Transplant International

Transplant International ISSN 0934-0874

REVIEW

Liver transplantation for colorectal liver metastases: revisiting the concept

Aksel Foss,[1,2] Rene Adam[3,4] and Svein Dueland[5]

1 Department of Transplantation, Oslo University Hospital – Rikshospitalet, Oslo, Norway
2 Institute for Surgical Research, Oslo University Hospital – Rikshospitalet, Oslo, Norway
3 AP-HP Hôpital Paul Brousse, Centre Hépato-Biliaire, Villejuif, France
4 European Liver Transplant Registry (ELTR), Paris, France
5 Department of Oncology, Oslo University Hospital – Radiumhospitalet, Oslo, Norway

Keywords
colorectal cancer, liver transplantation.

Correspondence
Aksel Foss, MD, PhD, Division of Surgery, Section for Transplantation, Oslo University Hospital – Rikshospitalet, N-0027 Oslo, Norway. Tel.: +4790833529;
e-mail: aksel.foss@rikshospitalet.no
(ClinicalTrials.gov number: NCT00294827)

Received: 9 February 2010
Revision requested: 17 February 2010
Accepted: 7 April 2010
Published online: 30 April 2010

doi:10.1111/j.1432-2277.2010.01097.x

Summary

Liver transplantation (Lt) for colorectal cancer (CRC) liver metastases is no more considered due to the poor outcome observed up to the 1990s. According to the European Liver Transplant Registry (ELTR), 1- and 5-year patient survival following Lt for CRC liver metastases performed prior to 1995 was 62% and 18%, respectively. However, 44% of graft loss or patient deaths were not related to tumor recurrence. Over the last 20 years there has been dramatic progress in patient survival after Lt, thus it could be anticipated that survival after Lt for CRC secondaries today would exceed from far, the outcome of the past experience. By utilizing new imaging techniques for proper patient selection, modern chemotherapy and aggressive multimodal treatment against metastases, long term survivors and even cure could be expected. Preliminary data from a pilot study show an overall survival rate of 94% after a median follow up of 25 months. While long term survival after the first Lt is 80% all indications confounded, 5-year survival after repeat Lt is no more than 50% to 55%. If patients transplanted for CRC secondaries can reach the latter survival rate, it could be difficult to discriminate them in the liver allocation system and live donation could be an option.

Introduction

Liver transplantation (Lt) for malignant diseases is feasible and induces excellent outcome in selected patients. Lt for malignant tumors comprises 14% of all Lt's in the European Liver Transplant Registry (ELTR) [1]. It is currently a treatment option for patients with primary carcinomas of the liver and liver metastases from endocrine tumors. Types of primary liver carcinomas eligible for transplantation include hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), hepatoblastoma, and hemangioendothelioma [2–4]. The most common secondary carcinomas that are considered for Lt include metastases from carcinoid tumors, neuroendocrine tumors and gastrinomas [2].

Lt for HCC within Milan- and the Up to Seven criteria show excellent short- and long term patient survival [4,5]. In recent studies of Lt for HCC even better results can be obtained in patients receiving immunosuppression containing the antiproliferative agent sirolimus [6,7]. In patients transplanted for cholangiocarcinoma using a multimodal approach with neoadjuvant radiation and chemotherapy a 5-year overall survival above 80% can be achieved in selected patients, compared to a corresponding 21% 5-year survival after liver resection [8].

Prior to 1995 several Lts for colorectal liver metastases were performed. However, the outcome of these transplantations were considered as poor and consequently, Lt for tumors of colorectal origin was abandoned. The aim of this paper is to review the past experience of Lt for

© 2010 The Authors
Journal compilation © 2010 European Society for Organ Transplantation

colorectal liver metastases and to address some issues that could possibly improve the results. Some preliminary data from an ongoing pilot study on Lt for colorectal secondaries are also included.

