# Liver Transplantation for Patients with Hepatobiliary Malignancies Other than Hepatocellular Carcinoma

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## EXECUTIVE SUMMARY

**Background** Controversy exists over the role of liver transplantation in patients with preexisting malignancies. Of primary concern is the possibility of tumor recurrence, a risk that must be weighed against the scarcity of available organs and the expense of organ transplantation. On the other hand, transplantation may offer the only opportunity for cure of the tumor and/or the underlying liver disease. This technology assessment reviews the available evidence regarding the outcomes of liver transplantation in patients with primary and metastatic liver tumors other than hepatocellular carcinoma (HCC), and patients with preexisting, non-hepatic malignancies.

**Methods** The primary sources of evidence for this report was the published literature identified by performing a search of the MEDLINE® database. Studies were categorized according to transplant center and author to eliminate duplicate reports. In addition, registry data from the United Network for Organ Sharing (UNOS) was used to estimate the frequency with which transplantation has been performed in the United States in patients with underlying malignancies during the past decade. UNOS, under contract with the Organ Procurement and Transplantation Network (OPTN), oversees a registry that includes information on almost every cadaveric transplant performed in the United States. However, the database is limited due to incomplete reporting of follow-up information.

**Results** One hundred ten reports met inclusion criteria. Forty-nine transplant centers published results that included a total of 1,011 transplant recipients. The largest experience was with cholangiocarcinoma and neuroendocrine tumors (total 822 patients). Other tumors included hemangioendothelioma as well as a variety of other sarcomas and rare tumors. Only a few reports described the outcomes in patients transplanted for metastatic disease and preexisting extrahepatic malignancy. All studies were individual case reports or case series. Details regarding patient and tumor characteristics, immunosuppression and outcomes of interest (patient, disease-free, and graft survival and quality of life) were reported with variable detail.

The UNOS Registry included 37,357 liver transplants performed in the United States between 1990 and 2001. Of these 889 patients had a malignancy at the time of transplant including 271 in which a malignancy other than HCC was described as the primary reason for transplantation. Despite an increase in the total number of transplants performed annually (from 2,177 in 1990 to 4,384 in 2000), the number of transplants performed for tumors other than HCC declined. In 1990, 52 recipients underwent OLT for non-HCC tumors compared to 13 in 2000. An average of 20 transplants was performed each year for the last five years, while an average of 32 transplants was performed each year from 1990-1995. Of over 200 living donor liver transplants to adult

recipients performed in the United States between 1997 and 2001, 9 have been to recipients with non-HCC tumors.

Patients and disease-free survival was generally lower than for transplantation performed for other indications. Nevertheless, long-term survival was described in individual patients with a variety of underlying malignancies. There were insufficient data to make definitive conclusions regarding patient, tumor, or transplant-related characteristics that predicted improved survival, although several were described in individual reports. Only a few reports described the effect of transplantation on quality of life. Most were in patients with neuroendocrine tumors in whom quality-of-life appeared to improve even in those with recurrent tumors.

No studies directly compared liver transplantation to other therapeutic options. As a result, it was not possible to directly compare the outcome of liver transplantation to other potential treatments. However, most patients undergoing transplantation were not considered to be eligible for or had failed other treatments, or were offered transplantation because it was considered to provide the only chance for cure of the tumor. In some cases the tumor was detected incidentally in patients who were undergoing transplantation for end-stage liver disease. The expected survival in such patients is typically less than three months.

**Conclusions** Liver transplantation for tumors other than HCC is performed uncommonly in the United States reflecting the infrequent occurrence of some of these tumors as well as the recognition that survival in such patients is poor compared to patients transplanted for nonmalignant causes. Nevertheless, long-term survivors continue to be described suggesting that transplantation may be beneficial in individual cases. The available evidence does not provide a clear profile of patients who might be optimal candidates for such therapy.

## BACKGROUND

Orthotopic liver transplantation (in situ replacement of a recipient's liver with a donor liver) has become the definitive therapy for patients with end stage liver disease due to a variety of causes. However, its role in the treatment of patients with preexisting malignancies is controversial. Included in this group are patients with primary and metastatic liver tumors, and those with a known history of extrahepatic malignancies. A number of studies have suggested that the risk of tumor recurrence (due to residual disease and the effects of immunosuppression) in these patients may be excessive to justify orthotopic liver transplantation (OLT). On the other hand, despite its many potential short and long-term complications, OLT may offer the only chance of cure for some patients while providing meaningful palliation for others.

Few transplant centers currently offer liver transplantation to patients with known hepatic malignancies other than hepatocellular carcinoma. However, a detailed understanding of patients with hepatic malignancies who might be optimal candidates for liver transplantation has become increasingly important. Technological advances are continuing to improve the ability to detect liver tumors in early stages offering the hope that patients with a relatively favorable prognosis can be identified. Furthermore, the growth of living donor transplantation has provided an additional source of organs. Potential living donor may be willing to provide an organ if it would offer a chance of a cure; these organs may otherwise have been unavailable. However, the chance for long-term survival must be sufficient to justify the operative risk of the donor.

Prognosis following transplantation may be influenced by several variables such as specific tumor characteristics, the type of transplant operation (e.g. standard OLT or multivisceral transplantation), and the use of neoadjuvant or adjuvant treatment strategies. The greatest experience has been with hepatocellular carcinoma in which long-term survival has been demonstrated following OLT in carefully selected patients. Neoadjuvant and adjuvant treatment strategies continue to be studied in an attempt to broaden the pool of potential candidates. The Medicare national coverage policy for liver transplantation for cancers was recently expanded to include coverage for hepatocellular carcinoma.

Much less is known regarding the efficacy of liver transplantation in patients with malignancies other than hepatocellular carcinoma. Thus, the primary aim of this report was to assess the available evidence regarding liver transplantation in these settings. Specific outcomes of interest included: patient and disease-free survival, graft survival, the effect on quality-of life, comparison to other available treatments for specific tumors, and comparison with the results of OLT for other indications.

# METHODS

## Sources of Evidence

The primary source of evidence for this report was the published literature. In addition, registry data from the United Network for Organ Sharing (UNOS) was used to estimate the frequency with which transplantation has been performed in the United States in patients with underlying malignancies during the past decade.

## Published Literature

The published literature regarding transplantation in the setting of malignancy was identified by performing a search of the MEDLINE® database. The search was restricted to articles published in English between January 1990 and July 2001. The final list of search terms was derived after consultation with hepatologists, oncologists and from terms identified from review articles. Search terms included: neoplasms, tumor$, canc$, carcin$, neoplas$, metasta$, malignan$, liver transplantation, liver transplant$, hepat$ transplant$, cholangiocarcinoma, hemangioendothelioma, hemangiosarcoma, leiomyosarcoma, lymphoma, neuroendocrine, ampudoma, islet cell. The MEDLINE® search was limited to human studies between 1990-2001, for adults aged 19 to 65.

### Inclusion criteria

Studies were included that described any outcomes following liver transplantation in adult patients (age >18) with primary or metastatic liver tumors (other than hepatocellular carcinoma), or in patients with a history of prior extrahepatic malignancy.

### Exclusion criteria

Studies were excluded if: they were published in languages other than English, focused exclusively on children (age <18), presented outcomes following liver transplantation that could not be differentiated from outcomes following other types of therapeutic interventions, described transplantation for a non-malignant tumor or premalignant state (eg, biliary papillomatosis), included only patients with concurrent hepatocellular carcinoma, presented outcomes following liver transplantation that were not distinguishable for individual tumors, presented only de novo cancers following liver transplantation, included tumors in the donor or donor graft, reviewed other sources of primary patient data or represented duplicate reports of previously-described patients.

Titles and abstracts were reviewed to identify relevant articles. The bibliographies from review articles and from reports that fulfilled the inclusion criteria were examined to identify other potentially relevant studies. All studies were reviewed in duplicate and consensus was achieved for all reports that were included in this evidence report based upon the inclusion and exclusion criteria described above.

Data extraction included information on the study location, patient characteristics, type of intervention (surgical procedure, neoadjuvant and adjuvant therapies), study duration, and outcomes of interest (patient survival, disease-free survival, graft-survival, quality of life, and comparisons to other therapies). The data-extraction instrument is included in Appendix I. Studies were categorized according to authors and transplant center to identify duplicate reports of the same patients. Duplicate reports were included if they provided additional follow-up data; however patients were counted only once. Emphasis was placed on the largest and most methodologically rigorous studies within each clinical category. Pooled data from studies describing outcomes on 10 or more patients was provided when possible by dividing the total number of patients reaching an endpoint in studies with adequate follow-up by the total number of patients transplanted.

### UNOS Registry

Information was requested from the United Network for Organ Sharing to provide an estimate of the frequency with which liver transplantation has been performed in the setting of malignancy in the United States during the last decade. The United Network of Organ Sharing (UNOS) under contract with the Organ Procurement and Transplantation Network (OPTN) oversees a registry that includes information on almost every cadaveric transplant performed in the United States. Some transplant centers have supplied data following living donor liver transplantation as well. In accordance with OPTN requirements, transplant centers report diagnostic information on patients at the time of listing for transplant, at the time of transplant, and at regular follow-up intervals after transplantation. Data collected include the recipient's primary liver disease and the presence of known malignancies at the time of listing. However, this database has limitations. It is generally believed that many liver transplant programs have been delinquent in submitting follow-up data. Detailed information on patients with prior non-hepatic malignancies was not available. It was not possible to correlate the patients included in the UNOS registry with those described in the literature. Further information about UNOS or the transplant registry can be found via the Internet at www.unos.org.

