Organogenesis 10:2, 241–249; April/May/June 2014; © 2014 Landes Bioscience

Current status of the organ replacement approach for malignancies and an overture for organ bioengineering and regenerative medicine

Taizo Hibi*, Masahiro Shinoda, Osamu Itano, and Yuko Kitagawa

Department of Surgery; Keio University School of Medicine; Tokyo, Japan

Keywords: transplant oncology, liver transplantation, intestinal transplantation, multivisceral transplantation, autotransplantation, malignant neoplasm

Abbreviations: LT, liver transplantation; HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma; HEHE, hepatic epithelioid hemangioendothelioma; NET, neuroendocrine tumor; GIST, gastrointestinal tumor

Significant achievements in the organ replacement approach for malignancies over the last 2 decades opened new horizons, and the age of "Transplant Oncology" has dawned. The indications of liver transplantation for malignancies have been carefully expanded by a strict patient selection to assure comparable outcomes with non-malignant diseases. Currently, the Milan criteria, gold standard for hepatocellular carcinoma, are being challenged by high-volume centers worldwide. Neoadjuvant chemoradiation therapy and liver transplantation for unresectable hilar cholangiocarcinoma has been successful in specialized institutions. For other primary and metastatic liver tumors, clinical evidence to establish standardized criteria is lacking. Intestinal and multivisceral transplantation is an option for low-grade neoplasms deemed unresectable by conventional surgery. However, the procedure itself is in the adolescent stage. Solid organ transplantation for malignancies inevitably suffers from "triple distress," i.e., oncological, immunological, and technical. Organ bioengineering and regenerative medicine should serve as the "triple threat" therapy and revolutionize "Transplant Oncology."

Introduction

Cancer is one of the leading causes of death worldwide and the number of cases increases steadily as the global society matures (http://www.who.int/topics/cancer/en/index.html). Three modalities, i.e., surgery, chemotherapy, and radiation therapy, are well-established cancer treatments. The organ replacement approach, i.e., solid organ transplantation, for malignant neoplasms in the abdomen is conducted only in rare situations where conventional means are not helpful. As we strive to save patients with devastating malignancies desperately seeking a cure, indications for transplantation have been carefully expanded over the last 2 decades with varying degrees of success. Overlap between transplantation and oncology continues to grow and now the age of "Transplant Oncology" has dawned. However, because transplantation is by nature totally dependent on donation and because its indications for cancer are largely heterogeneous, orthodox analytical approaches such as randomized control trials or meta-analyses are not easily undertaken. This review aims to provide a snapshot on the current status and summarize the controversial issues of solid organ transplantation for malignancies in the blooming stage. Finally, allotransplantation connotes fundamental limitations; forethoughts on organ bioengineering and regenerative medicine are mentioned.

*Correspondence to: Taizo Hibi; Email: taizohibi@z3.keio.jp
Submitted: 02/01/2014; Accepted: 05/14/2014; Published Online: 05/16/2014
http://dx.doi.org/10.4161/org.29245

Liver Transplantation (LT)

Primary tumors

Hepatocellular carcinoma (HCC)

The Milan criteria,[1] allowing LT for patients with up to 3 HCCs with none of them larger than 3 cm in diameter or a single HCC ≤ 5 cm without vascular invasion or extrahepatic metastases, was reported by Mazzaferro et al. in 1996. These criteria afford a 4-y survival of 75% and remain as the gold standard, yet they are too restrictive for selecting transplant candidates. A handful of transplant centers have made attempts to push the limit that was referred to as the "Metro Ticket."[2] Well-known expanded criteria include the University of California San Francisco (≤6.5 cm if single lesion, ≤4.5 cm if ≤3 lesions with total tumor diameter ≤ 8 cm),[3,4] up-to-seven (≤7 as the sum of the size of the largest tumor [in cm] and the number of tumors),[5] Tokyo (up to 5 lesions with a maximum diameter ≤ 5 cm),[6] Asan (up to 6 lesions with a maximum diameter ≤ 5 cm),[7] Hangzhou (total diameter ≤8 cm or histopathologic grade I or II and preoperative α fetoprotein level ≤ 400 ng/ml if total diameter > 8 cm),[8] Scientific Registry of Transplant Recipients database (total tumor volume ≤ 115 cm^3 or α fetoprotein ≤ 400 ng/ml),[9] Kyoto (up to 10 lesions, maximum diameter ≤ 5 cm, and des-gamma-carboxy prothrombin ≤ 400 mAU/ml),[10,11] and Kyushu (≤5 cm or des-gamma-carboxy prothrombin ≤ 300 mAU/ml).[12,13] The

last 4 are distinct from others because they have incorporated into the selection criteria surrogate markers of tumor biology in addition to morphological properties of HCC. The reported outcomes of these expanded criteria are all within the acceptable range achieving >70% 5-y survival, i.e., comparable to non-HCC LT. However, none of them have gained recognition to replace the original Milan criteria and an international consensus meeting is long awaited.

On the other hand, vigorous efforts have been employed to downstage HCC to meet criteria for LT and to select patients with favorable tumor biology. A wide variety of treatment modalities have been described, such as liver resection,[14,15] transarterial chemoembolization or chemoinfusion,[16-20] radiofrequency ablation,[14,15,20,21] ethanol injection,[14,15] and more recently, radioembolization with yttrium-90.[19,20] Each transplant center is using its own inclusion criteria, downstaging protocol, definition of successful downstaging, timing of LT, and immunosuppressive protocol.[22-24] Although a significant heterogeneity lies among studies, downstaging of HCC is arguably a promising alternative for those who would otherwise be out of options. Currently, patients with up to 5 HCCs (all lesions not exceeding 4 cm with total tumor diameter up to 12 cm) and single HCC up to 8 cm in diameter seem to be considered for downstaging (successful downstaging rate, 24–69%); their 5-y survival rates range from 55–94%.[22,23]

Meanwhile, liver resection vs. LT for early HCC is also a matter of dispute.[25-27] If LT is being considered for a patient with advanced HCC, the "success" rate using either the expanded Milan criteria or after downstaging needs to be carefully balanced with the scarcity of organs and ensuring equity with non-HCC transplant candidates on the waiting list. Treatment decision-making in HCC is influenced by surgeon- and institution-related factors and the importance of a multidisciplinary team approach cannot be overstated.[28-31]

Perihilar cholangiocarcinoma (CCA)

Surgical resection is the treatment of choice for resectable perihilar CCA. For unresectable disease, neoadjuvant chemo-radiation therapy followed by LT has been acknowledged as a curative option in selected cases.[32-35] It has provided an excellent recurrence-free 5-y survival rate reaching 68% while maintaining equal to or even better quality of life than those who underwent LT for other liver disease.[36,37] Encouraged by the success of the Mayo protocol, other transplant centers in the United States have applied a similar approach to unresectable perihilar CCA and have achieved equivalent results.[38] However, the definition of "resectability" of the disease demands extra caution. The candidates for surgical resection appear to be different when the studies from Western countries are compared with those of Japan. For example, there is a great difference in the portion of patients with Bismuth type IV, ranging from 0% to >40%.[39-48] Thus, the reported survival data needs to be interpreted carefully. The Nagoya group has recently reported that 73 patients who underwent resection for Bismuth type IV tumor and/or combined vascular resection, therefore fulfilling the "unresectability criteria" defined by the Mayo group, had a 60.4% survival rate at 5 y, similar to the survival of LT recipients.[49] A new staging system for perihilar CCA that is expected to become the "common language" to provide a basis for discussing surgical treatment of this disease has raised several concerns and warrants further international collaboration.[50-52]

Intrahepatic CCA

In contrast to perihilar CCA, LT for intrahepatic CCA fare worse. The disappointing results from the initial experiences with a 3-y survival in the 30% range are eloquently summarized in a recent review.[53] Most recently, a multicenter study from Spain demonstrated better survival rates in 27 patients reaching 51% at 5 y.[54] The University of California Los Angeles group described promising data of neoadjuvant and adjuvant therapy combined with LT in the treatment of intrahepatic and hilar CCA.[55] They further proposed a prognostic scoring system to identify patients who may benefit from LT.[56] Seven independent risk factors (multifocal tumor, perineural invasion, infiltrative subtype, lack of neoadjuvant and/or adjuvant therapies, primary sclerosing cholangitis, hilar CCA, and lymphovascular invasion) were assigned certain risk score points based on the corresponding parameter estimate using the Cox model. Patients in the low risk category (score 0–3) had a significantly higher 5-y survival of 78% compared with intermediate risk (score 4–7, 19%) and high risk (score 8–15, 0%) categories. In contrast to the Mayo group, they insist that a biopsy should be obtained before neoadjuvant therapy to evaluate tumor biology.[56,57] Although a marked progress has been made in understanding the pathogenesis of intrahepatic CCA,[58] LT as a treatment option remains highly controversial.