Colorectal cancer

Colorectal carcinoma (CRC) is one of the most frequent cancers in western societies. The incidence is 700 per million people (pmp). About half of the patients develop metastases from the primary tumor and liver is the primary metastatic site. Median survival for patients with untreated metastatic CRC is roughly 6 months [9]. The median survival for patients treated with 5-FU-, irinotecan and oxaliplatin containing regimens is about 20 months [10]. Antibodies against VEGF (bevacizumab) combined with 5-FU/irinotecan have shown increased response rate, prolonged time to progression and improved survival [11]. Cetuximab and panitumumab (EGFR antibody) provides increased response rates in patients with K-ras wild type tumors [12,13]. However, only about 10% of patients with metastatic CRC survive beyond 5 years [14]. Approximately one out of 10 patients with metastatic CRC exhibits metastases solely to the liver [15]. At present, the only curative treatment in patients with metastatic CRC is surgery of metastases, however, only a small subgroup (10–15%) of patients is eligible for this treatment. The majority of patients who undergo liver resection for metastases will experience relapse of the disease either intrahepatic and/or extrahepatic. Still, 5-year survival rates following radical liver resection range between 25% and 55% compared with 5–10% for non-operated patients [16].

Past experience of liver transplantation for CRC liver metastases

Prior to 1983, when Lt was considered as an experimental procedure, liver metastases as indication for Lt were not rare, but the results were disappointing [17–20]. In the European Liver Transplant Registry (ELTR) 58 secondary liver tumors of CRC origin have been registered as the primary indication for Lt by 2007 [1]. The vast majority of these procedures were performed before 1995 ($n = 50$) and ELTR has reported a 1- and 5-year survival of 62% and 18%, respectively [2]. Of the 50 reported patients nine survived beyond 5 years and two had no tumor recurrence at 9 and 21 years post transplantation. In 44% of cases, graft loss was not related to tumor recurrence.

The largest historical series on Lt in CRC liver metastases originates from Vienna, which include 25 patients transplanted from 1983 to 1994 [2,21–23]. Eleven of these patients were histologically lymph node negative at the time when the primary tumor was excised. Nine of these were eligible for examination of micrometastatic disease using mutant allele-specific amplification (MASA) of p53 or K-ras mutations. MASA revealed six of nine node negative patients to be positive for micrometastases by this technique. Three patients were negative by both histological and micrometastatic examinations and these patients showed a significantly longer overall survival than others; 4, 5, and 20 years, respectively ($P = 0.011$) [23].

The past experiences of Lt for CRC metastases induced long-term survivors and even cure in some patients. Such a result is actually not surprising since R0 liver resection for CRC liver metastases can induce over 50% 5-year survival. Lt for non-resectable liver only metastases is per definition a R0 surgical procedure since all macroscopic tumor tissue is excised. The past experiences of Lt for CRC liver metastases were, from an oncological perspective quite acceptable. However, from the Lt perspective (in light of organ shortage) the outcome was considered poor and inferior compared to other indications for Lt. Consequently, Lt for CRC liver metastases stopped and is currently regarded as an absolute contraindication for Lt.

Rationale for revisiting the concept

Survival following liver

When reviewing and analyzing the past data on Lt for CRC liver metastases (1983–1994), we should keep in mind that the overall survival following Lt has dramatically improved over the last 20 years. In the time period 1983–1994 ELTR showed a 1- and 5-years overall survival of 65% and 56%, respectively. In the Norwegian Liver Transplant Registry and Nordic Liver Transplant Registry (NLTR) 1- and 5-years overall survival was 64%/71% and 53%/61%, respectively [24]. These data are in concordance with survival data from the UNOS Liver Transplant Registry at that time [25]. At present, 1- and 5-years survival in ELTR are 85% and 74% years, respectively and in Norway and the NLTR it is 92%/89% and 81%/78%. Included in these numbers are patients transplanted for acute fulminant hepatic failure, advanced liver cirrhosis and patients with malignant tumors. Potential Lt candidates with CRC liver metastases are technically easier to operate than cirrhotic patients due to absence of portal hypertension and other complications of cirrhosis. Thus, these patients are to bee considered low-risk with respect to the surgical procedure and the perioperative mortality should be minimal although the procedure is extensive.

