of patients, the liver is the only site of metastatic spread.

Until the 1970s liver metastasis was considered a sign of incurability and survival beyond 5 years was rarely reported. However, from the 1970s onwards, selected patients with solitary colorectal liver metastases (CLM) underwent liver resection with 5-year survival rates of 20-30%.[2] These results, together with advances in patient selection, cross-sectional imaging, surgical technique and peri-operative care, saw a gradual expansion of resection to more patients. By 2000 liver resection was standard of care even for multiple resectable metastases, including bilobar distribution. Meanwhile systemic chemotherapy for colorectal cancer (5-Fluorouracil and Folinic Acid, Oxaliplatin and Irinotecan) demonstrated efficacy in a range of clinical settings, and together with newer biological agents (Bevacizumab, Cetuximab) increased the median survival for patients with inoperable metastatic disease from around 6 months to more than 2 years. More recently a new class of immunotherapy drugs, checkpoint inhibitors, have been shown efficacy in the subset of CRC patients with micro-satellite instability. [3]

The concept of down-staging initially inoperable CLM with chemotherapy to facilitate complete (R0) resection was first reported in the early 2000s and led to further expansion of the role of resection in patients who showed a good response to systemic therapy.[4, 5] New techniques were also added to the surgical armamentarium to extend resectability, including targeted ablation (cryotherapy, radiofrequency, microwave, irreversible electroporation, SBRT),[6] portal vein embolization (PVE) with or without concomitant hepatic vein embolization (liver venous deprivation; LVD) to increase the size of the future liver remnant,[7, 8] staged resections, and associated liver partition and portal ligation for staged hepatectomy (ALPPS).[9, 10]

Hence over the last two decades there has been a steady expansion of the role of resection to include any number and distribution of metastases as long as complete resection and/or ablation seems feasible, with or without prior down-staging by chemotherapy.[5, 11] Improved outcomes have been reported despite the broadening of eligibility criteria, attributed to the increased use of resection and chemotherapy to treat these patients.[12] Nevertheless, R0 resection remains unattainable for many patients with metastatic disease, including some with liver-only disease. The sub-set with non-resectable liver-only CLM could potentially derive long term benefit from total hepatectomy and orthoptic liver transplantation [13].

1.2 Defining Non-resectability

The basic requirements for resectability are ability to excise and/or ablate all viable disease while leaving behind a remnant with adequate size, vascular inflow and outflow and biliary drainage to support post-operative recovery and liver regeneration. Resection with a histologically tumour-free margin (R0) is always the aim, although resection of macroscopic disease with a histologically involved margin (R1) does not preclude long term benefit. [14] [15]

Resectability should be determined by an HPB multidisciplinary meeting (MDM) that involves as a minimum agreement by two experienced HPB surgeons, an experienced liver radiologist and a medical oncologist. Patients with resectable disease, including those successfully downstaged with chemotherapy or other

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therapies (intra arterial chemotherapy, SBRT, SIRT), and those amenable to resection via PVE, LVD, staged resection, or ALPPS, should be offered resection.

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1.3 Early Experience of Liver Transplantation for CLM

The early experience of LT for CLM was not encouraging. The largest reported multi-centre series, from the European Transplant Registry, reported outcome on 55 patients transplanted for non-resectable CLM between 1977 and 1995. The 5-years overall survival (OS) was only 18%. However, 44% of deaths were unrelated to tumour recurrence and the poor results, at least in part, reflect poorer outcomes overall in the early era of LT.[16] Nevertheless, these results and similar experience published by a few other single centres discouraged the allocation of scarce donor organs for this indication. Until 2020, CLM remained a contra-indication to LT in most transplant units around the world.

1.4 Recent Experience of Liver Transplantation for CLM

The best documented recent experience is from Norway, where there is a unique situation of excess supply over demand of donor livers and short waiting time after listing. This enabled the group from Oslo to prospectively examine the role of LT for CLM. In their initial study (Secondary Cancer; SECA I) 25 patients with non-resectable CLM were enrolled from 2006 to 2011, of whom 21 were transplanted.[17] The cohort was heterogeneous with respect to primary tumour stage, disease-free interval, tumour burden in the liver and chemo-responsiveness. Of note three quarters of the cohort progressed on chemotherapy prior to listing. An overall 5-year survival of 60% was obtained for all patients and 85% in a subset of 'low risk' patients (defined *post-hoc* as Oslo Clinical Risk Score 0-2). The high risk factors contributing to the Oslo score include; disease free interval < 24 months, CEA > 80μg/L, largest tumour >5.5cm and disease progression on chemotherapy.[18]