## RESULTS

### Study Characteristics

The Medline search revealed 1649 abstracts of which 269 were retrieved for further analysis. Review of the bibliographies of relevant studies produce an additional 23

studies. One hundred review articles were excluded because they did not contain primary data. Five studies were excluded because they focused on children. Forty-four studies were excluded because outcomes following liver transplantation could not be discerned from outcomes following other types of therapeutic interventions, 66 studies were excluded because outcomes following liver transplantation were not distinguishable for individual tumors, and 5 studies were excluded because transplantation was performed for a non-malignant tumor or premalignant state (eg, biliary papillomatosis). Thirteen studies were excluded because they described de novo cancers following OLT, and five studies were excluded because they described tumors in the donor or donor graft. Twenty-one studies were excluded because they included patients with concurrent hepatocellular carcinoma, 26 studies were excluded because they did not report outcomes following transplantation, and 6 studies were excluded because they represented duplicate reports of previously described patients. One hundred ten studies were included in the final analysis.

Forty-nine transplant centers published results following OLT for 1,011 patients with non-HCC malignancies. Twenty-four centers were in Europe, 22 in North America, 2 in Australia, and 1 in Asia. Forty-six percent of all series included transplants performed between 1980 and 1999. Twenty-three percent of all reports included transplants performed between 1966 and 1999, while 16% of all reports included transplants performed between 1970 and 1999. Only 9% included transplants performed from 1990 to 2000.

All publications were case reports or case series. Thirty-five were individual case reports. Twenty-three included a minimum of 10 recipients. The largest report included 207 patients from the Cincinnati Transplant Tumor Registry (now known as the Israel Penn International Transplant Registry).[1] Until 1999 all information reported to this registry was done so on a voluntary basis raising the possibility that there may have been bias toward reporting transplants with favorable outcomes. The reported malignancies included cholangiocarcinoma, neuroendocrine tumors, hemangioendothelioma and other sarcomas, metastatic disease, and preexisting extrahepatic malignancy, as well as a few more uncommon tumors. Outcomes of interest included patient survival, disease-free survival, graft survival, and quality of life following OLT.

The quality of reports varied. Although most included details regarding patient survival and disease-free survival, only a few described graft survival or quality of life. Details about stage of disease, adjuvant and neoadjuvant therapies, type of immunosuppression, and extended transplantations (those involving transplantation of additional organs or major resection of other organs in addition to the transplantation) were inconsistently included. Follow-up ranged from days to 132 months. However, several studies did not describe the follow-up period. The time interval defining “operative mortality” was frequently unspecified by study authors. When unspecified, deaths occurring within 30 days of transplantation were considered to represent operative mortality.

## UNOS Registry

The UNOS Registry included 37,357 liver transplants performed in the United States between 1990 and 2001. Of these 889 patients had a malignancy at the time of transplant, including 273 in which a malignancy other than HCC was described as the primary reason for transplantation. All transplants for malignancy other than HCC included in the UNOS Registry are summarized in Table 1. One hundred twelve transplants were performed for bile duct tumors, 59 for neuroendocrine tumors, 66 for mesenchymal tumors, 4 for metastatic disease, and 32 for other non-HCC tumors.

Despite an increase in the total number of liver transplants performed annually (from 2177 in 1990 to 4,384 in 2000), the number of transplants performed for tumors other than HCC declined (Figures 1 and 2). In 1990, 52 recipients underwent OLT for non-HCC tumors compared to13 in 2000. An average of 20 transplants was performed each year for the last five years, while an average of 32 transplants was performed each year from 1990-1995. The decrease was largely due to a reduction in the number of transplants being performed for patients with cholangiocarcinoma. For example, of the 75 transplants performed for cholangiocarcinoma in the last 10 years, 17 occurred in 1990, 13 in 1993, 8 in 1996, 7 in 1999, and 4 in 2000. A similar decrease has been observed for patients with leiomyosarcomas; 14 patients with leiomyosarcoma underwent OLT from 1990 to 1995 compared to only one from 1996 to 2000. Transplantation for hemangioendotheliomas has remained relatively stable with an average of 4 OLT performed each year. In contrast, twice as many transplants were performed each year for neuroendocrine tumors in the early 1990s compared to the last 5 years.

Of over 200 living donor liver transplants to adult recipients performed in the United States between 1997 and 2001 and reported to UNOS, 9 have been to recipients with non-HCC tumors. Three recipients were diagnosed with hemangioendothelioma, two with primary liver malignancy not otherwise specified, and one each with: cholangiocarcinoma, neuroendocrine tumor, spindle cell tumor, secondary liver malignancy not otherwise specified, and leiomyosarcoma.

The following sections will review the published experience with liver transplantation for malignancies other than hepatocellular carcinoma, including cholangiocarcinoma, neuroendocrine tumors, hemangioendothelioma and other sarcomas, metastatic disease, and preexisting extrahepatic malignancy. These non-HCC tumors were selected based on categories frequently described in the literature and groupings used in the UNOS Registry.

## CHOLANGIOCARCINOMA

Primary cholangiocarcinoma, a rare malignant mucin-producing adenocarcinoma arising from the biliary epithelium, accounts for 10-15% of all hepatobiliary tumors in the United

States.[2] Average five year-survival is approximately 5 to 10 %. Surgery offers the only possibility of a cure. Curative resection without transplantation has typically been reserved for patients who have no detectable affected lymph nodes or distant liver metastases, absence of vascular invasion, disseminated disease or involvement of adjacent organs. As a general rule, patients who have been offered liver transplantation have not been candidates other potentially curative surgical procedures.

Five orthotopic liver transplants were performed in the United States for cholangiocarcinoma in 2000 according to UNOS data. A total of 107 transplants have been performed since 1990. The annual number performed during the past 10 years ranged from 4 to 21, averaging 9 OLT per year. One living related liver transplant was performed for cholangiocarcinoma in 2000. In addition, two liver transplants were performed for cholangiocarcinoma in the setting of HCC.

Our literature search revealed 49 reports of cholangiocarcinoma from 28 transplant centers describing outcomes for 693 unique patients undergoing OLT or more extensive procedures. Studies are summarized in Table 2. There were no randomized controlled trials; all reports were case series that included a minimum of 1 and a maximum of 207 patients. Eighteen reports including at least 10 patients described outcomes for 555 OLT recipients (80% of all reported recipients)(Tables 3-5). Forty-nine reports described recipient survival while 47 described disease-free survival after OLT for cholangiocarcinoma. Information on quality of life after transplantation was included in only two reports. Five reports provided details about graft survival. Details regarding length of follow-up, tumor staging, tumor size, or other variables associated with prognosis following transplant were included sporadically. Nine transplant centers reported results for 173 multivisceral (cluster) transplants or transplants with abdominal exenteration (Table 6) in patients whose disease extended to organs adjacent to the liver. Cluster transplants involve transplantation of additional organs other than the liver.

Our literature search revealed 693 patients who received an OLT for cholangiocarcinoma. Four hundred thirty five transplants were performed in North America, 250 transplants were performed in Europe, and eight transplants were performed in Australia. The mean age of patients was 48 years. Sixty percent were male. Two hundred seven patients were reported in the Cincinnati Transplant Tumor Registry (known as the Israel Penn International Transplant Registry since 1999), a voluntary, international database of patients with cancer both before and after transplantation. The database was originally created in 1968 and contains data on transplant-related malignancies submitted from transplant centers and practitioners around the world. As mentioned above, a limitation of this database is that reporting was voluntary raising the potential for bias in the type of information that was reported.

**Patient Survival.** Overall survival for patients with cholangiocarcinoma was variable (Table 7). Median survival ranged from 3 to 58 months. The studies reporting 3[3] and 58[4] months were both individual case reports. The largest series reported a median survival of

8.4 months in 207 patients.[1] Fifteen reports of patient survival came from studies including a minimum of 10 recipients; their outcomes are summarized in Table 3. The approximate median survival combining the results of these 15 studies with a minimum of 10 patients (total 503 patients) was 11.8 months. The longest reported survivor was alive15 years following OLT without recurrence.[5]

Operative mortality was described in 17 reports. Combining the 15 studies that reported outcomes for a minimum of 10 patients (total 503 patients), an overall estimate of operative mortality was 14%. More recent studies appeared to have lower operative mortality rates.