Consequently, merely based on the better expertise of transplant surgeons and improved survival rates in Lt over the last 20 years, the outcome for patients transplanted for CRC metastases could be improved significantly, compared to the past experiences.

© 2010 The Authors

Patient selection

Impressive progress has been made in tumor diagnosis and management. Conventional imaging has been replaced or added by several new techniques. Spiral- and multidetector CT, MRI and gadolinium-enhanced MRI, PET/CT scan and contrast enhanced US (CEUS) are some of the new available tools for detection of intra- and extrahepatic metastases and thus improved patient selection, avoiding candidates with macroscopic spread of cancer. Two or more non-invasive imaging modalities are often combined to establish a definite diagnosis, e.g. US and CT angiography are regularly accepted as definite diagnosis of HCC in the liver [26]. Modern imaging can accurately detect and differentiate very small lesions and lymph nodes. Guided cytology diagnosis has improved radically by the use of modern US technique and minimal invasive surgery can very precisely map an area for metastases and extension of tumors. The wide use of these modalities has certainly increased the rate of preoperative identification of metastases, often missed earlier. This has resulted in a better patient selection and consequently in a better survival after liver surgery. Therefore, it is very likely that the same benefit could be obtained for potential transplant candidates. Excluding patients who in the past had unknown extrahepatic disease and selecting those who have only localized liver disease, would without doubts positively impact the post-transplant survival.

Several factors such as primary nodal status, tumor load, increased CEA and CA 19-9, liver only metastases and chemotherapy response have been identified as independent parameters influencing the prognosis of metastatic CRC. Prognostic factors determined pre- and post liver resection have been systematized in nomograms [27]. These nomograms could certainly contribute to refine the selection of good transplant candidates. Studies have shown that proliferation markers such as p53 expression, tritiated thymidine uptake, thymidylate synthase, Ki-67, K-ras, and human telomerase reverse transcriptase may be useful predictors of outcome after resection of hepatic CRC metastases [28,29]. Recently it has been shown that the type, density and location of immune cells infiltrating the tumor are a prognostic factors in metastatic CRC, and that these prognostic factors might be superior to the TNM staging system [30,31]. These prognostic factors may probably play an important role in the selection process by early identification and exclusion of patients with poor prognosis from the outset.

The efficacy of aggressive surgical treatment of CRC metastases

Due to the inherent complexity and disparity of cancer biology, cure from cancer is often difficult to achieve. Therefore, efforts are made to restrain the cancer, improve palliation and to attain extra quality-adjusted life-years by aggressive treatment of metastases [32]. It has been shown that surgical treatment of extrahepatic metastases can prolong survival [33–36]. Low morbidity and mortality rates after surgical interventions for metastases, contrasting with modest effect of other therapeutic options, justify aggressive surgical management. Over the last 20 years radiofrequency ablation (RFA) and different kinds of direct tumor embolization techniques (TACE, PEI) have been introduced. In CRC patients lung metastases treated with resection and/or radiofrequency ablation have shown a 5-year overall survival of 34–58% [37,38]. Single deposits, disease free interval above 36 months and normal prethoracotomy serum CEA have been identified as significant independent prognostic factors [39].

Even when initially unresectable, liver metastases could be downsized by effective chemotherapy and be switched to rescue surgery with a hope of long term survival and even of cure [40,41]. Repeat curative intent surgery (CIS) for recurrent CRC liver metastasis can be performed with low morbidity and mortality. Patients with no extrahepatic disease are best candidates for repeat CIS. In these patients, repeat CIS can offer a chance of long-term survival [42]. Thus, it seems that aggressive surgical and other interventional treatments of CRC metastases are able to induce significant life extension in these patients. Similar line of action could also be applied in transplanted patients.