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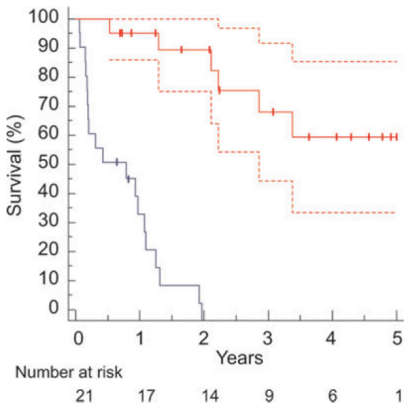
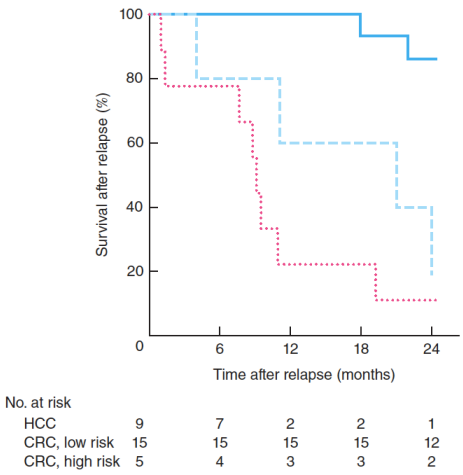
Figure 1. SECA I study (OS = solid red line, DFS = solid grey line) [17]



Although OS at 5 years was reasonable in the SECA I study, nearly all patients experienced disease recurrence, mostly within 2 years of transplant. The discordance between OS and disease-free survival (DFS) has been examined in detail. Most of the recurrences (75%) occurred in the lungs; some were able to be resected while others showed indolent growth, with or without further chemotherapy. Hence the high rate of recurrence had a limited impact of OS, at least to 5 years post-transplant. This is in stark contrast to the much shorter survival seen after post-transplant recurrence of HCC (figure 2). [18]

Figure 2. Survival after recurrence (Solid blue line = low risk CRC, broken blue line = high risk CRC, red line = HCC) from [18]



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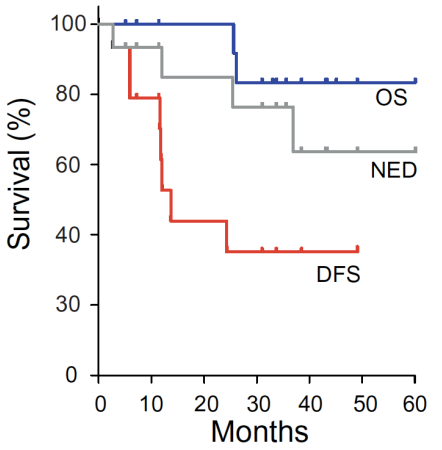
Informed by SECA I, the Oslo group went on to the SECA II study, using more restrictive entry criteria including; a minimum of 12 months from primary resection to listing, stable or chemo-responsive disease (defined as >10% response by mRECIST), some limits on tumour burden, and CEA <80ng/mL.[19] Fifteen patients were transplanted under the SECA II protocol with further improvement in outcome. Overall 5-year survival was 85% and although 5-year DFS was only 35%, many of the recurrences (predominantly lung) were resected and nearly two thirds of patients had no evidence of disease at 5 years follow up (figure 3).

Figure 3. SECA II study from [19]



Months	0	6	12	18	24	30	36	42	48	54	60
OS	15	14	12	12	12	10	6	5	2	1	2
DFS	15	11	6	5	5	4	2	1	1	0	0
NED	15	13	11	9	9	9	5	4	2	1	1

In SECA II, the factors associated with better outcome included Fong Clinical Risk Score 0-2, Oslo Clinical Risk Score 0-2, and metabolically active tumour volume (MTV) on PET scan <70cm^2 measured within 90 days of transplant. Factors associated with poor outcome included elevated CEA and right sided primary tumour, consistent with observations in the non-transplant setting.[20] The subset of patients with good prognostic factors had median post-transplant survival of 101 months, which compares favourably with outcomes after liver transplantation for other well established indications.