Table 7 summarizes the 1-, 2-, 3-, and 5-year patient survival rates in all studies. In the largest series, 207 tumor registry patients were reported to have 1-year, 2-year, and 5-year survival rates of 72%, 48%, and 23%, respectively.[1] Fifteen studies that included a minimum of 10 patients with cholangiocarcinoma (total 503 patients) reported 1-year survival rates of 14 to 100% (Table 3). Studies that followed recipients over 24 months described 2-year survival rates ranging from 27% to 83%. Three-year survival rates varied between 6.3% and 92%. Twenty-one studies reported 5-year survival rates that range from 0% to 100%. Combining 15 studies that reported a minimum of 10 patients (total 503 patients), overall estimates of 1-, 3-, and 5-year patient survival rates were 63%, 46%, and 22%, respectively.

**Incidental Tumors.** Whether the prognosis is better in patients with cholangiocarcinoma detected incidentally at the time of transplant compared to those in whom it was detected preoperatively is uncertain. Twelve studies reported patient survival following standard OLT for 47 patients with incidentally diagnosed tumors (Table 8); three of these studies reported patient survival for a minimum of 10 patients with incidental tumors (Table 3). For all reports median survival ranged from 3 to 23 months. Combining three studies with a minimum of 10 patients (total 28 patients), median survival was 23 months for 28 patients.[6-8]

Operative mortality rates were 12 to 50%. One-year patient survival ranged from 0 to 100%. The largest series of 11 patients described a 1-year survival of 72%.[6] A series of 10 patients with PSC reported 100% 1-year survival, compared to a 33% survival in patients with PSC and known tumors.[7] Combining three studies with a minimum of 10 patients (total 28 patients), 1-year survival was 86%.[6-8]

Although 1-year survival for incidental tumors appeared to be better than the overall 1-year survival for all patients undergoing OLT for malignancies, 2-, 3- and 5-year survival rates were similar. The largest series of 11 patients reported 2-year survival of 54.6%, and 5-year survival of 26.7%.[6] A series of 10 patients reported 2- and 5-year survival of 83% and 83%, respectively.[7] The most recent series included 4 patients, all of whom died; two died in the early postoperative period and two died from disseminated cancer at 10

months and 16 months following OLT.[9] Combining 3 studies that included a minimum of 10 patients (total 28 patients), 5-year patient survival was 52%.[6-8]

One series of 7 patients with PSC and incidental proximal bile duct cancers suggested that survival correlated with Union Internationale Centre le Cancer (UICC) tumor stage.[8] Median survival for patients with stage I and II tumors was 37.8 months, compared to those with stage III at 19.6 months, and stage IV at 5.8 months. Patients with stage I and II tumors survived longer with 1-year, 3-year, and 5-year survival rates of 88.9%, 55.6%, and 44.4%, respectively. Patients with stage III and IV tumors had 75% and 33% 1-year survival rates, respectively, but no patients survived beyond 24 months.

**Peripheral Cholangiocarcinoma.** Five reports described patient survival for 45 patients with peripheral cholangiocarcinoma (Table 9). Median survival ranged from 5.5 months to 48 months in two reports that included a minimum of 10 patients (total 40 patients).[8, 10] Overall patient survival following OLT for peripheral cholangiocarcinoma was estimated to be 5.5 months when combining two studies with a minimum of 10 patients (total 40 patients)(Table 3). One-year survival ranged from 20.8% to 100% in all reports. Combining two reports with a minimum of 10 patients (total 40 patients) 1-year patient survival was 45%.[10, 11] The two largest series reported 3-year survival rates of 29% and 6.3%, and 5-year survival rates of 18% and 0%.[10, 11] When combining these reports 3- and 5-year patient survival rates were 18% and 10%, respectively.[10, 11]

**Central Cholangiocarcinoma.** Fifteen reports described patient survival for 167 patients with central cholangiocarcinomas. All studies are summarized in Table 10. Five reports included a minimum of 10 patients (Table 3).[5, 11-14] Median survival varied from 3 months to 58 months; a series of 32 patients reported a median survival of 19.68 months.[13] Combining all five studies with a minimum of 10 patients (total 127 patients), median survival was estimated at 19.4 months.

One-year patient survival ranged from 60% to 100%. Three-year and 5-year survival rates ranged from 21% to 100%, and 17% to 36%, respectively. The largest series of 38 patients described outcomes for OLT and cluster transplant at 1-year, 3-year, and 5-year as 60%, 32%, and 25%, respectively.[5] Patients with OLT had slightly better outcomes compared to those with OLT-Cl with 1-year, 3-year and 5-year survival rates of 59.3%, 36.2, and 36.2%, compared to 54.6%, 9.1%, and 9.1%, respectively.

Combining all five studies with more than 10 patients (total 127 patients), estimated 1-, 3-, and 5-year patient survival rates were 63%, 28%, and 12%, respectively. The most recent report included 8 patients and described 1-year, 3-year, and 5-year survival rates of 100%, 92%, and 36%, respectively.[15]

**Cholangiocarcinoma in the Setting of PSC.** Survival in patients with cholangiocarcinoma developing in the setting of primary sclerosing cholangitis (PSC) may be different than those with spontaneous cholangiocarcinoma. Such patients typically have end-stage liver disease in addition to the tumor. Fifteen case series reported patient survival for 81 patients with PSC and cholangiocarcinoma. All studies are summarized in Table 11. Three reports included a minimum of 10 patients (Table 3).[7, 16, 17] The largest series included 14 patients and reported a median survival of 11.1 months during 14 months of follow-up.[16] One-year patient survival ranged from 0% to 100%, with the largest study reporting a 1-year survival of 53%.[7] Combining three studies with a minimum of 10 patients (total 38 patients), 1-, 3-, and 5-year patient survival was estimated at 71%, 57%, and 54%, respectively.[7, 16, 17] Of all reported patients, four survived at least 60 months following OLT.

One study of 14 patients included 10 with incidental diagnoses.[7] Survival results were better for the incidental tumors with 1-year, 2-year, and 5-year survival rates of 100%, 83%, and 83%, respectively, than for the known tumors with 1-year, 2-year, and 5-year survival rates of 33%, 33%, and 0%, respectively. These results were further compared to survival for all OLT patients with PSC at the same transplant center where 1-year, 2-year, and 5-year patient survival rates were 90%, 86%, and 85%, respectively, and to all PSC patients without cholangiocarcinoma at 90%, 88%, and 87%, respectively.

Patient survival following OLT was compared to 1-, 3- and 5-year survival rates for 25 patients with cholangiocarcinoma and PSC not treated with OLT.[18] Those undergoing OLT had 1-, 3-, and 5-year survival rates of 75%, 38%, and 0%, respectively, while those not treated with OLT had survival rates of 28%, 9%, and 0%, respectively.[18] Details regarding the extent of disease and other clinically-relevant variables at the time of transplant were not available; thus, it is unclear whether the better survival in those undergoing OLT may have been due to selection bias. One center compared patient survival following OLT for those with PSC and cholangiocarcinoma to those with PSC without cholangiocarcinoma.[19] Those with cholangiocarcinoma had 1-, 3-, and 5-year survival rates of 70%, 0%, and 0%, respectively, while those without cholangiocarcinoma had 1-, 3-, and 5-year survival rates of 88%, 85%, and 62%, respectively.[19]

**Stage of Disease.** Details regarding stage of disease were reported sporadically. Nevertheless, several reports described an association between prognosis and tumor stage. All studies are summarized in Table 12. Four of these studies (Table 3) included a minimum of 10 patients (total 210 patients). Patients with T-in situ, T1, and T2 tumors had significantly better survival than T3 (adjacent structure involvement) lesions.[5] Survival for both known and incidental proximal tumors correlated strongly with UICC tumor stage.[8, 11] Patients with stage I and II tumors had a median survival of 37.8 months, with 1-year, 3-year, and 5-year survivals of 88.9%, 55.6%, and 44.4%, respectively. Patients with stage III tumors had a median survival of 19.6 months, with 1-year and 3-year survival rates of 75% and 0%, respectively. Those with stage IV tumors

had a median survival of 5.8 months, with 1-year and 3-year survival rates of 33.3% and 0%, respectively.

Positive surgical margins were associated with a significantly reduced survival in patients undergoing OLT and OLT-Cl for hilar cholangiocarcinoma.[5] A positive margin on frozen sections was the only predictor of a "survival disadvantage" in an evaluation of 9 possible covariates.[7] Another center reported survival for 9 patients with lymph node negative, hilar tumors to be 90%, 64.8%, and 64.8% at 1-year, 3-year, and 5-years, respectively.[20] These outcomes were compared to 16 patients at the same center who did not undergo OLT, none of whom lived longer than 5 years. Another report of 4 patients showed that the only patient without nodal involvement was alive at 5.5 years following OLT, all others died from recurrence within 6 months.[21]

One study evaluated the association between prognosis and histologic tumor grade. Three-year survival varied at 82% in grade I, 68% in grade II, and 50% in grade III tumors in an analysis of 15 patients.[22]

**Adjuvant and Neoadjuvant Therapies.** Six studies provided details regarding adjuvant or neoadjuvant therapies for 54 patients with cholangiocarcinoma (Table 13). Regimens varied and included: 5-FU and external beam radiation; postoperative radiation; preoperative irradiation; external beam irradiation and 5-FU followed by transcatheter irradiation boost; or 5-FU, leucovorin, interferon alpha, and external beam radiation. The level of detail included in most reports was not sufficient to reproduce the regimen. Median survival ranged from 11.1 to 22 months. The largest series reported a median survival of 11.1 months in 21 patients treated with 5-FU and external beam radiation.[1] When combining results from 3 studies that included a minimum of 10 patients (total 47 patients), median survival was estimated to be 17.6 months.[1, 12, 16] Estimates of 1-, 3-, and 5-year patient survival were 68%, 25%, and 24%, respectively, when combining results from the three studies that included a minimum of 10 patients (total 47 patients).