Immunosuppression and chemotherapy

Lt requires lifelong immunosuppression to prevent allograft rejection. Traditional immunosuppressive protocols, containing drugs without antiproliferative properties targeting micrometastases post-transplant might accelerate the malignant disease. The immunosuppressive drug, rapamycin has shown a significant anti angiogenic effect in addition to a direct inhibitory effect on tumor growth and proliferation by blocking the intracellular pathway complex mTOR [43]. mTOR inhibitors have shown clinical effect and objective radiological responses and stabilization of disease in different types of cancer, such as advanced breast and renal cancer that has previously progressed on other treatments [44]. Inhibitor of mTOR (temsirolimus) has shown increased survival in high-risk metastatic renal cell carcinoma patients compared to previous interferon standard treatment [45]. Accordingly, mTOR inhibitors are effective anti-cancer drugs in addition to their immunosuppressive effects. This supports the use of rapamycin for patients with cancer after transplantation. Rapamycin was not in regular use as

© 2010 The Authors

immunosuppressive drug at the time of the early experiences of Lt for CRC liver metastases and could potentially benefit these patients.

Interestingly, most chemotherapeutic agents are cytotoxic in action and probably inhibit T-cell proliferation and can thus act as anti-rejectors in transplanted patients. In the early days of transplantation the anti-cancer drugs cyclophosphamide and azathioprine were used as immunosuppressive agents following allotransplantation [46]. Notably, it has been shown that regulatory T cells (T regs) appear more frequent in peripheral blood lymphocytes of cancer patients than healthy controls [47]. Coincident, it is suspected that elevated levels of T-regs is a prerequisite for allograft tolerance [48]. The role of regulatory T-cells in making tumor escape the immune system by inducing a tumor-specific local immune tolerance is under investigation with the aim of identifying downstream cell-signaling pathways involved in T-reg and T-effector cell function. Src-, PI3-, MEK and p38-kinase inhibitors are now under development for treatment of different malignancies and could probably prevent rejection and also reduce risk of recurrent disease in the patients transplanted for CRC liver metastases.

Further knowledge in this field would also have implications for patients with de novo cancer following allotransplantation.

Patient survival in a pilot study of Lt for CRC liver metastases (preliminary data)

Initiating a study on Lt for a disease which is considered as an absolute contraindication for transplantation raise a large number of questions regarding organ allocation, efficacy, cost-effectiveness and more. Norway has one transplantation center (Oslo University Hospital-Rikshospitalet) serving a population of 4.8 mill. people. The annual Lt rate is 17 pmp and the available number of deceased donor livers is 25 pmp (splits included). The surplus of donor organs provides an opportunity to explore liver transplantation for extended criteria indications such as treatment of malignant liver diseases.

In 2006 we acquired ethical approval (S-05409 Regional Ethics Committee, Helse Sor-Ost, Norway) for a clinical pilot study to investigate Lt for treatment in selected CRC patients with non-resectable liver metastases, using the mTOR inhibitor Rapamune® as standard immunosuppression from postoperative day 1 (SECA-study). The primary aim of the study was, in light of improved outcome of Lt and mTOR inhibitor as immunosuppression, to re-evaluate the potential of survival in CRC patients with liver only metastases and furthermore, determine quality of life (QoL) following the procedure. Major eligibility criteria in the study were: primary R0 colorectal surgery; one or more

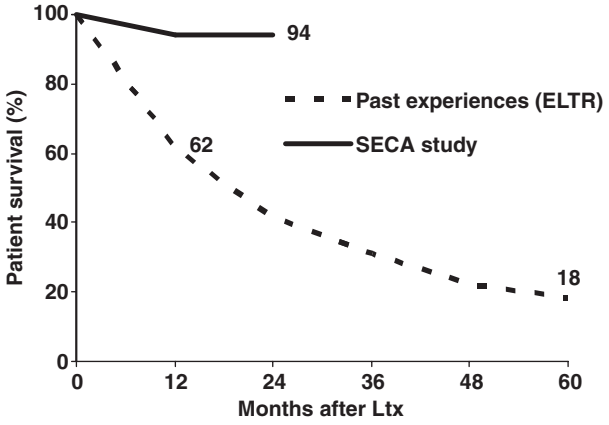

Figure 1 Lt for CRC liver metastases performed before 1995 show a 1- and 5-year survival of 62% and 18%, respectively (n = 50). In the SECA study patient survival is 94% with a median follow-up of 25 months (n = 16).