A systemic review and pooled analysis of the published literature has also demonstrated improved results of LT for CLM related in the more recent era (figure 4).[21] Nevertheless the data on outcome beyond 5 years is limited, especially for the most recent era. A more recent systematic review (last date of literature search December 2021) drew similar conclusions.[22]

Figure 4. Survival after LT for CLM (all patients and after 2005) from [21]

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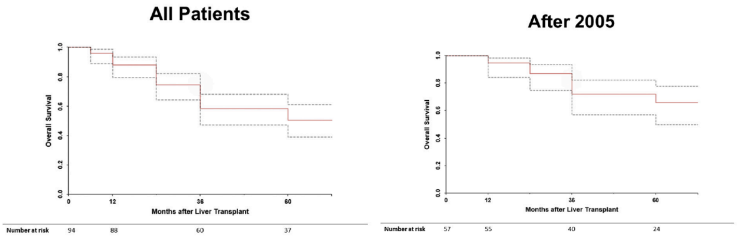

The first randomised controlled study comparing LT vs palliative treatment has been conducted in France by Adam et al (TransMet) [23] with the results presented at the American Society of Clinical Oncology in 2024. This trial included non-resectable liver only patients and compared LT+ chemotherapy to chemotherapy alone, 5y OS being the main endpoint. Of note, right-sided primary tumors and RAS mutated tumours were not excluded, although only present in small proportions (15% and 23%, respectively). All patients in the LT group had synchronous liver metastases. There were 94 patients randomised; 47 in each group. Patients randomized to the LT arm were prioritised on the deceased-donor waiting-list to receive a graft within 2 months. The protocol included post-LT chemotherapy. On intention-to-treat analysis, the 5y OS was 57% in the LT group vs 13% with chemotherapy alone (p=0.0003). On per protocol analysis, 5y OS were 73% in the LT group vs 9%in with chemotherapy alone (p<0.0001). In those patients who received a LT, 72% experienced recurrence, of whom 46% underwent resection or ablation. At a median follow-up of 50 months, 15/36 transplanted patients (46%) had no evidence of active disease.

In summary, this recent experience appears to justify cautious optimism for the role of LT in well selected patients with non-resectable CLM, but results are markedly worse in patients with multiple adverse prognostic factors. The outcomes for well selected patients reported from Norway and from the TransMet trial certainly exceed the minimal listing threshold of 50% 5-year survival expectation, as recommended by the TSANZ guidelines [24], and well selected patients had similar 5-year survival to patients transplanted within HCC criteria used in Australia and New Zealand [25]. Relatively high rates of post-transplant recurrence are seen but do not seem to impact greatly on 5-year survival, and restrictive selection criteria appear to result in an acceptable proportion of patients who are either recurrence-free at 5 years or rendered disease-free by resection of lung metastases.[19] [23] The only 10-year data in the modern era was reported recently from Norway [26]. They report 50% actual 10-year survival in patients with no more than 1 adverse prognostic factor (Oslo score 0-1), 33% actual 10-year survival in patients with 2 adverse factors (Oslo score 2), and zero 10-year survival in patients with more than 2 adverse factors (Oslo 3-4).

Despite some unanswered questions there is strong international interest in LT for CLM, culminating in a consensus guideline published by the International Hepato-Pancreato-Biliary Association (IHPBA) in 2021, before the results of the TransMet trial were available [27]. The aim of the guideline was to provide a framework by which LT for non-resectable CLM may be safely instituted. The guideline covers the key aspects of patient selection, evaluation of biological behaviour, graft selection and allocation, and recipient management [27]. The NZLTU protocol draws heavily on this consensus document and has been updated with the results of the TransMet trial. Sydney and Melbourne have developed a similar, though not identical, protocol with the potential to combine data for reporting, and other Australian transplant units are actively involved in discussion via the Transplant Oncology Sub-committee of the Liver and Intestinal Transplant Advisory Committee (LITAC) of the Transplant Society of Australia and New Zealand (TSANZ). The UK has recently developed and published a national protocol [28]. As of early 2024 there were 22 clinical trial protocols registered on Clinicaltrials.gov so more evidence will accrue in coming years. Included amongst

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these registered studies are 4 randomized controlled trials comparing transplantation with best oncological care for non-resectable CLM (EXCALIBUR Study Norway NCT 04898504, SECA III Study Norway NCT No. 03494946, SOULMATE Study Sweden NCT No. 04161092, COLT Italian study NCT03803436).

1.5 Donor Organ Supply and Demand

The scarcity of donor organs constrains the availability of LT and is a chief consideration when new indications for LT are proposed. The success of direct-acting antiviral therapy has resulted in a decline in demand for LT for decompensated hepatitis C, previously the leading indication for LT. New Zealand has also experienced an increase in organ donation over recent years resulting in a downward trend in waiting times. Donor organ utilisation is also likely to increase with the recent introduction of ex-situ machine perfusion, which will increase the proportion of extended criteria donor organs that are accepted for transplant. Finally, NZLTU has an established live donor liver transplant (LDLT) programme, although to date the majority of LDLTs have been done in children.