Others

For combined HCC-CCA, the data on the outcomes are scarce and the prognoses reported in the earlier series are not very promising, with the median overall survival ranging from 20 mo–3.6 y.[59-63] One study that analyzed patients in the Surveillance, Epidemiology, and End Results database (1973–2007) found that LT (19 patients) and resection (35 patients) for localized combined HCC-CCA had similar 3-y survival rates in the 50% range, which was inferior to LT for HCC (1447 patients, 78%).[63] At the moment, liver resection is preferred over LT for resectable combined HCC-CCA. Intriguingly, the Spanish study previously mentioned showed similar 5-y survival rates between combined HCC-CCA (15 patients, 78%) and the matched cohort of HCC (30 patients, 86%) after LT.[54] Precise imaging criteria for the pre-transplant diagnosis of HCC are important to identify lesions suspicious for combined HCC-CCA. Needle biopsy of the tumor should ideally be performed to confirm histology, although it might be difficult in a clinical setting.[54,62,63]

A recent systematic review described marginal outcomes of LT for fibrolamellar HCC with 5-y survival rates ranging from 29–55%.[64] However, most of the collected cases were from the 1980s and early 1990s before the proposal of the Milan criteria. In addition, perioperative patient management has made great progress since then and the disappointing results of the earlier series are not surprising. There are 2 publications to date reporting successful living donor LT (including 1 case of salvage transplantation after hepatectomy) as an effective alternative in highly selected cases.[65,66] The role of LT in the treatment of fibrolamellar HCC has yet to be defined.

Three large series (>50 patients) of LT for hepatic epithelioid hemangioendothelioma (HEHE) reported satisfactory 5-y survival rates ranging from 55–83%.[67-69] All of them have proposed an aggressive attitude toward unresectable HEHE even in patients with lymph node involvement or extrahepatic disease because both factors did not significantly affect survival when appropriate multimodal treatments were employed. Pretransplant medical condition and vascular invasion have been described as poor prognostic predictors.[68,69] The use of anti-vascular endothelial cell growth factor agents is expected to further improve outcomes.[68,70] Recently, Grotz et al. stated that patients with tumor size ≤ 10 cm, number up to 10, and extent of hepatic involvement up to 4 segments, are candidates for liver resection rather than LT and further investigations are warranted to clearly define the role of each surgical treatment.[71] In the pediatric population, LT remains a good treatment modality in patients with unresectable HEHE, although the prognoses may not be as promising as other primary liver tumors, i.e., hepatoblastoma and HCC.[72]

The data on LT for primary sarcoma are disappointing. Six patients with primary sarcomas showed recurrent disease at a median of 2 mo and all died early after LT with only 1 patient surviving the first year.[73] Likewise, Orlando et al. stated that hemangiosarcomas are an absolute contraindication to LT due to its diminished overall survival of 7.2 ± 2.6 mo.[74] However, for hepatic undifferentiated embryonal sarcoma, a rare malignancy in the pediatric population, 6 patients underwent LT combined with multimodal therapy and all remained disease-free with a median follow-up of 35 mo.[75]

For unresectable hepatoblastoma, LT continues to be the only treatment option. In the US, the number of new cases of hepatoblastoma increased by almost 4-fold during the last 3 decades and LT by 20-fold.[76] The 5-y overall survival rate has gradually improved to over 75%, similar to that for patients with HCC.[76-78] Patients are considered unamenable to LT only if there are one or more extrahepatic lesions that are unresponsive to chemotherapy.[78] A Japanese study has proposed a new algorithm to allocate patients to either LT or liver resection depending on their response to chemotherapy.[79]

Metastatic liver tumors

Neuroendocrine tumor (NET)

Several patient selection criteria and prognostic factors such as concurrent resection of other organs, primary tumor site, hepatomegaly, and recipient age have been proposed but there has been a lack of clinical evidence to clearly delineate candidates for transplantation.[80-84] Recently, a European registry study described outcomes of 213 cases that underwent LT for metastatic NET, the largest number of patients to date; 5-y overall and disease-free survival rates were 52% and 30%, respectively.[85] Hepatomegaly, poor tumor differentiation, and major resection concurrent with LT were revealed to be poor prognostic indicators and better survival rates of nearly 60% were achieved in cases performed after 2000 because of more favorable patient characteristics.[85] There is a growing consensus that LT for metastatic NET should be considered for unresectable disease, no extrahepatic disease, well-differentiated NET (NET G1/G2), and should not be associated with major extrahepatic resection.[85] Medical treatment continues to evolve and the timing of LT remains controversial.[85]

Colorectal cancer

Once deemed an absolute contraindication, LT for unresectable colorectal liver metastasis may become a viable option again.[86,87] By using a mammalian target of rapamycin inhibitor for primary immunosuppression, a Norwegian pilot study of 21 patients achieved 60% overall survival at 5 y, far exceeding the reported outcomes of chemotherapy in this subset of patients.[87] Although 19 of 21 (90%) patients had recurrent disease, a significant proportion of them were accessible to further local treatments and 7 (33%) had no evidence of disease at the last follow-up.[87] However, this study was conducted because of the exceptional situation in Norway where a surplus of organs exists and an ethical dilemma needs to be solved.[87,88] Meanwhile, an Austrian group has suggested a novel technology to detect micrometastases in histologically negative lymph nodes to select patients who may benefit from LT.[89] Tremendous progress in LT over the last several decades as well as new tools developed for patient selection and the notably improved efficacy of chemotherapy may evoke a paradigm shift in the treatment of colorectal cancer.

Others

Only a handful of cases of LT for unresectable gastrointestinal stromal tumor (GIST) metastases have been reported to date. Husted et al. strongly argued against the use of LT for metastatic GIST because of its dismal outcome.[73] However, others described more promising survival with the combination of imatinib, allowing disease-free intervals over 24 mo with the longest survival reaching 10 y at the time of publication.[90-93] LT for unresectable metastatic GIST may afford prolonged survival in highly selected patients with time to liver metastases > 2 y, low or intermediate risk level of GIST, and positive KIT (CD117) or PDGFR gene mutation status.[93]

Similarly, there are only 3 case reports of LT (2 living and 1 deceased donor) for unresectable liver metastases of solid pseudopapillary tumor of the pancreas.[94-96] The patients remain disease-free at 2 and 5 y after LT.[94-96] Selection criteria for LT have yet to be determined.

Intestinal and Multivisceral Transplantation

Multivisceral transplantation for extensive malignancies in the upper abdomen was first reported in 1989.[97] Since then, its short-term outcomes have improved significantly and indications of either intestinal, liver-intestinal, or multivisceral (full/modified) transplantations[98] have expanded for a wide variety of tumors such as desmoid (Gardner's syndrome), neuroendocrine, adenocarcinoma, schwannoma, lymphoma, and sarcoma that would otherwise be unresectable.[99-112] Currently, there is no standardized indication of intestinal and multivisceral transplantation for neoplastic disease. However, for high-grade malignancies such as adenocarcinoma and lymphoma, the disappointing oncological results in the earlier series obviously warrant deliberate patient selection, if not contraindicated.[103] Because all patients are subject to life-long, intensive immunosuppression, the biological behavior

of any neoplasm is essentially unpredictable and needs to be carefully weighed with the invasiveness of these procedures even if complete tumor removal is technically feasible. Novel immune monitoring techniques on the horizon[113-120] as well as accumulating evidence of the significance of donor specific antibodies[108,121-126] are critical to surmount the immunological dilemma of preventing intestinal rejection, the Achilles' heel of transplanting small bowel contained allografts,[127] and tumor progression.

Application of transplantation techniques in cancer surgery

Autotransplantation

Ex vivo tumor resection and organ reimplantation (autotransplantation) for extensive hepatic and gastrointestinal malignancies involving mesenteric and/or celiac root deemed unresectable by conventional surgery is an offspring of solid organ transplantation. It has now evolved from single organ[128-135] to multivisceral surgery.[136,137] The major advantages of this approach are excellent exposure enabling complete tumor eradication in a bloodless field at the back table and eliminating the use of immunosuppression.[136,137] Nevertheless, it is associated with potential risks of vascular thrombosis and ischemia reperfusion injury as well as uncertain oncological outcomes, similar to allotransplantations.[136,137] These complex transplantations are still far from perfect and each case should undergo comprehensive, multidisciplinary discussion in a combined transplant and oncology program.

Others

Several other surgical approaches derived from solid organ transplantation have given rise to other complex operations for extensive malignancies. Hannoun et al. first reported ante-situm (transection of the suprahepatic inferior vena cava followed by ventral rotation of the liver) hepatic resection with total vascular exclusion, venovenous bypass, and hypothermic perfusion (which has also been used in in situ liver resection) in 1991.[129] Since then, liver tumors involving the confluence of hepatic veins and/or the retrohepatic vena cava were resected by this approach in more than 50 patients and every report underscores the paramount importance of deliberate patient selection.[130,134,138-142] Ciancio et al. depicted the use of the mobilization technique in LT for resection of renal cell carcinoma with tumor thrombus in the inferior vena cava[143] and en bloc mobilization of the pancreas and spleen, which was derived from multivisceral transplantation as well as organ procurement, for resection of large tumors in the left upper abdomen.[144] Both procedures were successfully performed with minimum risk while maximizing the chance of complete resection.