chemotherapies for metastatic disease; non-rescerctable liver metatstases; no extrahepatic disease and good general condition as determined by a ECOG 0–1 score. Since November 2006, 16 patients have been transplanted in the study. Two-thirds had received two or three lines of chemotherapy prior to transplantation. The median follow up is 25 months (range, 3–38) and patient survival of January 2009 is 94% (Fig. 1). However, the recurrence rate is still high. Ten of the 16 patients (63%) have been treated for recurrent disease and at present, 6 of 15 patients (40%) have no evidence of disease. Post-transplant QOL is excellent measured by EORTC-C30 questionnaires [49]. Identification of variables predicting outcome are not yet available after preliminary analysis of this small patient cohort.

From an oncology perspective the initial data from the SECA-study could be interpreted as promising, however, it is obvious that refinement is needed, especially concerning patient selection.

Health care professionals have had concerns about costs of the study. In a recent meta-analysis mean cost of liver transplantation in OECD countries has been estimated to US$103.548 [50]. Estimated cost per life year gained by adding bevacizumab to standard first line treatment with irinotecan or oxaliplatin based chemotherapy has been calculated to ∼US$ 121.000 [51]. Estimated costs per life year gained for treatment with cetuximab+irinotecan has shown to be ∼US$ 124.000 [52].

Perspective

Preliminary survival data of the SECA study indicate that Lt is feasible in selected patients with unresectable liver

© 2010 The Authors

metastases from CRC. The procedure is safe, the perioperative mortality is nil and post-transplant QOL is excellent. As expected, overall patient survival is superior to the previous experiences on Lt for CRC liver metastases registered in ELTR (Fig. 1). However, the recurrence rate is still high requiring better patient selection and improved perioperative treatment.

Due to organ shortage there has been an international consensus that patient survival after Lt for malignancy should be at the same level as for non-malignant diseases [53]. In this perspective, it is of interest to review outcomes of repeat Lt for ordinary indications, since patients who need retransplantation are universally accepted according to MELD score on equal basis as first transplant recipients, both in European and American organ allocation systems. In the NLTR repeat Lt shows a 5-year survival of 55% [54]. In ELTR it is 56% and in the UNOS database it is currently 54.7% [55,56]. For specific diagnosis such as repeat Lt for HCV long term survival of less than 50% has been shown [57,58]. Consequently, if patients with CRC liver only metastases by selection can exhibit a 5-year survival rate of 50%, it would be difficult to discriminate this patient group in the liver allocation systems.

For ordinary indications 1- and -5 year survival after the first Lt is reaching 90% and 80%, respectively and the majority of patients can return to normal life activities following the procedure. In a situation where the limiting factor for treatment is organ shortage it is an understandable restrain in revisiting an indication for Lt which probably not will reach the success as seen for ordinary indications. Also, there is restrain due to the allegory that immunosuppressive drugs result in explosive cancer growth as well as concerns about costs. Therefore, in the pursuit to revisit the concept of Lt for colorectal liver only metastases, several major end points must be fulfilled. Lt in these patients must be cost-effective, patient survival and QoL must be better compared to chemotherapy and secondly 5 year survival should reach 50%.

To try to meet these obligations, we are currently preparing for a randomized controlled trial (RCT), Lt versus best available chemotherapy (SECA2 study). Based on data from the SECA-study and the large number of background data on survival following chemotherapy the assumption is that 3-year survival of the Lt group and chemotherapy group is 70% and 30%, respectively.

Evidently, to establish new indications for Lt in the presence of organ shortage will add to the existing donor problem. A potential donor source that is not fully utilized is donation after cardiac death (DCD). In Norway, a controlled DCD program is ready to be launched. After the early series of live liver donation, morbidity and mortality for the donor have persistently declined and the complication rate is low. For example is donor complication rate following left lateral liver resection reported to be at the level of live kidney donation which is routinely performed [59]. The liver-body mass ratio needed for successful Lt has also decreased and several reports document excellent outcomes by providing the recipient with a partial liver graft of 0.8% of body weight (GRWR) and even 0.6% [60]. Patients with liver malignancy who are candidates for Lt have normal liver function and presumably less demand for liver tissue, however there are concerns about liver regeneration and malignancy.