HCC is now the leading indication for transplant and makes up one third of adult liver transplants in New Zealand. In 2020 the Metroticket 2.0 criteria for HCC were introduced and the threshold for listing adjusted downwards in 2021 to 5-year predicted HCC-specific survival of 75%. This equates to threshold survival expectation 65-70% at 5 years, which is below the 5-year overall survival of 85% reported in SECA II. It is therefore increasingly difficult to justify denying well selected CRC patients access to transplant (see Ethical Considerations below).

On the demand side it is difficult to know precisely how many patients will come forward for transplant under the restrictive criteria of the current protocol, but it is possible to make an estimate based on experience elsewhere. The French TransMet Study [23] was a national multicenter protocol with similarly restrictive eligibility criteria. During the recruiting period non-resectable CLM made up less than 1% of all liver transplants in France (Rene Adam, ILTS Congress 2022). Norway has a population of 5.4 million, similar to New Zealand, with a similarly high incidence of CRC. The SECA I and SECA II studies recruited at a rate of 4-5 patients per annum. The NZLTU eligibility criteria are more restrictive than the SECA protocols so it seems reasonable to estimate an annual case load of 2-3 patients per annum coming to transplant. To place this in context, machine perfusion and the future normothermic regional perfusion program for donors after circulatory arrest is likely to add an addition 5-10 livers per annum to the donor pool.

1.6 Potential Donor Organ Sources

1.6.1 Deceased donor organs

Unlike most other patients awaiting liver transplantation, patients with CLM do not have underlying liver disease or portal hypertension. They would therefore be suitable to receive any deceased donor graft type, including whole liver from a brain-dead donor (DBD), split liver grafts (right or left), liver from a donor after circulatory death (DCD), and liver from an extended criteria donor following resuscitation with ex-situ machine perfusion. The absence of underlying liver failure and portal hypertension makes patients with CLM ideal recipients for these more marginal grafts.

1.5.2 Adult-to-adult LDLT

LDLT using right lobe graft would be possible for patients who have a suitable right lobe donor and fulfil the criteria laid out in the NZLTU LDLT protocol. A major advantage of LDLT is that it enables control of the timing of transplant, thereby averting the risk of disease progression while waiting.

1.5.3 RAPID Procedure

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The RAPID procedure (resection and partial segment II/III LT with delayed total hepatectomy) is a hybrid adaptation of two surgical techniques; ALPPS and auxiliary partial orthotopic liver transplantation (APOLT). The RAPID technique was first reported in 2015 as a novel technique to transplant a patient with CLM [29]. Essentially, it enables a very small graft, comprising segment II/III only, to be used to transplant an adult recipient in a two-stage procedure. Stage I involves recipient left hepatectomy, APOLT of the segment II/III graft, and ligation of the right portal vein (PVL). The PVL diverts portal flow to the graft and induces rapid graft hypertrophy. When hypertrophy is sufficient, usually after several weeks, a second stage procedure is performed to complete the native hepatectomy. The segment II/III graft can be sourced either from a living donor or split liver graft from a deceased donor [30,31]. The advantages of RAPID using a live donor graft include; optimal timing of the transplant, less risk for the donor than right lobe donation, and increased likelihood of compatible donor anatomy (compared with right lobe). In the DD split liver transplantation setting, the RAPID technique can provide a suitable graft for a CLM recipient without reducing the donor pool (only applicable if there is no paediatric recipient waiting).

Whilst the RAPID procedure is a promising technical advance, not all CLM recipients will be suitable for this option. For example, previous left hepatectomy, or inability to transect the liver without encroaching the tumour would make it impractical. Also, it is not yet known whether the two-stage procedure has an adverse impact on tumour biology and recurrence risk. There are several clinical trials underway to evaluate the RAPID procedure in setting of LT for CLM (Clinicaltrials.gov).

2. Ethical Considerations

LT is restricted by the availability of donor organs and graft allocation needs to consider both graft utility and equity of access, ie obtaining the most benefit for the most people while maintaining fairness.

The fundamental benchmarks of graft utility are graft and patient survival. Based on recent data LT for highly selected patients with non-resectable CLM meets the required threshold, at least to 5 years post-transplant, and its role in treatment is supported by recently published international guidelines [27]. It therefore seems unreasonable to exclude carefully selected patients from the benefits of LT. However, evidence is still accruing, in particular there is limited data regarding longer term outcomes (10 years or more) and selection criteria will need to be refined by new evidence. It will be important to track significant new developments and revise eligibility criteria and protocol settings accordingly.