**Results Published in 1995 of Later.** Surgical techniques, methods for immunosuppression, and preoperative imaging have improved during the past decade raising the possibility that patients undergoing OLT for cholangiocarcinoma in recent years may have had a more favorable prognosis. Thirty-two reports published in 1995 or later described patient survival following OLT for cholangiocarcinoma. All studies are summarized in Table 14. Thirteen of these reports include a minimum of 10 patients (total 471 patients). Median survival ranged from 5.5 months to 58 months. The largest series of 207 patients undergoing transplantation between 1968 and 1997 reported median survival of 8.4 months.[1] The report of the most recent transplants included 11 patients undergoing OLT between 1993 and 1998, all of whom were alive at a median follow-up of 44 months.[23] Combining all studies with a minimum of 10 patients (total 471 patients), median patient survival was estimated at 11.5 months.

Reports after 1995 showed a slightly higher 1-year survival rate than all studies when combined, with the majority of reports ranging between 50% and 100%. Combining studies with a minimum of 10 patients (total 471 patients), 1-, 3-, and 5-year patient survival rates were estimated at 66%, 29%, and 23%, respectively (Table 3).[1, 5, 7, 8, 10, 11, 13, 17, 22-26] Combining two reports prior to 1995 that included more than 10 patients (total 38 patients) provided an estimated patient survival at 1-, 3-, and 5-years of 58%, 24%, and 27%, respectively.[6, 16] However, the two studies prior to 1995 included only 38 patients, while the studies from 1995 and later included a total of 471 patients. Although 1-year estimated patient survival was slightly higher than all studies and those prior to 1995, 3- and 5-year estimated survivals were comparable to earlier reports.

**Extended Transplantation.** Seven reports described patient survival for a total of 39 patients with extrahepatic disease in organs adjacent to the liver who underwent a more extended surgical procedures than routine OLT. All reports are summarized in Table 15. Two studies included a minimum of 10 patients (Table 3).[5, 27] The largest series of 11 patients with hilar tumors reported an operative mortality of 18% following OLT-Cl.[5] One-, 3-, and 5-year survival rates were 54.6%, 9.1%, and 9.1%, respectively. These results were compared to 28 patients undergoing OLT, who experienced 1-, 3-, and 5-year survival rates of 59.3%, 36.2%, and 36.2%, respectively. One other study included more than 10 patients but did not provide more than 1-year follow-up in the majority of patients.[27]

**Disease-Free Survival.** Disease-free survival following OLT for cholangiocarcinoma was variable. Forty-six reports described recurrence or disease-free survival. All studies are summarized in Table 16. Eighteen studies including a minimum of 10 patients are summarized in Table 4. Combining all 18 studies with a minimum of 10 patients (total 543 patients), recurrence occurred in 52%. Twelve studies included a minimum of 10 patients (total 196 patients). Mean follow-up was 53 months. One-year disease-free survival ranged from 40 to 72%. Five-year disease-free survival rates ranged from 0 to 39%. Combining all 18 reports with a minimal of 10 recipients (total 543 patients), 1-, 3-, and 5-year disease-free survival rates were estimated to be 58%, 22%, and 13%, respectively.

One report of 17 recipients with PSC reported a 79% recurrence rate with a mean time to recurrence of 14.3 months.[16] The largest report described outcomes in 207 patients in a tumor registry.[1] Fifty-one percent of all patients developed recurrence. Median time to recurrence was 9.7 months, and median time between recurrence and death was 2 months. Sixty-five percent of recurrences occurred within 1 year of OLT, and 85% occurred within 2 years of OLT.

**Incidental Tumors.** Eight reports described disease-free survival rates following OLT for 81 patients with cholangiocarcinoma; sixty-three recipients had concurrent PSC. Two studies included a minimum of 10 patients.[1, 6] All studies are summarized in Table 7. Recurrence was described in 0 to 63% of cases; the largest series of 43 incidental tumors reported a recurrence rate of 63%.[1] Eleven patients with incidental tumors experienced a

55% recurrence rate; this was compared to a recurrence rate of 86% in 7 patients with known tumors.[6] When both studies with a minimum of 10 patients were combined (total 61 patients), the estimated rate of recurrence was 61%.[1, 6] Five year disease-free survival rate was 5% in the largest series.[1]

**Peripheral Cholangiocarcinoma.** Three reports described recurrence and disease-free survival in 23 patients with peripheral tumors; one study included more than 10 patients. All studies are summarized in Table 18. In the largest series of 20 recipients, recurrence was described in 55% of OLT recipients, and in 44% in those following OLT-Cl.[10] One-, 3-, and 5-year disease-free survival rates were 67%, 31%, and 31%, respectively.

**Central Cholangiocarcinoma.** Twelve studies reported limited recurrence details following OLT for 165 patients with central cholangiocarcinoma. Most studies were individual reports or small series, which tended to report patients who had long-term disease free survival. All studies are summarized in Table 19. Five studies included a minimum of 10 patients (Table 4). Recurrence occurred in 53% of patients when combining results for five studies that included a minimum of 10 patients (total 140 patients). Follow-up periods without recurrence were documented up to 15 years following OLT. A report of fifteen patients who did not receive adjuvant or neoadjuvant therapy described a 53% rate of recurrence.[25] The estimated 5-year disease-free survival was 18% when combining results for five studies with a minimum of 10 patients (total 140 patients).

**Cholangiocarcinoma in the Setting of PSC.** Recurrence was described in 13 reports of 91 patients with PSC (Table 20). Four studies included a minimum of 10 patients. Recurrence rates range from 0% to 100%. An overall recurrence rate was estimated to be 53% after combining all four studies with a minimum of 10 patients (total 59 patients)(Table 4). Two reports described an 86%[6] and 100%[7] recurrence rate for patients with known tumors. One study compared this to a 55% recurrence rate in patients with incidentally diagnosed tumors.[6] One-year survival was 40% in a report of 17 patients.[16]

**Stage of Disease.** Thirteen reports described details regarding the stage of disease and recurrence in 344 patients with cholangiocarcinoma; six studies include a minimum of 10 patients. Table 21 summarizes all studies. Results were inconsistently reported. The largest series described recurrence rates in those with known tumors under 5 cm and those with known tumors over 5cm at 40% and 84%, respectively.[1] Median time to recurrence for known tumors <5cm was 6.5 months, and mean time to recurrence for known tumors >5cm was 4 months. A multivariate analysis showed that patients with more differentiated tumors experienced a better disease-free survival.[22]

**Adjuvant and Neoadjuvant Therapies.** Three reports described limited data regarding recurrence following OLT with adjuvant and neoadjuvant therapies (Table 22).

Two reports included more than 10 patients.[1, 16] One patient survived without recurrence 5 years following OLT after receiving treatment with external beam irradiation and 5-FU.[28] For 17 patients that received external beam radiation and 5-FU 8 weeks before OLT, 79% experienced recurrence with a 1-year survival rate of 40%.[16] Twenty-one patients treated with 5-FU and radiation therapy experienced a 52% recurrence rate.[1] An estimated recurrence rate was 63% when combining two studies with a minimum of 10 patients (total 38 patients).[1, 16] Disease-free survival at 1-, 3-, and 5-years was 40%, 10%, and 5%, respectively.

**Results Published in 1995 or Later.** Thirty reports describing disease-free survival have been published after 1995 (Table 23). Most reports published prior to 1995 were individual case reports, while those published after 1995 were generally larger case series. Thirteen studies published in 1995 or later included a minimum of 10 patients (total 471 patients). Recurrence rates varied extensively, from 0 to 100%. Combining all 14 studies with a minimum of 10 patients (total 471 patients) provided an estimated recurrence rate of 52% over a mean follow-up period of 38 months. One report described a 100% recurrence for 14 patients with known tumors at OLT.[7] The largest study of 207 patients reporting transplants performed from 1968 to 1997 described a recurrence rate of 51%. Combining all studies published in 1995 or later with a minimum of 10 patients (total 471 patients), estimated 1-, 3-, and 5-year disease-free survival rates were 69%, 16%, and 11%, respectively. Combining all 5 studies with more than 10 patients (total 72 patients) published prior to 1995, estimated recurrence was 51%. For studies prior to 1995, estimated 1-, 3-, and 5-year disease-free survival rates were 65%, 75%, and 55%, respectively.