Dramatic progress in survival after Lt over the last 20 years alone, implicate that survival after Lt for CRC secondaries could be radically improved compared to the past experiences and probably induce survival far superior than modern chemotherapy. By utilizing new tools for preoperative patient selection, modern operative techniques for Lt and aggressive attitude against metastases, long term survivors and even cure could be expected.

Funding

Part of this work is funded by South-Eastern Norway Regional Health Authority

Acknowledgement

The authors thank the European Liver and Intestine Transplant Association, European Liver Transplant Registry, Steering Committee of the SECA-study, Prof. Bo-Goran Ericzon, Prof. Ole Korsgren, Prof. Halvdan Sorbye, Dr. Einar Martin Aandahl, Dr. Morten Hagness, Dr. Marit Andersen, Dr. Kai Hansen.

References

1. European Liver Transplant Registry. *Data Analysis Booklet*. Paris: 2007: http://www.eltr.org.
2. Hoti E, Adam R. Liver transplantation for primary and metastatic liver cancers. *Transpl Int* 2008; **12**: 1107.
3. Rea DJ, Rosen CB, Nagorney DM, Heimbach JK, Gores GJ. Transplantation for cholangiocarcinoma: when and for whom? *Surg Oncol Clin N Am* 2009; **2**: 325.
4. Onaca N, Davis GL, Goldstein RM, Jennings LW, Klintmalm GB. Expanded criteria for liver transplantation in patients with hepatocellular carcinoma: a report from the International Registry of Hepatic Tumors in Liver Transplantation. *Liver Transpl* 2007; **3**: 391.
5. Mazzaferro V, Llovet JM, Miceli R, *et al.* Metroticket Investigator Study Group. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009; **1**: 35.