In terms of equity, once activated on the waiting list, patients with CLM will be able to receive maintenance chemotherapy (see below). need to undergo transplantation before disease progression occurs, so timely access to a donor organ is necessary to achieve a good outcome. In the TransMet Study CLM patients were given priority on the waiting list for this reason, and in Norway waiting times were already short. In the UK, the aim is to provide a graft within 3 months of listing [28]. One way to receive a timely graft is with LDLT (right lobe or RAPID) but not everyone will have a suitable living donor. CLM patients are also well suited to receive extended criteria grafts, which may be less suitable for other recipients. Nevertheless, prioritisation will be needed to provide a realistic chance of receiving a deceased donor liver before disease progression occurs.

3. Eligibility Criteria

3.1 General Criteria

- Age $\leq$ 65 years
- BMI $\leq$ 35 *(the BMI cut-off may be reviewed later to ensure equity in access)*
- Meets medical and psychosocial criteria for LT

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3.2 Oncological Criteria

The oncological criteria will aim to select low risk patients with the goal of achieving 5-year patient survival similar to hepatocellular carcinoma (NZLTU currently uses an eligibility threshold of 70% 5-year HCC specific survival).[24] The criteria below are based on the recently published consensus guidelines of the IHPBA [27] as well as input from local specialists in medical oncology, hepatology, transplant and HPB surgery.

3.2.1. Primary Tumour

- Primary tumour completely resected with clear margins (R0), along with draining lymph nodes. (Note: there should be a minimum of 12 lymph nodes in the primary resection specimen for adequate staging, and circumferential resection margin ≥ 1mm for rectal cancer). Patients with rectal cancers, who have had a complete clinical response to chemotherapy/radiotherapy still require bowel resection prior to liver transplant.
- TNM stage according to AJCC 8th Edition. TNM N3 (≥ 7 LN involved) may be considered with caution [23,27].
- Undifferentiated or signet ring pathology excluded [27]
- Right sided primary tumour excluded.[20]

3.2.2. Liver Metastases

- Interval from diagnosis of CLM to LT at least 1 year.
- Liver metastases deemed non-resectable by an HPB MDM and confirmed by the transplant assessment group (assessment includes multi-phase liver CT and contrast MRI within 6 weeks of MDM).
- No present or past extra-hepatic metastases (staging should include baseline PET-CT if possible). If baseline PET-CT was not done, this should be carried out at the earliest opportunity off chemotherapy (4-6 weeks off chemotherapy).
- Criteria not based on size and number *per se*, but caution should be exercised if there is bulky disease (defined as metabolic tumour volume > 70cm^3 within 90 days of transplant).[20]
- CEA > 80μg/L relative contraindication [26], but is tolerated if there is a good response with chemotherapy (see below)
- Non-resectable recurrence confined to the liver after previous liver resection is not a contraindication to LT.

3.2.3. Molecular Criteria

- Presence of BRAF V600E mutation is an exclusion.
- MMR deficient tumours should be considered for immunotherapy with checkpoint inhibitors rather than liver transplant. Access to these drugs to be discussed with medical oncologist.
- RAS mutation is a negative prognostic factor but not an absolute contraindication, may consider in the absence of other unfavourable factors.

3.3.4. Treatment Response Criteria

- Radiological re-imaging and CEA repeated at least 3 monthly.
- Resection should be considered in patients with liver metastases that are down-staged by chemotherapy and become resectable.

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- Locoregional therapy may include selective internal radiotherapy (SIRT).
- Radiological response is assessed using CT:MRI. Patients with **non-progressive disease** will be included.
- *Duration of response to systemic therapy must be observed for at least 12 months. Patients may have time off chemotherapy during this period (for example, to manage side effects or limit toxicity or remove primary tumour).*
    - *At least 6 months of sustained response to a line of chemotherapy*
    - *Up to 3 lines of chemotherapy*
- Initial CEA > 80μg/L with an increasing trend during chemotherapy is a contraindication to LT.
- Initial CEA > 80μg/L and decreasing trend that is maintained on chemotherapy can be considered but is an unfavourable factor.
- *Synchronous CLM with asymptomatic primary*; Consider resection of the primary after approximately 6 months response to treatment. Following primary resection, continue treatment/observation until a total of 12 months duration of response has been observed.
- *Synchronous CLM with symptomatic primary*; Primary resection first followed by chemotherapy and assessment of treatment response, as specified above.