Closing Remarks

Cancer treatment evolves constantly and multidisciplinary team discussion is imperative. Surgery is only one part of cancer patient care and all transplant surgeons and physicians should work closely with the surgical and medical oncologists. If the removal of a tumor appears to be beneficial from an oncological viewpoint, its resectability should be carefully determined by a team of surgeons experienced in hepatopancreatobiliary, gastrointestinal, and transplant surgery; however, this is not always possible. More importantly, it is vital to recognize the "triple distress," fundamental limitations of solid organ transplantation for malignancies.

(1) Oncological distress: The so-called "selection criteria" for transplantation is totally dependent on 2 factors: (A) number of organs available, and (B) biological behavior of the disease. In the era of deteriorating organ availability, long-term outcomes after transplantation for malignancies cannot be inferior to other indications; otherwise, the principle of equity will be lost for other patients on the waiting list. On the contrary, in rare circumstances such as Norway where organ supply surpasses demand, clinical trials challenging the current consensus are permissive.[87]

(2) Immunological distress: Induction of immune tolerance after transplantation and the crosstalk between transplant and tumor immunity,[145,146] both organ- and disease-specific, has yet to be elucidated. How to determine an adequate level of immunosuppression to prevent rejection and tumor progression at the same time remains the key question.

(3) Technical distress: The history of transplantation is one of a series of innovation. Novel techniques have served as life-saving options in complicated cases that were once considered absolute contraindications.[147,148] However, these complex procedures carry significant risks of predominantly vascular complications.

As we endeavor on our arduous odyssey for patients with malignancies that cannot be treated by standard cancer therapy, the aforementioned hardships will inevitably block our way as the undefeated enemy. Transplantation is an ever-unfinished enterprise and a victim of its own success. No matter how close we get, allotransplantation does not allow us to accomplish the ultimate goal to bring definitive cure for all patients worldwide. Organ bioengineering and regenerative medicine is the only hope; the "triple threat" cancer therapy that serves as an ultimate solution to the necessary evils of solid organ transplantation for malignancies.

The clinical application of organ bioengineering and regenerative medicine may proceed in a stepwise manner. For example, it is well known that the limit of liver resection is determined by the hepatic reserve and future liver remnant. Patients with a normal liver who require extensive hepatectomy beyond this limit because of tumor size and location are at risk for liver failure. If we successfully assemble and implant a small liver derived from the patient's own cells by organ bioengineering, it can function as an auxiliary liver "autograft"[149] while the remnant liver regenerates rapidly. This autograft only needs to work until the patient's own liver becomes large enough to meet the physiological demands. As the new technology improves, larger and durable liver autografts should be available that can completely replace the deceased liver, similar to LT for end-stage liver cirrhosis performed in everyday clinical practice. Likewise, for intestinal transplantation, a first step might be the implantation of a short-lasting autograft for temporary nutritional support while the patient undergoes intestinal rehabilitation for short-gut syndrome.[150]

Organ bioengineering and regenerative medicine will revolutionize the field of "Transplant Oncology."

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996; 334:693-9; PMID:8594428; http://dx.doi.org/10.1056/NEJM199603143341104
2. Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. Semin Liver Dis 2005; 25:181-200; PMID:15918147; http://dx.doi.org/10.1055/s-2005-871198
3. Yao FY, Ferrell L, Bass NM, Bacchetti P, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: comparison of the proposed UCSF criteria with the Milan criteria and the Pittsburgh modified TNM criteria. Liver Transpl 2002; 8:765-74; PMID:12200775; http://dx.doi.org/10.1053/jlts.2002.34892
4. Yao FY, Xiao L, Bass NM, Kerlan R, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: validation of the UCSF-expanded criteria based on preoperative imaging. Am J Transplant 2007; 7:2587-96; PMID:17868066; http://dx.doi.org/10.1111/j.1600-6143.2007.01965.x
5. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, Camerini T, Roayaie S, Schwartz ME, Grazi GL, 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; 10:35-43; PMID:19058754; http://dx.doi.org/10.1016/S1470-2045(08)70284-5
6. Sugawara Y, Tamura S, Makuuchi M. Living donor liver transplantation for hepatocellular carcinoma: Tokyo University series. Dig Dis 2007; 25:310-2; PMID:17960065; http://dx.doi.org/10.1159/000106910
7. Lee SG, Hwang S, Moon DB, Ahn CS, Kim KH, Sung KB, Ko GY, Park KM, Ha TY, Song GW. Expanded indication criteria of living donor liver transplantation for hepatocellular carcinoma at one large-volume center. Liver Transpl 2008; 14:935-45; PMID:18581465; http://dx.doi.org/10.1002/lt.21445
8. Zheng SS, Xu X, Wu J, Chen J, Wang WL, Zhang M, Liang TB, Wu LM. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. Transplantation 2008; 85:1726-32; PMID:18580463; http://dx.doi.org/10.1097/TP.0b013e31816b67e4
9. Toso C, Asthana S, Bigam DL, Shapiro AM, Kneteman NM. Reassessing selection criteria prior to liver transplantation for hepatocellular carcinoma utilizing the Scientific Registry of Transplant Recipients database. Hepatology 2009; 49:832-8; PMID:19152426; http://dx.doi.org/10.1002/hep.22693
10. Ito T, Takada Y, Ueda M, Haga H, Maetani Y, Oike F, Ogawa K, Sakamoto S, Ogura Y, Egawa H, et al. Expansion of selection criteria for patients with hepatocellular carcinoma in living donor liver transplantation. Liver Transpl 2007; 13:1637-44; PMID:18044766; http://dx.doi.org/10.1002/lt.21281
11. Kaido T, Ogawa K, Mori A, Fujimoto Y, Ito T, Tomiyama K, Takada Y, Uemoto S. Usefulness of the Kyoto criteria as expanded selection criteria for liver transplantation for hepatocellular carcinoma. Surgery 2013; 154:1053-60; PMID:24074704; http://dx.doi.org/10.1016/j.surg.2013.04.056
12. Soejima Y, Taketomi A, Yoshizumi T, Uchiyama H, Aishima S, Terashi T, Shimada M, Maehara Y. Extended indication for living donor liver transplantation in patients with hepatocellular carcinoma. Transplantation 2007; 83:893-9; PMID:17460559; http://dx.doi.org/10.1097/01.tp.0000259015.46798.ec