**Extended Transplantation.** Three reports described recurrence following cluster transplantation (Table 24).[24, 29, 30] One of these studies included a minimum of 10 patients.[24] The largest study reports 57% recurrence in 20 patients.[24] Three patients were alive without recurrence at 52 to 59 months. Two reports of recurrence with death were described at 21 months and 48 months following OLT-Cl.[29, 31]

**Graft Survival.** Five reports include details regarding graft survival; two of these reports included a minimum of 10 patients.[23, 32] All studies are summarized in Table 25. One-year graft survival ranged from 67-100%. The largest series reported a 91% 1-year graft survival in 13 patients.[33] Etiologies for the five graft failures include hepatic artery thrombosis (2), chronic rejection (2), and diagnosis not stated (1). Survival following retransplant was reported between 7 to 76 months, with 4 of 5 patients alive at time of report. One patient retransplanted for chronic rejection at 37 months died with recurrence at 58 months following OLT.[4]

**Quality of Life.** Two reports included information regarding quality of life following transplantation for cholangiocarcinoma (Table 26). A report of two patients with hilar tumors reported the recipients in “good health” at follow-up intervals of 18 and 28

months.[34] Another report described the working status of six recipients.[35] Four of the six were working at the time of follow-up. Two patients described as “good” were working. Two patients described as “excellent” were working, and two others described as “excellent” were not working. One patient died 6 months following OLT with diffuse metastasis but was “excellent for 4 months.” Another patient was “excellent” for 6 months and then developed recurrence.

**Comparison of Transplantation to Other Treatments.** Liver transplantation has not been compared directly to other treatment options for patients with cholangiocarcinoma. In most reports liver transplantation was performed in patients who were ineligible or had not responded to other treatments. A few reports retrospectively compared outcomes for a minimum of 10 patients following OLT with those following partial hepatectomy for cure performed at their transplant centers. However, these reports did not adjust for potential differences in stage of disease between those receiving OLT and those undergoing resection.

- 20 patients undergoing liver transplantation for intrahepatic tumors had 1-year, 3year, and 5-year survival rates of 10%, 29%, and 18%, respectively. Patients with intrahepatic tumors treated by resection had 1-year, 3-year, and 5-year survival rates of 60%, 37%, and 31%.[10]
- 12 patients with extrahepatic tumors treated with postoperative radiation and OLT had 1-year, 3-year, and 5-year survival rates of 68%, 22%, and 22%, were compared to survival rates to those receiving “conservative therapy” with 1-year, 3-year, and 5-year survivals of 28%, 8%, and 0%.[12]
- 14 patients undergoing extended bile duct resection reported a 4-year survival including postoperative mortality of 30% compared to patients undergoing right trisegmentectomy with 4-year survival of 59%.[26]
- 25 patients with proximal bile duct cancers had 1-year, 3-year, and 5-year survival rates of 60%, 21.4%, and 17.1%. The resected group showed 1-year survival of 65% and 5-year survival of 27.1%.[8]

**Summary.** One hundred seven transplants have been performed in the United States since 1990 for cholangiocarcinoma. Our search revealed 49 reports of liver transplantation for cholangiocarcinoma from 28 transplant centers describing outcomes for 693 patients undergoing OLT or extended procedures (Table 2). All studies were individual case reports, or case series. Eighteen included at least 10 patients (total 555 patients)(Tables 3-5). Studies varied widely regarding length of follow-up and details of reported outcomes. Nevertheless, the available data support the following general conclusions:

- Median patient survival was 11.8 months when combining all studies that included a minimum of 10 patients. Overall 1-, 3-, and 5-year patient survival was 63%, 46%, and 22%, respectively. For comparison, 1-, 3-, and 5-year patient survival following liver transplantation for chronic hepatitis C is 79, 79, and 66, respectively, and 1-, 5-, and 7-year patient survival following transplantation for alcoholic liver disease is 84, 72, and 63%, respectively.

- Recurrence was reported in 52% of patients when combining all studies that included a minimum of 10 patients (total 543 patients). The mean follow-up was 53 months. Overall 1-, 3-, and 5-year disease-free survival in all patients was 58%, 22%, and 13%, respectively.

- Graft survival was reported in two studies including a minimum of 10 patients. One-year graft survival was 92% in 24 patients.

- There were insufficient data describing quality of life following OLT forcholangiocarcinoma to make general conclusions.

- There were insufficient data to make firm conclusions regarding patient, tumor, or transplant characteristics that were associated with a favorable prognosis. However, limited data suggested that one-year patient survival was better in patients with tumors diagnosed incidentally compared to those in whom it was diagnosed preoperatively. In addition, prognosis appeared to be better in patients with negative lymph nodes and no residual disease after surgery.

- Adjuvant and neoadjuvant chemotherapy did not appear to improve survival.

- Patient and disease-free survival did not appear to improve during the last decade.

## NEUROENDOCRINE TUMORS

Neuroendocrine tumors are uncommon tumors that are capable of secreting peptide hormones into the circulation, which can result in a variety of clinical signs and symptoms. The most common neuroendocrine tumor causing liver metastases is carcinoid, occurring in 85% of cases followed for 10 to 20 years.[36] Metastatic disease in the liver is rarely solitary, and only a small number of patients have lesions that are sufficiently localized to allow curative resection. In some patients, metastases may develop many years after resection of the primary tumor. Several other neuroendocrine

tumors have been described that secrete a variety of peptide hormones such as glucagon and vasoactive intestinal polypeptide.

Neuroendocrine tumors tend to recur, and patients ultimately die of slow growing metastases. Principal treatment options include medical therapy aimed at reducing tumor size and inhibiting hormone secretion, and invasive methods such as infra-arterial infusion of cytotoxic drugs, hepatic artery embolization, or irradiation and surgical resection or transplantation. The 5-year survival rate of patients with liver metastases without resection varies between 13 to 43% depending on the degree of differentiation for metastatic disease, with occasional survival extending 20 years.[36] Curative liver resection is the best treatment, with a 4-year survival rate of 73%, but this is possible in only 10% of cases.[37] Clinical trials of chemotherapy have been scarce, and have primarily included streptozotocin. When used alone streptozotocin is associated with a response in 30 to 50% of patients with a median response duration of 13 months.[38]

UNOS reports the performance of three orthotopic liver transplants for metastatic carcinoid tumors in 2001. A total of 17 have been performed during the past 10 years. Eighteen transplants for other metastatic neuroendocrine tumors have been performed during this same time period. One transplant for a metastatic neuroendocrine tumor was performed with a living donor graft in 1998. Between 1990 and 2000, UNOS reports transplants for the following specific neuroendocrine tumors: neuroendocrine (18), carcinoid (17), islet cell tumor (8), gastrinoma (7), VIPoma (5), insulinoma (2), and glucagonoma (1).

The published literature included 129 patients in 26 reports of liver transplantation from 22 centers (Table 26). Ninety transplants were performed in Europe and 39 were performed in North America. Metastatic neuroendocrine tumors in these reports include: carcinoid (83), neuroendocrine (44), glucagonoma (34), islet cell tumor (28), gastrinoma (12), ampudoma (5), nonfunctioning neuroendocrine (4), and VIPoma (3). The mean age was 45 years. Fifty-three percent were male.

**Patient Survival.** Patient survival following OLT for neuroendocrine tumors was variable (Table 27). Median survival ranged from 1.7 to 33 months. The studies reporting 1.7[39] and 33 months[40] were an individual case report and a series of 10 patients. Five reports of patient survival came from studies including a minimum of 10 recipients (total 81 patients); their outcomes are summarized in Table 3. The approximate median survival combining the results of these 5 studies reporting a minimum of 10 patients (total 81 patients) was 30.7 months.

Operative mortality ranged from 0 to 50%, with the largest study reporting an operative mortality of 19%.[41] The approximate operative mortality was 15% combining the results of 5 studies that included a minimum of 10 patients (total 81 patients).

Survival at 1-, 2-, 3-, and 5-years was 58%, 51%, 47%, and 36%, respectively, in the largest series of 31 patients.[41] One study of 15 patients with different types of neuroendocrine tumors reported a 5-year survival rate of 86.7%.[11] Combining the five studies that reported outcomes for a minimum of 10 patients (total 81 patients), an overall estimate of 1, 3-, and 5-year patient survival was 64%, 60%, and 53%, respectively. Patients with carcinoid tumors appeared to have a significantly better prognosis than those with other types of neuroendocrine tumors.

**Stage of Disease.** Stage of disease was not routinely identified in patients with neuroendocrine tumors. When reported, patient survival for specific stage of disease could not be separated from outcomes of all patients undergoing OLT.

**Adjuvant and Neoadjuvant Therapies.** Twelve studies report details regarding adjuvant or neoadjuvant therapies. Table 27 summarizes all studies. Two reports included a minimum of 10 patients.[41, 42] Reported therapies include: adriamycin and tumor embolization; 5-FU and streptozocin; indomethacin, steroids, pancreatic enzymes, somatostatin, and alpha interferon; somatostatin and local resection; radiation, 5-FU, and streptozocin; hepatic artery chemoembolization, streptozocin, and doxorubicin; and chemoembolization. Each of these regimens was used in a small number of patients using different dosing regimens, and none was directly compared. Survival results for patients receiving adjuvant and neoadjuvant therapies were not reported separately from all patients undergoing OLT for neuroendocrine tumors.