4. Patient Assessment

Figure 5 summarises the patient pathway. Patients are referred for consideration of transplant if they appear meet the inclusion criteria listed above (3.2.1 – 3.2.4).

Note, some of the criteria are time-dependent (see section 3.4) however early discussion and referral is encouraged. Referrals will be triaged by a sub-committee comprising at least one transplant surgeon, hepatologist and medical oncologist. Potential candidates will be entered onto a register and progress tracked in collaboration with referring specialists. Formal transplant assessment will be carried as soon as practicable after treatment response criteria have been met.

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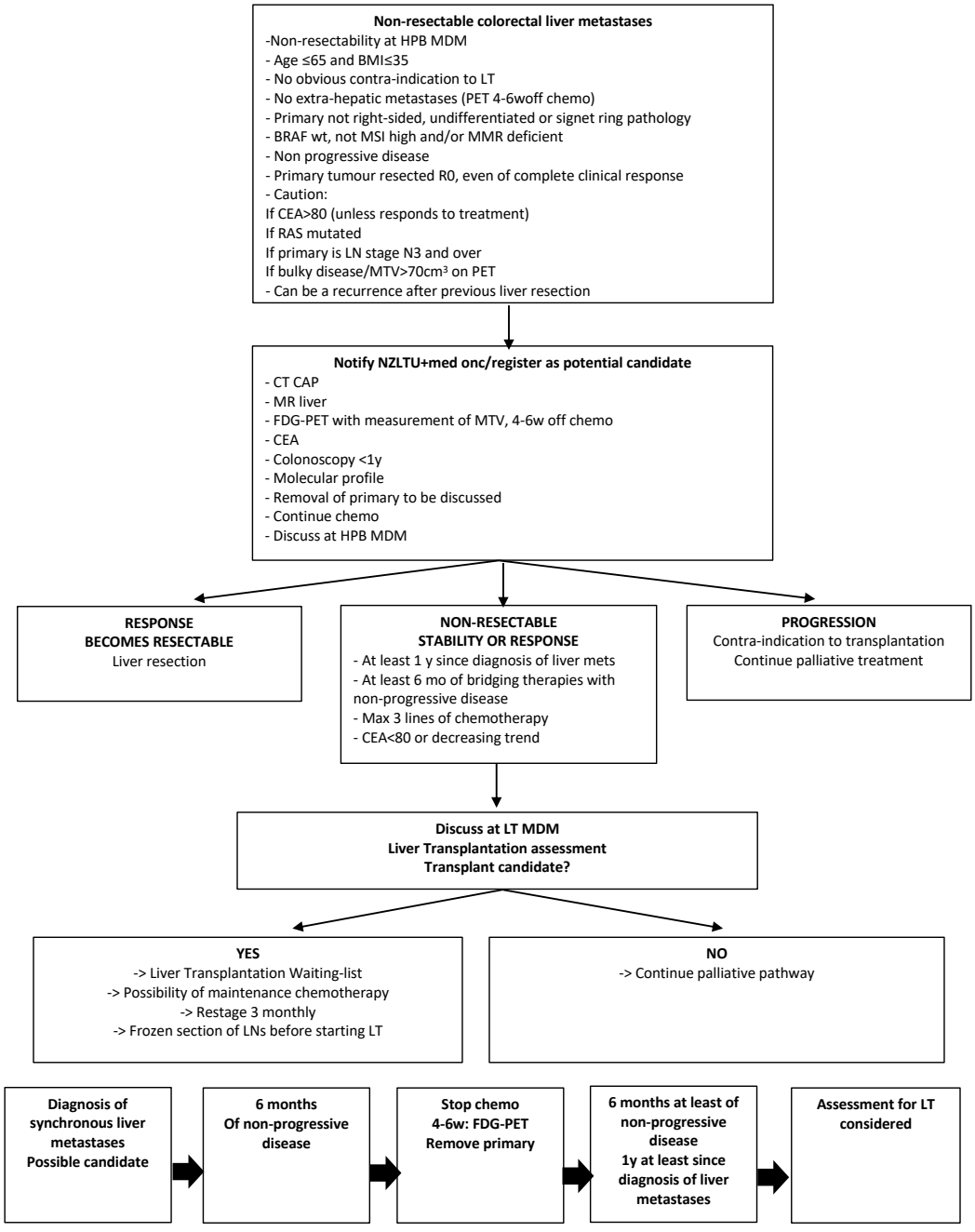
Figure 5. Patients pathway



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4.1 Oncological Assessment

The following baseline investigations are required.