13. Shirabe K, Taketomi A, Morita K, Soejima Y, Uchiyama H, Kayashima H, Ninomiya M, Toshima T, Maehara Y. Comparative evaluation of expanded criteria for patients with hepatocellular carcinoma beyond the Milan criteria undergoing living-related donor liver transplantation. Clin Transplant 2011; 25:E491-8; PMID:21518000; http://dx.doi.org/10.1111/j.1399-0012.2011.01463.x
14. Cillo U, Vitale A, Grigoletto F, Gringeri E, D'Amico F, Valmasoni M, Brolese A, Zanus G, Srsen N, Carraro A, et al. Intention-to-treat analysis of liver transplantation in selected, aggressively treated HCC patients exceeding the Milan criteria. Am J Transplant 2007; 7:972-81; PMID:17391137; http://dx.doi.org/10.1111/j.1600-6143.2006.01719.x
15. Ravaioli M, Grazi GL, Piscaglia F, Trevisani F, Cescon M, Ercolani G, Vivarelli M, Golfieri R, D'Errico Grigioni A, Panzini I, et al. Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. Am J Transplant 2008; 8:2547-57; PMID:19032223; http://dx.doi.org/10.1111/j.1600-6143.2008.02409.x
16. Otto G, Herber S, Heise M, Lohse AW, Mönch C, Bittinger F, Hoppe-Lotichius M, Schuchmann M, Victor A, Pitton M. Response to transarterial chemoembolization as a biological selection criterion for liver transplantation in hepatocellular carcinoma. Liver Transpl 2006; 12:1260-7; PMID:16826556; http://dx.doi.org/10.1002/lt.20837
17. Chapman WC, Majella Doyle MB, Stuart JE, Vachharajani N, Crippin JS, Anderson CD, Lowell JA, Shenoy S, Darcy MD, Brown DB. Outcomes of neoadjuvant transarterial chemoembolization to downstage hepatocellular carcinoma before liver transplantation. Ann Surg 2008; 248:617-25; PMID:18936575
18. De Luna W, Sze DY, Ahmed A, Ha BY, Ayoub W, Keeffe EB, Cooper A, Esquivel C, Nguyen MH. Transarterial chemoinfusion for hepatocellular carcinoma as downstaging therapy and a bridge toward liver transplantation. Am J Transplant 2009; 9:1158-68; PMID:19344435; http://dx.doi.org/10.1111/j.1600-6143.2009.02576.x
19. Lewandowski RJ, Kulik LM, Riaz A, Senthilnathan S, Mulcahy MF, Ryu RK, Ibrahim SM, Sato KT, Baker T, Miller FH, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant 2009; 9:1920-8; PMID:19552767; http://dx.doi.org/10.1111/j.1600-6143.2009.02695.x
20. Barakat O, Wood RP, Ozaki CF, Ankoma-Sey V, Galati J, Skolkin M, Toombs B, Round M, Moore W, Mieles L. Morphological features of advanced hepatocellular carcinoma as a predictor of downstaging and liver transplantation: an intention-to-treat analysis. Liver Transpl 2010; 16:289-99; PMID:20209588
21. Yao FY, Kerlan RK Jr., Hirose R, Davern TJ 3rd, Bass NM, Feng S, Peters M, Terrault N, Freise CE, Ascher NL, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. Hepatology 2008; 48:819-27; PMID:18688876; http://dx.doi.org/10.1002/hep.22412
22. Toso C, Mentha G, Kneteman NM, Majno P. The place of downstaging for hepatocellular carcinoma. J Hepatol 2010; 52:930-6; PMID:20385428; http://dx.doi.org/10.1016/j.jhep.2009.12.032
23. Gordon-Weeks AN, Snaith A, Petrinic T, Friend PJ, Burls A, Silva MA. Systematic review of outcome of downstaging hepatocellular cancer before liver transplantation in patients outside the Milan criteria. Br J Surg 2011; 98:1201-8; PMID:21618496; http://dx.doi.org/10.1002/bjs.7561
24. Yao FY, Breitenstein S, Broelsch CE, Dufour JF, Sherman M. Does a patient qualify for liver transplantation after the down-staging of hepatocellular carcinoma? Liver Transpl 2011; 17(Suppl 2):S109-16; PMID:21584927; http://dx.doi.org/10.1002/lt.22335
25. Koniaris LG, Levi DM, Pedroso FE, Franceschi D, Tzakis AG, Santamaria-Barria JA, Tang J, Anderson M, Misra S, Solomon NL, et al. Is surgical resection superior to transplantation in the treatment of hepatocellular carcinoma? Ann Surg 2011; 254:527-37, discussion 537-8; PMID:21865950; http://dx.doi.org/10.1097/SLA.0b013e31822ca66f
26. Ho CM, Lee PH, Chen CL, Ho MC, Wu YM, Hu RH. Long-term outcomes after resection versus transplantation for hepatocellular carcinoma within UCSF criteria. Ann Surg Oncol 2012; 19:826-33; PMID:21879276; http://dx.doi.org/10.1245/s10434-011-1975-x
27. Sapisochin G, Castells L, Dopazo C, Bilbao I, Minguez B, Lázaro JL, Allende H, Balsells J, Caralt M, Charco R. Single HCC in cirrhotic patients: liver resection or liver transplantation? Long-term outcome according to an intention-to-treat basis. Ann Surg Oncol 2013; 20:1194-202; PMID:22965574; http://dx.doi.org/10.1245/s10434-012-2655-1
28. Nathan H, Bridges JF, Schulick RD, Cameron AM, Hirose K, Edil BH, Wolfgang CL, Segev DL, Choti MA, Pawlik TM. Understanding surgical decision making in early hepatocellular carcinoma. J Clin Oncol 2011; 29:619-25; PMID:21205759; http://dx.doi.org/10.1200/JCO.2010.30.8650
29. Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A; OLT for HCC Consensus Group. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol 2012; 13:e11-22; PMID:22047762; http://dx.doi.org/10.1016/S1470-2045(11)70175-9
30. Barone C, Koeberle D, Metselaar H, Parisi G, Sansonno D, Spinzi G. Multidisciplinary approach for HCC patients: hepatology for the oncologists. Ann Oncol 2013; 24(Suppl 2):ii15-23; PMID:23715939; http://dx.doi.org/10.1093/annonc/mdt053
31. Nathan H, Segev DL, Bridges JF, Massie AB, Cameron AM, Hirose K, Schulick RD, Choti MA, Pawlik TM. Influence of nonclinical factors on choice of therapy for early hepatocellular carcinoma. Ann Surg Oncol 2013; 20:448-56; PMID:22941170; http://dx.doi.org/10.1245/s10434-012-2619-5
32. De Vreede I, Steers JL, Burch PA, Rosen CB, Gunderson LL, Haddock MG, Burgart L, Gores GJ. Prolonged disease-free survival after orthotopic liver transplantation plus adjuvant chemoirradiation for cholangiocarcinoma. Liver Transpl 2000; 6:309-16; PMID:10827231; http://dx.doi.org/10.1053/lv.2000.6143
33. Sudan D, DeRoover A, Chinnakotla S, Fox I, Shaw B Jr., McCashland T, Sorrell M, Tempero M, Langnas A. Radiochemotherapy and transplantation allow long-term survival for nonresectable hilar cholangiocarcinoma. Am J Transplant 2002; 2:774-9; PMID:12243499; http://dx.doi.org/10.1034/j.1600-6143.2002.20812.x
34. Rea DJ, Heimbach JK, Rosen CB, Haddock MG, Alberts SR, Kremers WK, Gores GJ, Nagorney DM. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. Ann Surg 2005; 242:451-8, discussion 458-61; PMID:16135931
35. Heimbach JK, Gores GJ, Haddock MG, Alberts SR, Pedersen R, Kremers W, Nyberg SL, Ishitani MB, Rosen CB. Predictors of disease recurrence following neoadjuvant chemoradiotherapy and liver transplantation for unresectable perihilar cholangiocarcinoma. Transplantation 2006; 82:1703-7; PMID:17198263; http://dx.doi.org/10.1097/01.tp.0000253551.43583.d1
36. Darwish Murad S, Kim WR, Therneau T, Gores GJ, Rosen CB, Martenson JA, Alberts SR, Heimbach JK. Predictors of pretransplant dropout and post-transplant recurrence in patients with perihilar cholangiocarcinoma. Hepatology 2012; 56:972-81; PMID:22290335; http://dx.doi.org/10.1002/hep.25629