**Results Published in 1995 or Later.** Thirteen reports of OLT for neuroendocrine tumors in 108 patients were published in 1995 or later (Table 27). Five of these studies included a minimum of 10 patients (total 81 patients), and represent all studies reported since 1990 with a minimum of 10 recipients. It is difficult to compare the results to earlier reports since no report prior to 1995 included more than 4 patients.

**Extended Transplantation.** Seventeen reports described cluster transplant or extended surgery for neuroendocrine tumors (Table 27). One of these reports included a minimum of 10 patients, however, outcomes were not reported separately from patients underling routine OLT.[24]

**Disease-Free Survival.** Twenty-three studies reported disease-free survival or recurrence following OLT for neuroendocrine tumors (Table 28). Five reports included a minimum of 10 patients (total 81 patients). Series including a minimum of 10 transplant recipients reported recurrence rates of 39 to 80%. The largest series of 31 patients reported a recurrence rate of 39%.[41] Recurrence occurred in approximately 52% of patients when combining all 5 studies with a minimum of 10 patients (total 81 patients).

A retrospective analysis of 22 French transplant centers in a series of 31 patients reported an overall disease-free survival of 17% (we were asked to confirm the time frame – the

authors of the article did not report a disease-free survival).[41] Five patients survived more than 60 months.

One report described outcomes separately for 6 patients with carcinoid and 5 patients with other neuroendocrine tumors.[42] Recurrence was 83% for patients with carcinoid tumors and 20% for patients with ampudomas. Overall median time to recurrence was 14 months. Carcinoid tumors recurred at a mean of 9 months.

**Adjuvant and Neoadjuvant Therapies.** Nine studies report details regarding adjuvant or neoadjuvant therapies and disease-free survival outcomes (Table 28). Reported therapies include: adriamycin and tumor embolization; 5-FU and streptozocin; indomethacin, steroids, pancreatic enzymes, somatostatin, and alpha interferon; somatostatin and local resection; radiation, 5-FU, and streptozocin; hepatic artery chemoembolization, streptozocin, and doxorubicin; and chemoembolization. Each of these regimens was used in a small number of patients using different dosing regimens, and none were directly compared to each other. Disease-free survival results for patients receiving adjuvant and neoadjuvant therapies were not reported separately from all patients undergoing OLT for neuroendocrine tumors.

**Extended Transplantation.** Seventeen reports described cluster transplant or extended surgery for neuroendocrine tumors. One of these reports included a minimum of 10 patients, however, outcomes were not reported separately from patients undergoing routine OLT.[24]

**Graft Survival.** Four reports described 6 events of graft failure following OLT (Table 29). Primary graft failure led to repeat OLT at day 6 day and month 8 in 2 patients,[43] and repeat liver-islet cell transplant was performed at day 2. Portal vein thrombosis on day 83 required retransplantation.[43] One patient receiving OLT-Cl required retransplant of small intestines 48 hours following OLT and died 4 days later from sepsis.[44]

**Quality of Life.** Fourteen studies reported quality of life following OLT for neuroendocrine tumors (Table 30). Two studies included a minimum of 10 patients (total 21 patients).[40, 42] Periods of symptom-free survival following OLT ranged from 5 months to 106 months. Studies with longer follow-ups demonstrated palliation of clinical symptoms, although most patients were still affected by tumor recurrence. One report described four recipients who returned to work following OLT, including an attorney, an architect, and a housewife.[45]

**Comparison to other Treatment Modalities.** Liver transplantation has not been directly compared to other treatment options for patients with neuroendocrine tumors.

**Summary.** Fifty-eight transplants have been performed in the United States since 1990 for neuroendocrine tumors. Our search revealed 26 reports of liver transplantation for neuroendocrine tumors from 22 transplant centers describing outcomes for 129 patients

(Table 26). All studies were individual case reports or case series. Five included at least 10 patients (total 81 patients). Studies varied widely regarding length of follow-up and details of reported outcomes. Nevertheless, the available data support the following general conclusions:

- Median patient survival was 30.7 months when combining all studies that included a minimum of 10 patients (total 81 patients). Overall 1-, 3-, and 5-year patient survival was 64%, 60%, and 53%, respectively. For comparison, 1-, 3-, and 5-year patient survival following liver transplantation for chronic hepatitis C is 79, 79, and 66, respectively, and 1-, 5-, and 7-year patient survival following transplantation for alcoholic liver disease is 84, 72, and 63%, respectively.

- Recurrence was reported in 52% of patients when combining all studies that included a minimum of 10 patients (total 81 patients). Not enough details are provided to estimate 1-, 3-, and 5-year disease-free survival following OLT for neuroendocrine tumors.

- Graft survival was reported in four reports including a total of 17 patients. None of these reports included a minimum of 10 patients. Six patients experienced graft failure.

- Fourteen reports included details describing quality of life following OLT for neuroendocrine tumors. Two studies included a minimum of 10 patients (total 21 patients). Periods of symptom-free survival following OLT ranged from 5 to 106 months. Studies with longer follow-up periods demonstrated palliation of clinical symptoms, although most patients were still affected by tumor recurrence.

- There were insufficient data to make firm conclusions regarding patient, tumor, or transplant characteristics that were associated with a favorable prognosis.

- There were insufficient data to make conclusions regarding affect of adjuvant and neoadjuvant therapies, or extended transplantation, or prognosis following OLT.

## EPITHELIOID HEMANGIOENDOTHELIOMA

Tumors that arise from the soft tissues are classified according to the mesenchymal tissue they most closely resemble histologically. In this section we assess the evidence for OLT

as treatment for hepatic epithelioid hemangioendothelioma; all other mesenchymal tumors of the liver are addressed in a separate section of this report.

The nomenclature of mesenchymal tumors is evolving with an increased understanding of the molecular, histologic, and clinical features that distinguish different types of tumors. Because the categorization of hepatic epithelioid hemangioendothelioma has remained consistent during this evolution, the body of evidence is more homogeneous than that for other mesenchymal tumors.

Hepatic epithelioid hemangioendothelioma is a rare, low-grade malignant neoplasm of vascular origin. An association with oral contraceptive use has been reported. Right upper quadrant abdominal pain and abdominal discomfort are the most common symptoms at presentation. Other nonspecific presenting complaints often include weight loss, weakness, and fatigue.

The staging of hepatic epithelioid hemangioendothelioma incorporates tumor size, pathologic grade, histologic subtype, and presence of metastases. A close correlation exists between tumor stage at presentation and outcome. The American Joint Committee on Cancer (AJCC) staging system incorporates grade, size, depth, nodes, and presence of metastases.

Because hepatic epithelioid hemangioendothelioma has an unpredictable course and prognosis, treatment modalities are not standardized. Partial hepatectomy, chemotherapy, and radiotherapy have all been used. The wide variability in natural history of the disease limits assessment of treatment efficacy. Surgical resection is thought to be the treatment of choice, however reports are limited. Twenty percent of patients die within the first 2 years after presentation, whereas 20% have extended survival for 5 to 28 years, irrespective of treatment.[46]

UNOS Registry data provides general details regarding soft tissue tumors, however the evolving nomenclature for mesenchymal tumors limits the interpretation to specific histopathologic tumors. Over the last decade mesenchymal tumors have been included under the categories hemangiosarcoma-hepangiosarcoma-hemagioendothelioma, epithelioid hemangioendothelioma, hemangioendothelioma-hemangiosarcoma, spindle cell tumor, leiomyosarcoma, sarcoma with metastases, metastatic GIST, and lymphoma. It is unclear if the categories “recurrent disease” and “metastatic disease” include mesenchymal tumors as well.

According to UNOS data, the only OLT for “epithelioid hemangioendothelioma” was performed in 1997. Forty-five transplants have been performed for a diagnosis category of “hemangioendothelioma-hemangiosarcoma” and 1 for the category “hemangiosarcoma-hepangiosarcoma-hemangioendothelioma” since 1990. Two of those

with "hemangioendothelioma-hemangiosarcoma" received liver grafts from living donors (22% of all living donors for non-HCC tumors).

Fifteen reports described the international experience with transplantation for mesenchymal tumors. Eight reports from seven transplant centers described outcomes for 42 patients with hepatic epithiolioid hemangioendothelioma treated with OLT (Table 31). Thirty-nine transplants were performed in North America, 10 in Europe, and 1 in Asia. The largest study included 16 patients.[47] One series included 7 patients referred from different institutions for pathology review.[48] The mean age was 41 years. Fifty-five percent were male.

**Patient Survival**. Eight studies reported patient survival in 42 patients (Table 32). One study included a minimum of 10 recipients.[47] Overall patient survival following OLT for hepatic epithelioid hemangioendothelioma was inconsistently reported. Follow-up ranged from 9 to 65 months. Median survival was 69 months (range 40-120 months) in a report of 7 patients in a pathology database.[48] One-year survival ranged from 88 to 100%. Three-year survival ranged from 73 to 100%. Five-year survival ranged from 48 to 71.3%. The largest series reported 1-, 3-, and 5-year survival rates of 100%, 85.7%, and 71.3%, respectively.[47] The longest survival was reported at 11 years following OLT.[48]

**Stage of Disease.** One study of 16 patients described stage of disease.[47] Fourteen patients had Stage IVa disease and two had Stage IVb disease. However, patient survival was not reported according to tumor stage.