- Histologically proven CRC with radiologically evident CLM
- Analysis of primary tumour or metastases, or both, for BRAF and RAS mutations, and MMR status
- Liver evaluation with multi-slice CT and contrast MRI
- CT CAP
- CT-PET scan (at baseline to exclude extrahepatic disease, and at transplant assessment to measure metabolic tumour volume, must be 4-6 weeks off chemo)
- CEA
- A complete colonoscopy should be performed within 1 year before inclusion

Re-staging investigations are undertaken 3 monthly to evaluate response to treatment and eligibility to proceed on LT pathway.

NZLTU will maintain a register of potential LT candidates and monitor their progress in consultation with the referring team. NZLTU will be available to provide advice and information at all stages, including consultation with potential LT candidates.

4.2 Transplant Assessment

- Transplant assessment will be carried out according to NZLTU protocol.
- In addition to the usual investigations, up to date imaging and tumour markers, plus PET-CT to assessment of metabolic tumour volume (PET to be done after 4-6 weeks off chemotherapy).
- Medical oncology assessment to confirm oncological criteria are met and determine treatment on waiting list.
- Surgical assessment will document suitability for the different graft options including the RAPID procedure.
- Information provided regarding living donation, however donor assessment is a separate process.

4.3 Informed Consent

Patients need to be informed regarding the limitations in the existing data, as well as the risks and benefits of transplantation. They need to understand and accept the procedural and medical risks, the risk of waiting list dropout if no suitable graft is available prior to documented progression.

5. Waiting List Management

This section refers to ongoing management after activation on the waiting list.

5.1 Chemotherapy

Once activated on the waiting list patients will receive either no further chemotherapy or maintenance chemotherapy. The maintenance chemotherapy can consist of either single agent capecitabine/infusional 5-FU or combination FOLFOX or FOLFIRI treatment. The chemotherapy can incorporate cetuximab (Nb. bevacizumab will be avoided during maintenance). Growth factor support should be considered with those demonstrating neutropenia on blood tests. This decision will be individualised in consultation with medical oncology advice, considering likely waiting time, tolerance, and risk of disease progression.

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5.2 Re-staging

Patients will have monthly CEA and 3 monthly re-staging with CT-CAP while active on the waiting. If these tests raise suspicion of disease progression the patient will be suspended until clarification is obtained.

5.3 Organ allocation

Patients will be eligible for the following graft options:

5.3.1 Living donor

- Segment II/III graft from a living donor, implanted using the RAPID technique (recipient deemed technically suitable).
- Standard LDLT using right lobe graft (liver replacement).
- NB: independent donor evaluation undertaken according to the NZLTU LDLT Protocol. Donors must meet all usual criteria.

5.3.2 Deceased donor

- Leftlobe of a split liver graft may be allocated to a patient with non-resectable CLM for implantation using the RAPID technique (recipient must be technically suitable and no paediatric recipient competing for the graft).
- Right lobe of a split liver graft may be allocated to a patient with non-resectable CLM.
- Standard or extended criteria deceased donor organs (including ECD DBD and DCD grafts undergoing ex-vivo machine perfusion).

5.3.3 Waiting list prioritisation

- Under the NZLTU prioritization system, patients with non-resectable CLM will receive Median MELD at Transplant (MMaT) exception points at the time of listing. This should provide realistic chance of access to a donor organ within 3 months of listing, without disadvantaging high MELD patients or long-waiting patients with HCC. Beyond 3 months an extra 2 MELD exception points are allocated for each additional 3 month waiting period.

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6 Liver Transplant Surgery

6.1 Exploratory laparotomy

If a live donor graft is used, recipient laparotomy may be performed prior to starting the donor surgery to assess for extra-hepatic disease, including systematic sampling of lymph nodes of the porta hepatis with frozen section examination [34].

If a deceased donor is used, a backup patient should be arranged in case extra-hepatic disease is found at laparotomy. Meanwhile, the donor organ will be maintained with ex-vivo machine perfusion.

6.2 Liver replacement

Unless the RAPID is being performed, liver replacement will be performed according to standard NZLTU Protocol. The recipient hepatectomy will include a lymphadenectomy of the hepatoduodenal ligament lymph nodes (stations 12a, 12b, 12p).

6.3 RAPID procedure

Details of the procedure may vary depending on donor and recipient anatomy and volumetry[29] [30] [33, 34] however the main steps are as follows.