© 2010 The Authors

6. Zimmerman MA, Trotter JF, Wachs M, *et al.* Sirolimus-based immunosuppression following liver transplantation for hepatocellular carcinoma. *Liver Transpl* 2008; **5**: 633.
7. Toso C, Meeberg GA, Bigam DL, *et al.* De novo sirolimus-based immunosuppression after liver transplantation for hepatocellular carcinoma: long-term outcomes and side effects. *Transplantation* 2007; **83**: 1162.
8. Rea DJ, Heimbach JK, Rosen CB, *et al.* Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. *Ann Surg* 2005; **3**: 451.
9. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. *Br J Cancer* 2006; **7**: 982.
10. Tournigand C, Andre T, Achille E, *et al.* FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced CRC: a randomized GERCOR study. *J Clin Oncol* 2004; **2**: 229.
11. Hurwitz H, Fehrenbacher L, Novotny W, *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic CRC. *N Engl J Med* 2004; **23**: 2335.
12. Van Cutsem E, Köhne CH, Hitre E, *et al.* Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009; **14**: 1408.
13. Amado RG, Wolf M, Peeters M, *et al.* Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008; **10**: 1626.
14. McCarter MD, Fong Y. Metastatic liver tumors. *Semin Surg Oncol* 2000; **2**: 177.
15. Mentha G, Majno P, Terraz S, *et al.* Treatment strategies for the management of advanced colorectal liver metastases detected synchronously with the primary tumour. *Eur J Surg Oncol* 2007; **33**(Suppl 2): S76.
16. Van den Eynde M, Hendlisz A. Treatment of colorectal liver metastases: a review. *Rev Recent Clin Trials* 2009; **1**: 56.
17. National Institutes of Health Consensus Development Conference Statement: liver transplantation – June 20–23, 1983. *Hepatology* 1984; **4** (1 Suppl): 107S.
18. Aune S, Schistad G, Skulberg A. Human liver transplantation without azathioprine. *Surg Gynecol Obstet* 1972; **5**: 727.
19. Pichlmayr R, Neuhaus P. Liver transplantation. *Chirurg* 1985; **4**: 211.
20. Pichlmayr R. Is there a place for liver grafting for malignancy? *Transplant Proc* 1988; **1**(Suppl 1): 478.
21. Mühlbacher F, Piza F. Orthotopic liver transplantation for secondary malignancies of the liver. *Transplant Proc* 1987; **19**: 2396.
22. Mühlbacher F, Huk I, Steininger R, *et al.* Is orthotopic liver transplantation a feasible treatment for secondary cancer of the liver? *Transplant Proc* 1991; **23**: 1567.
23. Kappel S, Kandioler D, Steininger R, *et al.* Genetic detection of lymph node micrometastases: a selection criterion for liver transplantation in patients with liver metastases after colorectal cancer. *Transplantation* 2006; **1**: 64.
24. Nordic Liver Transplant Registy. http://www.sts.org
25. Belle SH, Beringer KC, Detre KM. An update on liver transplantation in the United States: recipient characteristics and outcome. *Clin Transpl* 1995; 19.
26. Robinson P. Hepatocellular carcinoma: development and early detection. *Cancer Imaging* 2008; **8**(Suppl A): S128.
27. Kattan MW, Gönen M, Jarnagin WR, *et al.* A nomogram for predicting disease-specific survival after hepatic resection for metastatic colorectal cancer. *Ann Surg* 2008; **247**: 282.
28. Pawlik TM, Choti MA. Shifting from clinical to biologic indicators of prognosis after resection of hepatic colorectal metastases. *Curr Oncol Rep* 2007; **3**: 193.
29. Nagorsen D, Voigt S, Berg E, Stein H, Thiel E, Loddenkemper C. Tumor-infiltrating macrophages and dendritic cells in human colorectal cancer: relation to local regulatory T cells, systemic T-cell response against tumor-associated antigens and survival. *J Transl Med* 2007; **5**: 62.
30. Sandel MH, Dadabayev AR, Menon AG, *et al.* Prognostic value of tumor-infiltrating dendritic cells in colorectal cancer: role of maturation status and intratumoral localization. *Clin Cancer Res* 2005; **7**: 2576.
31. Galon J, Costes A, Sanchez-Cabo F, *et al.* Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science* 2006; **313**: 1960.
32. Abdel-Misih SR, Schmidt CR, Bloomston PM. Update and review of the multidisciplinary management of stage IV colorectal cancer with liver metastases. *World J Surg Oncol* 2009; **7**: 72.
33. Abdalla EK, Vauthey JN, Ellis LM, *et al.* Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg* 2004; **239**: 818.
34. Nordlinger B, Van Cutsem E, Gruenberger T, *et al.* European Colorectal Metastases Treatment Group; Sixth International Colorectal Liver Metastases Workshop. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: recommendations from an expert panel. *Ann Oncol* 2009; **6**: 985.
35. Neeff H, Hörth W, Makowiec F, *et al.* Outcome after resection of hepatic and pulmonary metastases of colorectal cancer. *J Gastrointest Surg* 2009; **13**: 1813.
36. Carpizo DR, D'Angelica M. Liver resection for metastatic colorectal cancer in the presence of extrahepatic disease. *Ann Surg Oncol* 2009; **16**: 2411.
37. Rama N, Monteiro A, Bernardo JE, Eugénio L, Antunes MJ. Lung metastases from colorectal cancer: surgical resection and prognostic factors. *Eur J Cardiothorac Surg* 2009; **35**: 444.
38. Yamakado K, Inoue Y, Takao M, *et al.* Long-term results of radiofrequency ablation in colorectal lung metastases: single center experience. *Oncol Rep* 2009; **22**: 885.
39. de Jong MC, Mayo SC, Pulitano C, *et al.* Repeat Curative Intent Liver Surgery is Safe and Effective for Recurrent