**Adjuvant and Neoadjuvant Therapies.** Eight patients in four reports received adjuvant or neoadjuvant therapies.[47-49] Five received adriamycin based chemotherapy regimens and three received external beam radiation.[47] However, reported results did not distinguish those receiving neoadjuvant therapies from those who do not.[47] One patient who underwent liver transplant after receiving interferon 8 months prior to OLT was alive 42 months following OLT.[48] One patient received postoperative chemotherapy for lymph node metastases and was alive at 40 months without recurrence.[48] One patient treated with devascularization surgery prior to OLT was alive at 2 years with metastatic disease throughout the mesentery.[49]

**Results Published in 1995 or Later.** Thirty-eight of 42 patients (90%) patients were described in literature published in 1995 or later. Outcomes from these patients were not different from the overall analysis of all 42 patients.

**Extended Transplantation.** Use of cluster transplant or extended transplant with abdominal exenteration has not been reported for the treatment of hepatic epithelioid hemangioendothelioma.

**Disease-Free Survival**. Eight reports described disease-free survival following OLT for hemangioendothelioma (Table 33). Disease-free survival following OLT for hepatic epithelioid hemangioendothelioma was variable. Rates of recurrence from studies reporting outcomes for more than 2 patients ranged from 55 to 60%, with the largest series reporting 55% recurrence in 16 patients at a median of 52 months of follow-up.[47] One-, 3-, and 5-year disease-free survival rates were 81.3%, 68.8%, and 60.2%, respectively. Median time to death from metastatic disease was 43 months following OLT.[47]

**Stage of Disease.** One study of 16 patients undergoing OLT for hepatic epithelioid hemangioendothelioma described stage of disease.[47] Fourteen patients had Stage IVa disease and 2 had Stage IVb disease. However, disease-free survival was not reported according to tumor stage.

**Adjuvant and Neoadjuvant Therapies.** Eight patients in four reports received adjuvant or neoadjuvant therapies for hemangioendothelioma (Table 33).[47-49] However, disease-free survival was not routinely reported. One patient who underwent devascularization surgery prior to transplantation was alive at 2 years despite visualization of metastatic nodules in the mesentery at time of OLT.[49] One patient undergoing OLT and chemotherapy was alive with no evidence of disease at 40 months.[48] One patient who received postoperative chemotherapy for lymph node metastases was disease-free at 40 months.[48]

**Results Published in 1995 or Later.** Thirty-eight of 42 patients (90%) patients were described in literature published in 1995 or later. All studies are summarized in Table 33. Disease-free survival for these patients was not different from overall analysis of all 42 patients.

**Extended Transplantation.** Use of cluster transplant or extended transplant with abdominal exenteration has not been reported as a treatment for hepatic epithelioid hemangioendothelioma.

**Graft Survival**. One report described graft survival in 16 transplant recipients (Table 34). Three patients required retransplantation. Reasons for graft failure included: a recurrence of disease in the graft at 4 years, a nonfunctioning graft 2 days postoperatively, and a nonfunctioning graft 4 days postoperatively.

**Quality of Life.** Two reports addressed quality of life issues following OLT (Table 35). One patient was alive with residual, "asymptomatic" disease 32 months following OLT.[50] Two additional patients had "normal quality of life" at 9 month and 44 month follow-ups, respectively.[4]

**Comparison of Transplantation to Other Treatments.** Liver transplantation has not been directly compared to other therapies for patients with hepatic epithelioid hemangioendothelioma.

**Summary.** At least 66 liver transplantation have been performed in the United States since 1990 for soft tissue tumors. Forty-five of these transplants were performed for "hemangioendothelioma-hemangiosarcoma." Our search revealed 15 reports of liver transplantation for soft tissue tumors. Eight reports from seven transplant centers describe outcomes for 42 patients with hepatic epithelioid hemangioendothelioma (Table 31). All studies were individual case reports or case series. Only one study included a minimum of 10 patients (total 16 patients). Studies varied widely regarding length of follow-up and details of reported outcomes. Nevertheless, the available data support the following general conclusions:

- Median survival ranged from 9 to 65 months. The largest study did not report median survival. Overall 1-, 3-, and 5-year survival rates were 100%, 85.7%, and 71.3%, respectively. For comparison, 1-, 3-, and 5-year patient survival following liver transplantation for chronic hepatitis C is 79, 79, and 66, respectively, and 1-, 5-, and 7-year patient survival following transplantation for alcoholic liver disease is 84, 72, and 63%, respectively.

- Recurrence was reported in 55% of patients in the largest series (total 16 patients) with a median follow-up of 52 months. One, 3-, and 5-year disease-free survival was 81.3%, 68.6%, and 60.2%, respectively.

- Graft survival was reported in one study that included a minimum of 10 patients. Three of 16 patients required retransplantation at 2 days, 4 days, and 4 years.

- Two reports included details describing quality of life following OLT. One patient was alive with residual, "asymptomatic" disease 32 months following OLT. Two additional patients had "normal quality of life" at 9 month and 44 month follow-ups.

- There were insufficient data to make firm conclusions regarding patient, tumor, or transplant characteristics that were associated with a favorable prognosis.

## SOFT TISSUE SARCOMA

Soft tissue tumors are classified according to which mesenchymal tissue they most closely resemble histologically. The nomenclature of mesenchymal tumors is evolving with an increased understanding of the molecular, histologic, and clinical features that distinguish different types of tumors. For example, one of the most common mesenchymal tumors in the gastrointestinal tract, gastrointestinal stromal tumors (GISTs), were initially thought to be of smooth muscle origin. However, a more complete understanding of molecular markers and biologic behavior has demonstrated that they encompass a heterogeneous group of tumors with respect to cell of origin, cellular differentiation, and prognosis.

This evolving nomenclature has essentially transformed the terms we use to describe different histopathologic types of mesenchymal tumors over the last decade. Understanding this limitation is important when interpreting the transplant literature, since tumors described in earlier reports may more appropriately be renamed if histologically reviewed. Here we assess the evidence of OLT for all mesenchymal tumors of the liver except for hemangioendothelioma, which is addressed in a separate section of this report.

The staging of soft tissue sarcomas incorporates tumor size, pathologic grade, histologic subtype, and presence of metastases. A close correlation exists between tumor stage at presentation and outcome. The American Joint Committee on Cancer (AJCC) staging system incorporates grade, size, depth, nodes, and presence of metastases.

The natural history of soft tissue sarcomas and hepatic metastases from soft tissue tumors has not been well described, in part due to extensive heterogeneity of tumor types. Median survival after diagnosis of hepatic metastases has been described to be 12 months, and 5-year survival is uncommon.[51] Chemotherapy has not been shown to have a substantial impact on survival. Resection of isolated liver metastases has not been reported to improve survival, primarily because of limited surgical options because of the frequency of multicentric and bilobar lesions at the time of diagnosis.[51]

UNOS Registry data provides general information regarding soft tissue tumors, however the evolving nomenclature for mesenchymal tumors limits the interpretation to specific histopathologic tumors. Over the last decade mesenchymal tumors have been included under the categories hemangiosarcoma-hepangiosarcoma-hemangioendothelioma, epithelioid hemangioendothelioma, hemangioendothelioma-hemangiosarcoma, spindle cell tumor, leiomyosarcoma, sarcoma with metastases, metastatic GIST, and lymphoma. It is unclear if the categories “recurrent disease” and “metastatic disease” include mesenchymal tumors as well. Using data for all identifiable soft tissue tumors, 66 OLT have been performed in the United States since 1990. Six of these received liver grafts from living donors (76% of all living donors for non-HCC tumors). Of 66 transplants, 16

were performed for leiomyosarcoma and 45 for hemangioendothelioma-hemangiosarcoma.

Fifteen published reports described the international experience with transplantation for sarcomas. Ten reports from six transplant centers described outcomes for 20 patients following OLT for soft tissue tumors other than hemangioendothelioma (Table 36). Fourteen transplants were performed in North America and six were performed in Europe. Those addressing results for patients with hemangioendothelioma are discussed elsewhere. None of the 10 studies reported on more than 6 patients. Length of follow-up was variable, and often less than 6 months. The largest study included 6 patients undergoing OLT or OLT-Cl. The mean age was 44 years. Fifty-six percent were male.

**Patient Survival.** Nine studies provided patient survival data in a total of 19 patients (Table 37). No report included more than 10 patients. Overall survival for patients following OLT for soft tissue tumors was variable. Mean survival ranged from 2.5 months to 24 months. The largest series of patients reported 1-, 3-, and 5-year survival rates of 100%, 44%, and 44%, respectively, in 6 patients.[24] Of the 6 patients included in that series, 66% died from tumor related causes. Of all 19 reported patients, 10 died within one year of transplant, including 9 who died within 6 months. Five patients were alive at follow-up 12 to 70 months following OLT. Only two patient survived beyond 5-years.

**Incidental Tumors.** One incidental angiosarcoma was reported in the literature.[52] Despite two cycles of chemotherapy for lung nodules diagnosed two months following OLT, the patient died at 6 months with spine metastases.