37. Darwish Murad S, Heimbach JK, Gores GJ, Rosen CB, Benson JT, Kim WR. Excellent quality of life after liver transplantation for patients with perihilar cholangiocarcinoma who have undergone neoadjuvant chemoradiation. Liver Transpl 2013; 19:521-8; PMID:23447435; http://dx.doi.org/10.1002/lt.23630
38. Darwish Murad S, Kim WR, Harnois DM, Douglas DD, Burton J, Kulik LM, Botha JF, Mezrich JD, Chapman WC, Schwartz JJ, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. Gastroenterology 2012; 143:88, e3, quiz e14; PMID:22504095; http://dx.doi.org/10.1053/j.gastro.2012.04.008
39. Sano T, Shimada K, Sakamoto Y, Yamamoto J, Yamasaki S, Kosuge T. One hundred two consecutive hepatobiliary resections for perihilar cholangiocarcinoma with zero mortality. Ann Surg 2006; 244:240-7; PMID:16858186; http://dx.doi.org/10.1097/01.sla.0000217605.66519.38
40. Hirano S, Kondo S, Tanaka E, Shichinohe T, Tsuchikawa T, Kato K, Matsumoto J, Kawasaki R. Outcome of surgical treatment of hilar cholangiocarcinoma: a special reference to postoperative morbidity and mortality. J Hepatobiliary Pancreat Sci 2010; 17:455-62; PMID:19820891; http://dx.doi.org/10.1007/s00534-009-0208-1
41. Igami T, Nishio H, Ebata T, Yokoyama Y, Sugawara G, Nimura Y, Nagino M. Surgical treatment of hilar cholangiocarcinoma in the "new era": the Nagoya University experience. J Hepatobiliary Pancreat Sci 2010; 17:449-54; PMID:19806294; http://dx.doi.org/10.1007/s00534-009-0209-0
42. Miyazaki M, Kimura F, Shimizu H, Yoshidome H, Otuka M, Kato A, Yoshitomi H, Furukawa K, Takeuchi D, Takayashiki T, et al. One hundred seven consecutive surgical resections for hilar cholangiocarcinoma of Bismuth types II, III, IV between 2001 and 2008. J Hepatobiliary Pancreat Sci 2010; 17:470-5; PMID:19936600; http://dx.doi.org/10.1007/s00534-009-0207-2
43. Unno M, Katayose Y, Rikiyama T, Yoshida H, Yamamoto K, Morikawa T, Hayashi H, Motoi F, Egawa S. Major hepatectomy for perihilar cholangiocarcinoma. J Hepatobiliary Pancreat Sci 2010; 17:463-9; PMID:19941010; http://dx.doi.org/10.1007/s00534-009-0206-3
44. de Jong MC, Hong SM, Augustine MM, Goggins MG, Wolfgang CL, Hirose K, Schulick RD, Choti MA, Anders RA, Pawlik TM. Hilar cholangiocarcinoma: tumor depth as a predictor of outcome. Arch Surg 2011; 146:697-703; PMID:21690446; http://dx.doi.org/10.1001/archsurg.2011.122
45. Hemming AW, Mekeel K, Khanna A, Baquerizo A, Kim RD. Portal vein resection in management of hilar cholangiocarcinoma. J Am Coll Surg 2011; 212:604-13, discussion 613-6; PMID:21463797; http://dx.doi.org/10.1016/j.jamcollsurg.2010.12.028
46. de Jong MC, Marques H, Clary BM, Bauer TW, Marsh JW, Ribero D, Majno P, Hatzaras I, Walters DM, Barbas AS, et al. The impact of portal vein resection on outcomes for hilar cholangiocarcinoma: a multi-institutional analysis of 305 cases. Cancer 2012; 118:4737-47; PMID:22415526; http://dx.doi.org/10.1002/cncr.27492
47. Matsuo K, Rocha FG, Ito K, D'Angelica MI, Allen PJ, Fong Y, Dematteo RP, Gonen M, Endo I, Jarnagin WR. The Blumgart preoperative staging system for hilar cholangiocarcinoma: analysis of resectability and outcomes in 380 patients. J Am Coll Surg 2012; 215:343-55; PMID:22749003; http://dx.doi.org/10.1016/j.jamcollsurg.2012.05.025
48. Zaydfudim VM, Clark CJ, Kendrick ML, Que FG, Reid-Lombardo KM, Donohue JH, Farnell MB, Nagorney DM. Correlation of staging systems to survival in patients with resected hilar cholangiocarcinoma. Am J Surg 2013; 206:159-65; PMID:23746658; http://dx.doi.org/10.1016/j.amjsurg.2012.11.020
49. Nagino M, Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, Nimura Y. Evolution of surgical treatment for perihilar cholangiocarcinoma: a single-center 34-year review of 574 consecutive resections. Ann Surg 2013; 258:129-40; PMID:23059502; http://dx.doi.org/10.1097/SLA.0b013e3182708b57
50. Deoliveira ML, Schulick RD, Nimura Y, Rosen C, Gores G, Neuhaus P, Clavien PA. New staging system and a registry for perihilar cholangiocarcinoma. Hepatology 2011; 53:1363-71; PMID:21480336; http://dx.doi.org/10.1002/hep.24227
51. Nagino M. Perihilar cholangiocarcinoma: A much needed but imperfect new staging system. Nat Rev Gastroenterol Hepatol 2011; 8:252-3; PMID:21487382
52. DeOliveira ML, Clavien PA. A common language to describe perihilar cholangiocarcinoma. Br J Surg 2012; 99:885-6; PMID:22556154; http://dx.doi.org/10.1002/bjs.8782
53. Rana A, Hong JC. Orthotopic liver transplantation in combination with neoadjuvant therapy: a new paradigm in the treatment of unresectable intrahepatic cholangiocarcinoma. Curr Opin Gastroenterol 2012; 28:258-65; PMID:22333563; http://dx.doi.org/10.1097/MOG.0b013e32835168db
54. Sapisochin G, de Lope CR, Gastaca M, de Urbina JO, López-Andujar R, Palacios F, Ramos E, Fabregat J, Castroagudín JF, Varo E, et al. Intrahepatic cholangiocarcinoma or mixed hepatocellular-cholangiocarcinoma in patients undergoing liver transplantation: a spanish matched cohort multicenter study. Ann Surg 2014; 259:944-52; PMID:24441817; http://dx.doi.org/10.1097/SLA.0000000000000494
55. Hong JC, Jones CM, Duffy JP, Petrowsky H, Farmer DG, French S, Finn R, Durazo FA, Saab S, Tong MJ, et al. Comparative analysis of resection and liver transplantation for intrahepatic and hilar cholangiocarcinoma: a 24-year experience in a single center. Arch Surg 2011; 146:683-9; PMID:21690444; http://dx.doi.org/10.1001/archsurg.2011.116
56. Hong JC, Petrowsky H, Kaldas FM, Farmer DG, Durazo FA, Finn RS, Saab S, Han SH, Lee P, Markovic D, et al. Predictive index for tumor recurrence after liver transplantation for locally advanced intrahepatic and hilar cholangiocarcinoma. J Am Coll Surg 2011; 212:514-20, discussion 520-1; PMID:21463781; http://dx.doi.org/10.1016/j.jamcollsurg.2010.12.005
57. Rosen CB, Darwish Murad S, Heimbach JK, Nyberg SL, Nagorney DM, Gores GJ. Neoadjuvant therapy and liver transplantation for hilar cholangiocarcinoma: is pretreatment pathological confirmation of diagnosis necessary? J Am Coll Surg 2012; 215:31-8, discussion 38-40; PMID:22621893; http://dx.doi.org/10.1016/j.jamcollsurg.2012.03.014
58. Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. Gastroenterology 2013; 145:1215-29; PMID:24140396; http://dx.doi.org/10.1053/j.gastro.2013.10.013
59. Chan AC, Lo CM, Ng IO, Fan ST. Liver transplantation for combined hepatocellular cholangiocarcinoma. Asian J Surg 2007; 30:143-6; PMID:17475587; http://dx.doi.org/10.1016/S1015-9584(09)60149-4
60. Maganty K, Levi D, Moon J, Bejarano PA, Arosemena L, Tzakis A, Martin P. Combined hepatocellular carcinoma and intrahepatic cholangiocarcinoma: outcome after liver transplantation. Dig Dis Sci 2010; 55:3597-601; PMID:20848202; http://dx.doi.org/10.1007/s10620-010-1402-3
61. Panjala C, Senecal DL, Bridges MD, Kim GP, Nakhleh RE, Nguyen JH, Harnois DM. The diagnostic conundrum and liver transplantation outcome for combined hepatocellular-cholangiocarcinoma. Am J Transplant 2010; 10:1263-7; PMID:20420633; http://dx.doi.org/10.1111/j.1600-6143.2010.03062.x
62. Sapisochin G, Fidelman N, Roberts JP, Yao FY. Mixed hepatocellular cholangiocarcinoma and intrahepatic cholangiocarcinoma in patients undergoing transplantation for hepatocellular carcinoma. Liver Transpl 2011; 17:934-42; PMID:21438129; http://dx.doi.org/10.1002/lt.22307
63. Groeschl RT, Turaga KK, Gamblin TC. Transplantation versus resection for patients with combined hepatocellular carcinoma-cholangiocarcinoma. J Surg Oncol 2013; 107:608-12; PMID:23386397; http://dx.doi.org/10.1002/jso.23289
64. Mavros MN, Mayo SC, Hyder O, Pawlik TM. A systematic review: treatment and prognosis of patients with fibrolamellar hepatocellular carcinoma. J Am Coll Surg 2012; 215:820-30; PMID:22981432; http://dx.doi.org/10.1016/j.jamcollsurg.2012.08.001
65. Fouzas I, Sotiropoulos GC, Molmenti EP, Beckebaum S, Schmitz KJ, Broelsch CE, Lang H, Malagó M. "Preemptive" live donor liver transplantation for fibrolamellar hepatocellular carcinoma: a case report. Transplant Proc 2008; 40:3806-7; PMID:19100497; http://dx.doi.org/10.1016/j.transproceed.2008.09.050
66. Slater K, Bak TE, Kam I, Wachs ME. Living donor liver transplant for fibrolamellar hepatocellular carcinoma using a deceased donor graft to reconstruct inferior vena cava. Liver Transpl 2004; 10:555-6; PMID:15048801; http://dx.doi.org/10.1002/lt.20132
67. Mehrabi A, Kashfi A, Fonouni H, Schemmer P, Schmied BM, Hallscheidt P, Schirmacher P, Weitz J, Friess H, Buchler MW, et al. Primary malignant hepatic epithelioid hemangioendothelioma: a comprehensive review of the literature with emphasis on the surgical therapy. Cancer 2006; 107:2108-21; PMID:17019735; http://dx.doi.org/10.1002/cncr.22225
68. Lerut JP, Orlando G, Adam R, Schiavo M, Klempnauer J, Mirza D, Boleslawski E, Burroughs A, Sellés CF, Jaeck D, et al.; European Liver Transplant Registry. The place of liver transplantation in the treatment of hepatic epitheloid hemangioendothelioma: report of the European liver transplant registry. Ann Surg 2007; 246:949-57, discussion 957; PMID:18043096; http://dx.doi.org/10.1097/SLA.0b013e31815c2a70
69. Rodriguez JA, Becker NS, O'Mahony CA, Goss JA, Aloia TA. Long-term outcomes following liver transplantation for hepatic hemangioendothelioma: the UNOS experience from 1987 to 2005. J Gastrointest Surg 2008; 12:110-6; PMID:17710508; http://dx.doi.org/10.1007/s11605-007-0247-3
70. Emamaullee JA, Edgar R, Toso C, Thiesen A, Bain V, Bigam D, Kneteman N, Shapiro AM. Vascular endothelial growth factor expression in hepatic epithelioid hemangioendothelioma: Implications for treatment and surgical management. Liver Transpl 2010; 16:191-7; PMID:20104492; http://dx.doi.org/10.1002/lt.21964
71. Grotz TE, Nagorney D, Donohue J, Que F, Kendrick M, Farnell M, Harmsen S, Mulligan D, Nguyen J, Rosen C, et al. Hepatic epithelioid haemangioendothelioma: is transplantation the only treatment option? HPB (Oxford) 2010; 12:546-53; PMID:20887322; http://dx.doi.org/10.1111/j.1477-2574.2010.00213.x
72. Guiteau JJ, Cotton RT, Karpen SJ, O'Mahony CA, Goss JA. Pediatric liver transplantation for primary malignant liver tumors with a focus on hepatic epithelioid hemangioendothelioma: the UNOS experience. Pediatr Transplant 2010; 14:326-31; PMID:20051026; http://dx.doi.org/10.1111/j.1399-3046.2009.01266.x