6.3.1 Stage 1 Recipient Operation

- Exploratory laparotomy to exclude extra-hepatic disease. Systematic sampling of lymph nodes of the porta hepatis with frozen section examination. Mobilise liver by dividing falciform, left triangular, gastrohepatic, right triangular and coronary ligaments. Completely mobilise the liver by dividing all minor hepatic veins. (to facilitate stage II).
- Extra-Glissonian dissection of the hepatoduodenal ligament with division of LHA and full mobilisation of main PV and PV bifurcation. Divide LPV and encircle RPV ready for subsequent division.
- Use intraoperative ultrasound (IOUS) to define transection line. Avoid tumour transgression and anatomical resection preferred to reduce the risk of remnant cut surface bile leakage. Ideal transection is Cantlie's line to right of MHV with preservation of the MHV/LHV confluence as outflow tract for the graft.
- Divide LHD during transection and oversew remnant side securely.
- After removal of left liver check haemostasis and biliostasis on the remnant cut surface.
- Graft LHV anastomosed to recipient MHV/LHV confluence.
- Divide recipient RPV and recipient PV anastomosed end-to-end to graft LPV.
- Re-perfuse graft and secure cut surface haemostasis.
- Arterial reconstruction achieved either by i) recipient LHA to graft LHA anastomosis, ii) graft end LHA to recipient side CHA, iii) divide recipient CHA immediately proximal to the GDA and anastomose recipient CHA to graft LHA (this leaves the arterial supply to remnant dependent on the GDA via the pancreatico-duodenal arcade from the SMA – confirm anatomy on pre-op imaging prior to dividing CHA), or iv) saphenous interposition between CHA and graft artery.
- Assess flows in PV and HA with Doppler ultrasound and flowmeter. If PV flow >200mL/min/100gm graft weight consider modulation by proximal splenic artery ligation.
- Complete graft biliary reconstruction with Roux-en-Y hepatico-jejunostomy or duct to duct anastomosis.[36] Reconstitute falciform ligament and keep cut surfaces apart.
- Place drains and close.

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6.3.2 Initial Post-operative care

- Standard post-operative management according to NZLTU protocol.
- Doppler ultrasound on Day of transplant and thereafter as indicated clinically.
- Standard thromboembolic prophylaxis.
- CT scan with graft volumetry at 2 weeks, then weekly until graft volume adequate for stage 2 (aim for GRWR > 1.0)
- HIDA/mebrofenin scintography at 2 weeks to assess differential graft and native liver function.

6.3.3 Stage 2 Recipient Operation

- Carefully re-enter abdomen, remobilize the remnant liver and complete the hepatectomy.
- Graft trucut biopsy.

7 Post-transplant management

7.1 Immunosuppression

Initial immunosuppression is with Tacrolimus and steroids, as per NZLTU protocol. At 8-12 weeks post-transplant if there are no complications that might require further surgical intervention, and no rejection episodes, careful consideration can be done about switching from Tacrolimus to mTOR inhibitor.

7.2 Surveillance

In addition to usual post-transplant care, surveillance for tumour recurrence will be done.

- CEA 1 month post-transplant then 3 monthly.
- CT CAP 3 monthly for first year, then 6 monthly for 5 years.
- Colonoscopy as per standard follow-up after CRC.

7.3 Management of Tumour Recurrence

The management of tumour recurrence will be individualized, depending on the site and pattern of disease. The most common site of recurrence is the lungs. [18] In general, oligometastatic disease that is resectable will be treated surgically where feasible. Small volume stable metastatic disease may be observed, and progressive disease and disease treated with systemic therapy according to medical oncology advice.

If not already on mTOR inhibitor, consider switching to mTOR inhibitor at diagnosis of recurrence.

7.4 Prospective Audit

As an emerging therapy it is important to closely audit all aspects of the experience with LT for non-resectable CLM. This will be done on an intent-to-treat basis to include all patients who are referred and enter the protocol. De-identified data will be uploaded to the ANZ Liver Transplant Registry (in common with all transplants undertaken by NZLTU), and contribute to an international /TSANZ registry of LT for CLM (to be confirmed when registry established).

Data categories will include:

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- Baseline clinico-pathological characteristics
- Co-morbidities
- Pre-transplant oncological treatments and response data
- Waiting list outcome (transplant or delisting, with reason for delisting)
- Transplant details including graft type, peri-operative course, and post-operative complications
- Post-transplant tumour pathology
- Cancer-related outcome; recurrence, treatment of recurrence, survival

The data will be formally examined on an annual basis along with emerging evidence from the international literature. Protocol updates will be made according to evolving evidence and international guidelines.

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