© 2010 The Authors

Colorectal Liver Metastasis: Results from an International Multi-institutional Analysis. *J Gastrointest Surg* 2009; **13**: 2141.
40. Adam R, Delvart V, Pascal G, *et al.* Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg* 2004; **240**: 644.
41. Adam R, Wicherts D, de Haas RJ, *et al.* Patients with initially unresectable colorectal Liver Metastases: Is There a Possibility of Cure? *J Clin Oncol* 2009; **27**: 1829.
42. de Jong MC, Pulitano C, Ribero D, *et al.* Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. *Ann Surg* 2009; **250**: 440.
43. Fung J, Kelly D, Kadry Z, Patel-Tom K, Eghtesad B. Immunosuppression in liver transplantation: beyond calcineurin inhibitors. *Liver Transpl* 2005; **11**: 267.
44. Chan S, Scheulen ME, Johnston S, *et al.* Phase II study of temsirolimus (CCI-779), a novel inhibitor of mTOR, in heavily pretreated patients with locally advanced or metastatic breast cancer. *J Clin Oncol* 2005; **23**: 5314.
45. Atkins MB, Hidalgo M, Stadler WM, *et al.* Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *J Clin Oncol* 2004; **22**: 909.
46. Yadav RV, Indudhara R, Kumar P, Chugh KS, Gupta KL. Cyclophosphamide in renal transplantation. *Transplantation* 1988; **45**: 421.
47. Gallimore AM, Simon AK. Positive and negative influences of regulatory T cells on tumour immunity. *Oncogene* 2008; **27**: 5886.
48. Kingsley CI, Karim M, Bushell AR, Wood KJ. CD25+CD4+ regulatory T cells prevent graft rejection: CTLA-4- and IL-10-dependent immunoregulation of alloresponses. *J Immunol* 2002; **168**: 1080.
49. Dueland S, Andersen M, Foss A. Quality of life (QoL) in colorectal cancer liver transplant patients. *J Clin Oncol* 2009 (27), ASCO-GI abstract nr. 438.
50. van der Hilst CS, Ijtsma AJ, Slooff MJ, Tenvergert EM. Cost of liver transplantation: a systematic review and meta-analysis comparing the United States with other OECD countries. *Med Care Res Rev* 2009; **66**: 3.
51. Aaserud M, Kristiansen I S, Neilson A, *et al.* Helseøkonomisk evaluering av bevacizumab ved metastatisk kolorektalcancer. Rapport fra Kunnskapssenteret nr 23 - 2007. ISBN 978-82-8121-186-5 ISSN 1890-1298. (Summary in english at: http://www.kunnskapssenteret.no)
52. Movik E, Hamidi V, Aaserud M, Neilson AR, Klemp M. Helseøkonomisk evaluering av cetuximab ved metastatisk kolorektalcancer. Rapport Nr 10-2008 Nasjonalt kunnskapssenter. (Summary in english at: http://www.kunnskapssenteret.no).
53. Margarit C, Charco R, Hidalgo E, Allende H, Castells L, Bilbao I. Liver transplantation for malignant diseases: selection and pattern of recurrence. *World J Surg* 2002; **26**: 257.
54. At http://www.sts.org
55. At http://www.eltr.org.
56. At http://www.unos.org.
57. Watt KD, Lyden ER, McCashland TM. Poor survival after liver retransplantation: is hepatitis C to blame? *Liver Transpl* 2003; **9**: 1019.
58. McCashland T, Watt K, Lyden E, *et al.* Retransplantation for hepatitis C: results of a U.S. multicenter retransplant study. *Liver Transpl* 2007; **13**: 1246.
59. Clavien PA, Petrowsky H, DeOliveira ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. *N Eng Med* 2007; **356**: 1545.
60. Yamada T, Tanaka K, Uryuhara K, Ito K, Takada Y, Uemoto S. Selective hemi-portocaval shunt based on portal vein pressure for small-for-size graft in adult living donor liver transplantation. *Am J Transplant* 2008; **8**: 847.

© 2010 The Authors
Journal compilation © 2010 European Society for Organ Transplantation **23** (2010) 679–685