73. Husted TL, Neff G, Thomas MJ, Gross TG, Woodle ES, Buell JF. Liver transplantation for primary or metastatic sarcoma to the liver. Am J Transplant 2006; 6:392-7; PMID:16426326; http://dx.doi.org/10.1111/j.1600-6143.2005.01179.x
74. Orlando G, Adam R, Mirza D, Soderdahl G, Porte RJ, Paul A, Burroughs AK, Seiler CA, Colledan M, Graziadei I, et al. Hepatic hemangiosarcoma: an absolute contraindication to liver transplantation--the European Liver Transplant Registry experience. Transplantation 2013; 95:872-7; PMID:23354302; http://dx.doi.org/10.1097/TP.0b013e318281b902
75. Walther A, Geller J, Coots A, Towbin A, Nathan J, Alonso M, Sheridan R, Tiao G. Multimodal therapy including liver transplantation for hepatic undifferentiated embryonal sarcoma. Liver Transpl 2014; 20:191-9; PMID:24142883; http://dx.doi.org/10.1002/lt.23773
76. Cruz RJ Jr., Ranganathan S, Mazariegos G, Soltys K, Nayyar N, Sun Q, Bond G, Shaw PH, Haberman K, Krishnamurti L, et al. Analysis of national and single-center incidence and survival after liver transplantation for hepatoblastoma: new trends and future opportunities. Surgery 2013; 153:150-9; PMID:23331862; http://dx.doi.org/10.1016/j.surg.2012.11.006
77. Austin MT, Leys CM, Feurer ID, Lovvorn HN 3rd, O'Neill JA Jr., Pinson CW, Pietsch JB. Liver transplantation for childhood hepatic malignancy: a review of the United Network for Organ Sharing (UNOS) database. J Pediatr Surg 2006; 41:182-6; PMID:16410130; http://dx.doi.org/10.1016/j.jpedsurg.2005.10.091
78. Faraj W, Dar F, Marangoni G, Bartlett A, Melendez HV, Hadzic D, Dhawan A, Mieli-Vergani G, Rela M, Heaton N. Liver transplantation for hepatoblastoma. Liver Transpl 2008; 14:1614-9; PMID:18975296; http://dx.doi.org/10.1002/lt.21586
79. Tajiri T, Kimura O, Fumino S, Furukawa T, Iehara T, Souzaki R, Kinoshita Y, Koga Y, Suminoe A, Hara T, et al. Surgical strategies for unresectable hepatoblastomas. J Pediatr Surg 2012; 47:2194-8; PMID:23217875; http://dx.doi.org/10.1016/j.jpedsurg.2012.09.006
80. Mazzaferro V, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? J Hepatol 2007; 47:460-6; PMID:17697723; http://dx.doi.org/10.1016/j.jhep.2007.07.004
81. Le Treut YP, Grégoire E, Belghiti J, Boillot O, Soubrane O, Mantion G, Cherqui D, Castaing D, Ruszniewski P, Wolf P, et al. Predictors of long-term survival after liver transplantation for metastatic endocrine tumors: an 85-case French multicentric report. Am J Transplant 2008; 8:1205-13; PMID:18444921; http://dx.doi.org/10.1111/j.1600-6143.2008.02233.x
82. Bonaccorsi-Riani E, Apestegui C, Jouret-Mourin A, Sempoux C, Goffette P, Ciccarelli O, Borbath I, Hubert C, Gigot JF, Hassoun Z, et al. Liver transplantation and neuroendocrine tumors: lessons from a single centre experience and from the literature review. Transpl Int 2010; 23:668-78; PMID:20478000; http://dx.doi.org/10.1111/j.1432-2277.2010.01086.x
83. Gedaly R, Daily MF, Davenport D, McHugh PP, Koch A, Angulo P, Hundley JC. Liver transplantation for the treatment of liver metastases from neuroendocrine tumors: an analysis of the UNOS database. Arch Surg 2011; 146:953-8; PMID:21844436; http://dx.doi.org/10.1001/archsurg.2011.186
84. Máthé Z, Tagkalos E, Paul A, Molmenti EP, Kóbori L, Fouzas I, Beckebaum S, Sotiropoulos GC. Liver transplantation for hepatic metastases of neuroendocrine pancreatic tumors: a survival-based analysis. Transplantation 2011; 91:575-82; PMID:21200365; http://dx.doi.org/10.1097/TP.0b013e3182081312
85. Le Treut YP, Grégoire E, Klempnauer J, Belghiti J, Jouve E, Lerut J, Castaing D, Soubrane O, Boillot O, Mantion G, et al.; For ELITA. Liver transplantation for neuroendocrine tumors in Europe-results and trends in patient selection: a 213-case European liver transplant registry study. Ann Surg 2013; 257:807-15; PMID:23532105; http://dx.doi.org/10.1097/SLA.0b013e31828ee17c
86. Foss A, Adam R, Dueland S. Liver transplantation for colorectal liver metastases: revisiting the concept. Transpl Int 2010; 23:679-85; PMID:20477993; http://dx.doi.org/10.1111/j.1432-2277.2010.01097.x
87. Hagness M, Foss A, Line PD, Scholz T, Jørgensen PF, Fosby B, Boberg KM, Mathisen O, Gladhaug IP, Egge TS, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg 2013; 257:800-6; PMID:23360920; http://dx.doi.org/10.1097/SLA.0b013e3182823957
88. Chapman WC. Liver transplantation for unresectable metastases to the liver: a new era in transplantation or a time for caution? Ann Surg 2013; 257:816-7; PMID:23532106; http://dx.doi.org/10.1097/SLA.0b013e3182908c8d
89. Kappel S, Kandioler D, Steininger R, Längle F, Wrba F, Ploder M, Berlakovich G, Soliman T, Hetz H, Rockenschaub S, et al. Genetic detection of lymph node micrometastases: a selection criterion for liver transplantation in patients with liver metastases after colorectal cancer. Transplantation 2006; 81:64-70; PMID:16421478; http://dx.doi.org/10.1097/01.tp.0000189711.98971.9c
90. Bompas E, Boillot O, Bringuier PP, Dumortier J, Blay JY. Imatinib in patients with metastatic gastrointestinal stromal tumours relapsing after hepatic transplantation. Eur J Cancer 2004; 40:1456-7; PMID:15177508; http://dx.doi.org/10.1016/j.ejca.2004.03.002
91. Serralta AS, Sanjuan FR, Moya AH, Orbis FC, López-Andújar R, Pareja EI, Vila JC, Rayón M, Juan MB, Mir JP. Combined liver transplantation plus imatinib for unresectable metastases of gastrointestinal stromal tumours. Eur J Gastroenterol Hepatol 2004; 16:1237-9; PMID:15489588; http://dx.doi.org/10.1097/00042737-200411000-00025
92. Cameron S, Ramadori G, Füzesi L, Sattler B, Gunawan B, Müller D, Ringe B, Lorf T. Successful liver transplantation in two cases of metastatic gastrointestinal stromal tumors. Transplantation 2005; 80:283-4; PMID:16041278; http://dx.doi.org/10.1097/01.TP.0000164141.34293.6B
93. Frilling A, Malago M, Testa G, Schleyer E, Grabellus F, Kronenberger R, Li J, Broelsch CE. Liver transplantation for metastasized extragastrointestinal stromal tumor: a case report and an overview of literature. Transplant Proc 2010; 42:3843-8; PMID:21094867; http://dx.doi.org/10.1016/j.transproceed.2010.06.016
94. Sumida W, Kaneko K, Tainaka T, Ono Y, Kiuchi T, Ando H. Liver transplantation for multiple liver metastases from solid pseudopapillary tumor of the pancreas. J Pediatr Surg 2007; 42:e27-31; PMID:18082688; http://dx.doi.org/10.1016/j.jpedsurg.2007.08.056
95. Kocman B, Jadrijevic S, Skopljanac A, Mikulic D, Gustin D, Buhin M, Matasic H, Gasparov S, Suknaic S, Ivanovic D. Living donor liver transplantation for unresectable liver metastases from solid pseudo-papillary tumor of the pancreas: a case report. Transplant Proc 2008; 40:3787-90; PMID:19100491; http://dx.doi.org/10.1016/j.transproceed.2008.03.169
96. Łagiewska B, Pacholczyk M, Lisik W, Cichocki A, Nawrocki G, Trzebicki J, Chmura A. Liver transplantation for nonresectable metastatic solid pseudopapillary pancreatic cancer. Ann Transplant 2013; 18:651-3; PMID:24280737; http://dx.doi.org/10.12659/AOT.889979
97. Starzl TE, Todo S, Tzakis A, Podesta L, Mieles L, Demetris A, Teperman L, Selby R, Stevenson W, Stieber A, et al. Abdominal organ cluster transplantation for the treatment of upper abdominal malignancies. Ann Surg 1989; 210:374-85, discussion 385-6; PMID:2673085; http://dx.doi.org/10.1097/00000658-198909000-00013
98. Abu-Elmagd KM. The small bowel contained allografts: existing and proposed nomenclature. Am J Transplant 2011; 11:184-5; PMID:21199364; http://dx.doi.org/10.1111/j.1600-6143.2010.03354.x
99. Calne RY, Pollard SG, Jamieson NV, Friend PJ, Rasmussen A, Neale G, Wight DG, Joysey V, Wraight EP. Intestinal transplant for recurring mesenteric desmoid tumour. Lancet 1993; 342:58-9; PMID:7686241; http://dx.doi.org/10.1016/0140-6736(93)91927-E
100. Chatzipetrou MA, Tzakis AG, Pinna AD, Kato T, Misiakos EP, Tsaroucha AK, Weppler D, Ruiz P, Berho M, Fishbein T, et al. Intestinal transplantation for the treatment of desmoid tumors associated with familial adenomatous polyposis. Surgery 2001; 129:277-81; PMID:11231455; http://dx.doi.org/10.1067/msy.2001.110770
101. Jovine E, Masetti M, Cautero N, Di Benedetto F, Gelmini R, Sassi S, Quintini C, Andreotti A, Begliomini B, Siniscalchi A, et al. Modified multivisceral transplantation without a liver graft for Gardner/Desmoid syndrome and chronic intestinal pseudo-obstruction. Transplant Proc 2002; 34:911-2; PMID:12034234; http://dx.doi.org/10.1016/S0041-1345(02)02665-9
102. Lauro A, Di Benedetto F, Masetti M, Cautero N, Ercolani G, Vivarelli M, De Ruvo N, Cescon M, Varotti G, Dazzi A, et al. Twenty-seven consecutive intestinal and multivisceral transplants in adult patients: a 4-year clinical experience. Transplant Proc 2005; 37:2679-81; PMID:16182782; http://dx.doi.org/10.1016/j.transproceed.2005.06.071
103. Moon JI, Selvaggi G, Nishida S, Levi DM, Kato T, Ruiz P, Bejarano P, Madariaga JR, Tzakis AG. Intestinal transplantation for the treatment of neoplastic disease. J Surg Oncol 2005; 92:284-91; PMID:16299803; http://dx.doi.org/10.1002/jso.20416
104. Tzakis AG, Kato T, Levi DM, Defaria W, Selvaggi G, Weppler D, Nishida S, Moon J, Madariaga JR, David AI, et al. 100 multivisceral transplants at a single center. Ann Surg 2005; 242:480-90, discussion 491-3; PMID:16192808
105. Olausson M, Friman S, Herlenius G, Cahlin C, Nilsson O, Jansson S, Wängberg B, Ahlman H. Orthotopic liver or multivisceral transplantation as treatment of metastatic neuroendocrine tumors. Liver Transpl 2007; 13:327-33; PMID:17318853; http://dx.doi.org/10.1002/lt.21056
106. Abu-Elmagd KM, Costa G, Bond GJ, Soltys K, Sindhi R, Wu T, Koritsky DA, Schuster B, Martin L, Cruz RJ, et al. Five hundred intestinal and multivisceral transplantations at a single center: major advances with new challenges. Ann Surg 2009; 250:567-81; PMID:19730240
107. Fishbein TM. Intestinal transplantation. N Engl J Med 2009; 361:998-1008; PMID:19726774; http://dx.doi.org/10.1056/NEJMra0804605
108. Farmer DG, Venick RS, Colangelo J, Esmailian Y, Yersiz H, Duffy JP, Cortina GR, Artavia K, Ngo K, McDiarmid SV, et al. Pretransplant predictors of survival after intestinal transplantation: analysis of a single-center experience of more than 100 transplants. Transplantation 2010; 90:1574-80; PMID:21107306; http://dx.doi.org/10.1097/TP.0b013e31820000a1

109. Cruz RJ Jr., Costa G, Bond GJ, Soltys K, Rubin E, Humar A, Abu-Elmagd KM. Modified multivisceral transplantation with spleen-preserving pancreaticoduodenectomy for patients with familial adenomatous polyposis "Gardner's Syndrome". Transplantation 2011; 91:1417-23; PMID:21512435; http://dx.doi.org/10.1097/TP.0b013e31821ab93b
110. Mangus RS, Tector AJ, Kubal CA, Fridell JA, Vianna RM. Multivisceral transplantation: expanding indications and improving outcomes. J Gastrointest Surg 2013; 17:179-86, discussion 186-7; PMID:23070622; http://dx.doi.org/10.1007/s11605-012-2047-7
111. Nikeghbalian S, Aliakbarian M, Shamsaeefar A, Kazemi K, Bahreini A, Malekhosseini SA. Multivisceral transplantation for the treatment of intra-abdominal tumors. Transplant Proc 2013; 45:3528-30; PMID:24314950; http://dx.doi.org/10.1016/j.transproceed.2013.09.002
112. Varkey J, Simrén M, Bosaeus I, Krantz M, Gäbel M, Herlenius G. Survival of patients evaluated for intestinal and multivisceral transplantation - the Scandinavian experience. Scand J Gastroenterol 2013; 48:702-11; PMID:23544434; http://dx.doi.org/10.3109/00365521.2013.775327
113. Akpinar E, Vargas J, Kato T, Smith L, Hernandez E, Selvaggi G, Nishida S, Moon J, Island E, Levi D, et al. Fecal calprotectin level measurements in small bowel allograft monitoring: a pilot study. Transplantation 2008; 85:1281-6; PMID:18475184; http://dx.doi.org/10.1097/TP.0b013e31816dcea2
114. Fishbein T, Novitskiy G, Mishra L, Matsumoto C, Kaufman S, Goyal S, Shetty K, Johnson L, Lu A, Wang A, et al. NOD2-expressing bone marrow-derived cells appear to regulate epithelial innate immunity of the transplanted human small intestine. Gut 2008; 57:323-30; PMID:17965060; http://dx.doi.org/10.1136/gut.2007.133322
115. Ashokkumar C, Gupta A, Sun Q, Ningappa MB, Higgs BW, Mazariegos G, Fazzolare T, Remaley L, Soltys K, Bond G, et al. Allospecific CD154+ T cells identify rejection-prone recipients after pediatric small-bowel transplantation. Surgery 2009; 146:166-73; PMID:19628070; http://dx.doi.org/10.1016/j.surg.2009.04.006
116. Andreev VP, Tryphonopoulos P, Blomberg BB, Tsinoremas N, Weppler D, Neuman DR, Volsky A, Nishida S, Tekin A, Selvaggi G, et al. Peripheral blood gene expression analysis in intestinal transplantation: a feasibility study for detecting novel candidate biomarkers of graft rejection. Transplantation 2011; 92:1385-91; PMID:22183870; http://dx.doi.org/10.1097/TP.0b013e3182370db1
117. Tsai HL, Island ER, Chang JW, Gonzalez-Pinto I, Tryphonopoulos P, Nishida S, Selvaggi G, Tekin A, Moon J, Levi D, et al. Association between donor-specific antibodies and acute rejection and resolution in small bowel and multivisceral transplantation. Transplantation 2011; 92:709-15; PMID:21804443; http://dx.doi.org/10.1097/TP.0b013e318229f752
118. Asaoka T, Sotolongo B, Island ER, Tryphonopoulos P, Selvaggi G, Moon J, Tekin A, Amador A, Levi DM, Garcia J, et al. MicroRNA signature of intestinal acute cellular rejection in formalin-fixed paraffin-embedded mucosal biopsies. Am J Transplant 2012; 12:458-68; PMID:22026534; http://dx.doi.org/10.1111/j.1600-6143.2011.03807.x
119. Girlanda R, Cheema AK, Kaur P, Kwon Y, Li A, Guerra J, Matsumoto CS, Zasloff M, Fishbein TM. Metabolomics of human intestinal transplant rejection. Am J Transplant 2012; 12(Suppl 4):S18-26; PMID:22759354; http://dx.doi.org/10.1111/j.1600-6143.2012.04183.x
120. Hibi T, Nishida S, Garcia J, Tryphonopoulos P, Tekin A, Selvaggi G, Weppler D, Levi DM, Ruiz P, Tzakis AG. Citrulline level is a potent indicator of acute rejection in the long term following pediatric intestinal/multivisceral transplantation. Am J Transplant 2012; 12(Suppl 4):S27-32; PMID:22812705; http://dx.doi.org/10.1111/j.1600-6143.2012.04155.x
121. Gerlach UA, Schoenemann C, Lachmann N, Koch M, Pascher A. Salvage therapy for refractory rejection and persistence of donor-specific antibodies after intestinal transplantation using the proteasome inhibitor bortezomib. Transpl Int 2011; 24:e43-5; PMID:21155900; http://dx.doi.org/10.1111/j.1432-2277.2010.01203.x
122. Abu-Elmagd KM, Wu G, Costa G, Lunz J, Martin L, Koritsky DA, Murase N, Irish W, Zeevi A. Preformed and de novo donor specific antibodies in visceral transplantation: long-term outcome with special reference to the liver. Am J Transplant 2012; 12:3047-60; PMID:22947059; http://dx.doi.org/10.1111/j.1600-6143.2012.04237.x
123. Hawksworth JS, Rosen-Bronson S, Island E, Girlanda R, Guerra JF, Valdiconza C, Kishiyama K, Christensen KD, Kozlowski S, Kaufman S, et al. Successful isolated intestinal transplantation in sensitized recipients with the use of virtual crossmatching. Am J Transplant 2012; 12(Suppl 4):S33-42; PMID:22947089; http://dx.doi.org/10.1111/j.1600-6143.2012.04238.x
124. Campbell P. Clinical relevance of human leukocyte antigen antibodies in liver, heart, lung and intestine transplantation. Curr Opin Organ Transplant 2013; 18:463-9; PMID:23838652; http://dx.doi.org/10.1097/MOT.0b013e3283636c71
125. Gerlach UA, Lachmann N, Sawitzki B, Arsenic R, Neuhaus P, Schoenemann C, Pascher A. Clinical relevance of the de novo production of anti-HLA antibodies following intestinal and multivisceral transplantation. [Epub ahead of print]. Transpl Int 2013; 27; PMID:24279605
126. Tait BD, Süsal C, Gebel HM, Nickerson PW, Zachary AA, Claas FH, Reed EF, Bray RA, Campbell P, Chapman JR, et al. Consensus guidelines on the testing and clinical management issues associated with HLA and non-HLA antibodies in transplantation. Transplantation 2013; 95:19-47; PMID:23238534; http://dx.doi.org/10.1097/TP.0b013e31827a19cc
127. Berger M, Zeevi A, Farmer DG, Abu-Elmagd KM. Immunologic challenges in small bowel transplantation. Am J Transplant 2012; 12(Suppl 4):S2-8; PMID:23181675; http://dx.doi.org/10.1111/j.1600-6143.2012.04332.x
128. Pichlmayr R, Grosse H, Hauss J, Gubernatis G, Lamesch P, Bretschneider HJ. Technique and preliminary results of extracorporeal liver surgery (bench procedure) and of surgery on the in situ perfused liver. Br J Surg 1990; 77:21-6; PMID:2302506; http://dx.doi.org/10.1002/bjs.1800770107
129. Hannoun L, Panis Y, Balladur P, Delva E, Honiger J, Levy E, Parc R. Ex-situ in-vivo liver surgery. Lancet 1991; 337:1616-7; PMID:1675751; http://dx.doi.org/10.1016/0140-6736(91)93321-Y
130. Raab R, Schlitt HJ, Oldhafer KJ, Bornscheuer A, Lang H, Pichlmayr R. Ex-vivo resection techniques in tissue-preserving surgery for liver malignancies. Langenbecks Arch Surg 2000; 385:179-84; PMID:10857488; http://dx.doi.org/10.1007/s004230050262
131. Tzakis AG, Tryphonopoulos P, De Faria W, Kato T, Nishida S, Levi DM, Madariaga J, Weppler D, Mittal N, Ruiz P, et al. Partial abdominal evisceration, ex vivo resection, and intestinal autotransplantation for the treatment of pathologic lesions of the root of the mesentery. J Am Coll Surg 2003; 197:770-6; PMID:14585412; http://dx.doi.org/10.1016/S1072-7515(03)00756-7
132. Quintini C, Di Benedetto F, Diago T, Lauro A, Cautero N, De Ruvo N, Romano A, Di Sandro S, Ramacciato G, Pinna AD. Intestinal autotransplantation for adenocarcinoma of pancreas involving the mesenteric root: our experience and literature review. Pancreas 2007; 34:266-8; PMID:17312468; http://dx.doi.org/10.1097/MPA.0b013e31802edee9
133. Amano H, Miura F, Toyota N, Wada K, Katoh K, Hayano K, Kadowaki S, Shibuya M, Maeno S, Eguchi T, et al. In situ surgical procedures for locally advanced pancreatic cancer: partial abdominal evisceration and intestinal autotransplantation. J Hepatobiliary Pancreat Surg 2009; 16:771-6; PMID:19902139; http://dx.doi.org/10.1007/s00534-009-0188-1
134. Malde DJ, Khan A, Prasad KR, Toogood GJ, Lodge JP. Inferior vena cava resection with hepatectomy: challenging but justified. HPB (Oxford) 2011; 13:802-10; PMID:21999594; http://dx.doi.org/10.1111/j.1477-2574.2011.00364.x
135. Hemming AW, Mekeel KL, Zendejas I, Kim RD, Sicklick JK, Reed AI. Resection of the liver and inferior vena cava for hepatic malignancy. J Am Coll Surg 2013; 217:115-24, discussion 124-5; PMID:23376028; http://dx.doi.org/10.1016/j.jamcollsurg.2012.12.003
136. Kato T, Lobritto SJ, Tzakis A, Raveh Y, Sandoval PR, Martinez M, Granowetter L, Armas A, Brown RS Jr., Emond J. Multivisceral ex vivo surgery for tumors involving celiac and superior mesenteric arteries. Am J Transplant 2012; 12:1323-8; PMID:22300017; http://dx.doi.org/10.1111/j.1600-6143.2011.03945.x
137. Tzakis AG, Pararas NB, Tekin A, Gonzalez-Pinto I, Levi D, Nishida S, Selvaggi G, Garcia J, Kato T, Ruiz P. Intestinal and multivisceral autotransplantation for tumors of the root of the mesentery: Long-term follow-up. Surgery 2012; 152:82-9; PMID:22386709; http://dx.doi.org/10.1016/j.surg.2012.01.003
138. Yamamoto Y. Ante-situm hepatic resection for tumors involving the confluence of hepatic veins and IVC. J Hepatobiliary Pancreat Sci 2013; 20:313-23; PMID:22696247; http://dx.doi.org/10.1007/s00534-012-0525-7
139. Mehrabi A, Fonouni H, Golriz M, Hofer S, Hafezi M, Rahbari NN, Weitz J, Büchler MW, Schmidt J. Hypothermic ante situm resection in tumors of the hepatocaval confluence. Dig Surg 2011; 28:100-8; PMID:21540594; http://dx.doi.org/10.1159/000323818
140. Kim Z, Jeong GA, Chung JC, Chu CW, Shin EJ, Kim HC. Ante-situm liver resection in recurrent liver metastasis from colorectal cancer. Hepatogastroenterology 2009; 56:508-11; PMID:19579631
141. Hemming AW, Langham MR, Reed AI, van der Werf WJ, Howard RJ. Resection of the inferior vena cava for hepatic malignancy. Am Surg 2001; 67:1081-7, discussion 1087-8; PMID:11730225
142. Fabre JM, Domergue J, Fagot H, Guillon F, Souche B, Joswik M, Baumel H. Leiomyosarcoma of the inferior vena cava presenting as Budd-Chiari syndrome. Vena cava replacement under veno-venous bypass and liver hypothermic perfusion. Eur J Surg Oncol 1995; 21:86-7; PMID:7851563; http://dx.doi.org/10.1016/S0748-7983(05)80076-9
143. Ciancio G, Gonzalez J, Shirodkar SP, Angulo JC, Soloway MS. Liver transplantation techniques for the surgical management of renal cell carcinoma with tumor thrombus in the inferior vena cava: step-by-step description. Eur Urol 2011; 59:401-6; PMID:20724064; http://dx.doi.org/10.1016/j.eururo.2010.07.028
144. Ciancio G, Vaidya A, Shirodkar S, Manoharan M, Hakky T, Soloway M. En bloc mobilization of the pancreas and spleen to facilitate resection of large tumors, primarily renal and adrenal, in the left upper quadrant of the abdomen: techniques derived from multivisceral transplantation. Eur Urol 2009; 55:1106-11; PMID:19167808; http://dx.doi.org/10.1016/j.eururo.2008.12.038

145. Ohira M, Nishida S, Tryphonopoulos P, Tekin A, Selvaggi G, Moon J, Levi D, Ricordi C, Ishiyama K, Tanaka Y, et al. Clinical-scale isolation of interleukin-2-stimulated liver natural killer cells for treatment of liver transplantation with hepatocellular carcinoma. Cell Transplant 2012; 21:1397-406; PMID:22469170; http://dx.doi.org/10.3727/096368911X627589

146. Chandrasekharan D, Issa F, Wood KJ. Achieving operational tolerance in transplantation: how can lessons from the clinic inform research directions? Transpl Int 2013; 26:576-89; PMID:23517251; http://dx.doi.org/10.1111/tri.12081

147. Hibi T, Nishida S, Levi DM, Selvaggi G, Tekin A, Fan J, Ruiz P, Tzakis AG. When and Why Portal Vein Thrombosis Matters in Liver Transplantation: A Critical Audit of 174 Cases. Ann Surg 2014; 259:760-6; PMID:24299686

148. Hibi T, Nishida S, Levi DM, Sugiyama D, Fukazawa K, Tekin A, Fan J, Selvaggi G, Ruiz P, Tzakis AG. Long-term deleterious effects of aortohepatic conduits in primary liver transplantation: proceed with caution. Liver Transpl 2013; 19:916-25; PMID:23897778; http://dx.doi.org/10.1002/lt.23689

149. Faraj W, Dar F, Bartlett A, Melendez HV, Marangoni G, Mukherji D, Vergani GM, Dhawan A, Heaton N, Rela M. Auxiliary liver transplantation for acute liver failure in children. Ann Surg 2010; 251:351-6; PMID:20054274; http://dx.doi.org/10.1097/SLA.0b013e3181bdfef6

150. Jeppesen PB. Modern treatment of short bowel syndrome. Curr Opin Clin Nutr Metab Care 2013; 16:582-7; PMID:23924950