**Adjuvant and Neoadjuvant Therapies.** One of nine reports described the use of adjuvant chemotherapy.[53] A patient with undifferentiated spindle cell neurosarcoma was treated with doxorubicin and hyperthermia and died 4 months following OLT with tumor recurrence.[53]

**Results Published in 1995 or Later.** Five reports of 10 patients undergoing OLT for mesenchymal tumors have been published since 1995 (Table 37). These patients represented the majority of all patients with published outcomes. Thus, the results did not differ for patient survival from that reported above. Of these 10 patients, 3 died within 6 months.[11, 54] One patient was still alive at 49 months follow-up.[24]

**Extended Transplantation.** Two studies reported results following OLT-Cl. The largest report does not distinguish OLT-Cl results from those of OLT.[24] One report of two patients with cluster transplant for spindle cell sarcoma reported survival at 12 months and 15 months.[27]

**Disease-Free Survival**. Eight reports provided details regarding disease-free survival or recurrence following OLT for soft tissue tumors. All studies are summarized in Table 38. Recurrence rates ranged from 50-100%. The largest series reported recurrence in 83% of patients with at least 3 months of follow-up.[24] One-year disease free survival was reported at 50%, although the two studies that reported this rate included a total of only 4 patients.[53, 55]

The median time to tumor-related mortality was 32 months in a series of 6 patients.[24] Six patients with death from recurrence died within 12 months following OLT, five within 6 months. Of patients alive and tumor free, the longest length of follow-up was 70 months in a patient with leiomyosarcoma.[53]

**Incidental Tumors.** One incidental angiosarcoma tumor was reported in the literature.[52] A 59 year old was found to have pulmonary nodules two months following OLT, and despite two cycles of chemotherapy died at six months with spine metastases.

**Stage of Disease.** Three studies described details of stage of disease; all studies are summarized in Table 38. The size of four tumors was described: one 8 cm spindle cell tumor,[27] one 15 cm spindle cell sarcoma[27], and two 15 cm angiosarcomas.[52, 56] Published reports did not describe enough details regarding tumors to conclude on effect of disease factors on disease-free survival.

**Adjuvant and Neoadjuvant Therapies.** One report described the use of adjuvant chemotherapy.[53] A patient with undifferentiated spindle cell neurosarcoma was treated with doxorubicin and hyperthermia and died 4 months following OLT with tumor recurrence.[53]

**Results Published in 1995 or Later.** Five reports that included minimum of 10 patients undergoing OLT for mesenchymal tumors have been published since 1995 (Table 38). These patients represented the majority of all patients with published outcomes. Thus, the results did not differ for patient survival from that reported above.

**Extended Transplantation.** One study reported disease-free survival following OLT-Cl, but do not separate outcomes from results following OLT.[24]

**Graft Survival**. No report described graft survival following OLT for mesenchymal tumors.

**Quality of Life.** One report described quality of life in two patients with spindle cell sarcoma (Table 39). Following OLT-Cl, these two patients were alive at 12 months and 15 months without early satiety or pain with meals.[27]

Comparison of Transplantation to Other Treatments. No studies compared transplantation to other treatment options for patients with mesenchymal tumors.

**Summary.** At least 66 transplants have been performed in the United States since 1990 for soft tissue sarcomas. Forty-five were for epithelioid hemangioendothelioma and are reviewed elsewhere in this report. Our search revealed 15 reports of liver transplantation for sarcomas. Ten reports from six transplant centers reported outcomes for 20 patients following OLT for soft tissue tumors other than hemangioendothelioma (Table 36). All studies were individual case reports or case series. None of the studies included a minimum of 10 patients. Studies varied widely regarding length of follow-up and details of reported outcomes. Given these limitations, the available data support the following general conclusions:

- Mean patient survival ranged from 2.5 to 24 months for all 19 reported patients. Overall 1-, 3-, and 5-year patient survival was 100%, 44%, and 44%, respectively, in the largest series (total 6 patients). For comparison, 1-, 3-, and 5-year patient survival following liver transplantation for chronic hepatitis C is 79, 79, and 66, respectively, and 1-, 5-, and 7-year patient survival following transplantation for alcoholic liver disease is 84, 72, and 63%, respectively.

- Recurrence ranged from 50 to 100% in all reports. The largest series reported recurrence in 83% of patients.

- Graft survival was not reported in any study describing outcomes following OLT for soft tissue tumors other than hemangioendothelioma.

- One report included details describing quality of life following OLT for soft tissue tumors other than hemangioendothelioma. Two patients were reported to be “alive” without early satiety or pain with meals 12 and 15 months following OLT.

- There was insufficient data to make firm conclusions regarding patient, tumor, or transplant characteristics that were associated with a favorable prognosis.

# METASTATIC TUMORS

Metastatic tumors are the most common malignant neoplasms of the liver in the United States. The most frequent tumors to metastasize to the liver include those originating in the gastrointestinal tract, lung, and breast. Other solid tumors that metastasize to the liver include bladder cancer, neuroendocrine tumors, melanoma, and renal cell carcinoma. Metastatic neuroendocrine tumors are addressed in a separate section of this report. Often, hepatic metastases are either clinically silent, or their symptoms are overshadowed by those of the primary tumor. Occasionally, the symptoms and signs attributable to metastases are the presenting features of the primary tumors and include malaise, weight loss, and upper abdominal pain.

Prognosis is poor once tumor metastases have been found, with a mean survival after diagnosis of 6 months. Selected patients may be surgical candidates for resection of isolated metastases, particularly those from colorectal adenocarcinoma, if the primary tumor has been removed and spread is confined to the liver. Less invasive methods of treatment, such as ethanol infection, cryotherapy, and laser vaporization are currently under evaluation. It is estimated that approximately 5 to 10% of patients with liver metastasis are potential candidates for curative resection.[57] The 5-year survival following liver resection for colorectal metastasis is reported in many large series to be 25 to 37%.[58] The data regarding liver resection for other metastatic tumors types are less clear.

Liver transplantation, with or without chemotherapy, has been performed in only a few patients. It is unclear from available UNOS data how many transplants for metastatic cancer have been performed in the United States. Categorical descriptions of liver disease etiology do not specifically identify metastatic disease. One transplant was performed in 1994 for “Meta Disease – lung ca”, one transplant was performed in 2001 for “metastatic carcinoma”, and one transplant was performed in 1992 for “sigmoid carcinoma 12/89”. Other categories that may include patients with metastatic disease include 1 patient with “Unk Chemo:Breast ca”, 18 patients with “Secondary hepatic malignancy not otherwise specified”, and 1 patient with recurrent disease.

The published literature described 26 patients in 7 reports of OLT for metastatic disease from 4 transplant centers (Table 40). Thirteen transplants were performed in the United States and 13 were performed in Europe. All study outcomes were reported within 6 months of OLT except for one case of colon carcinoma followed for 31 months. Metastatic diseases reported included: 9 patients with colorectal cancer, 8 patients with lymphoma, 5 patients with pancreatic cancer, 2 patients with melanoma, and 2 patients with choriocarcinoma. One study included a minimum of 10 patients.[11] Mean age was 55 years. Fifty percent were male.

**Patient Survival**. Seven reports described patient survival in 25 recipients (Table 41). Patient survival following transplantation for metastatic tumors was variable. Mean survival ranged from 5 to 31 months. Both 5 month[59] and 31 month[60] reports were from

individual case reports. Operative mortality was 38% in one series of eight patients undergoing retransplantation following de novo development of lymphoma following first OLT.[61]

One study combining patients with pancreatic and colorectal carcinomas reported a 1-year survival of 20%.[24] The largest series that included patients with a variety of diagnoses reported no survivors beyond 3 years.[11] The longest survivor was alive 56.5 months following transplantation for lymphoma that developed following the first OLT.[24]

**Stage of Disease.** Although stage of disease or tumor features were not reported in these case reports, all studies described OLT for metastatic disease. One patient with a 6 x 6 cm mass in the body and tail of the pancreas died within 5 months of foregut resection and OLT from tumor recurrence.[59]

**Adjuvant and Neoadjuvant Therapies.** Use of adjuvant of neoadjuvant therapies for liver metastases are not described in these published reports.

**Results Published in 1995 of Later.** Because reports were primarily single cases of heterogeneous disease states, no conclusions can be made regarding survival outcomes before and after 1995.

**Extended Transplantation.** Two studies reported outcomes following extended transplantation.[24, 62] These studies did not distinguish outcomes for patients following OLT from those following extended transplantation.

**Disease-Free Survival.** Five reports described disease-free survival or recurrence following OLT for 15 patients with metastatic disease (Table 42). Recurrence rates ranged from 75 to 100% in patients with at least 3 months of follow-up. Mean time to tumor related mortality was 8.3 months.[24] Time to tumor related death in all studies ranged from 2 weeks to 31 months.

Limited clinical and experimental evidence suggests that tumors may experience accelerated growth in the setting of immunosuppression. Whether immunosuppression was associated with accelerated tumor growth was not evident because a few studies described post-OLT immunosuppression regimens. Thus, it is unclear if tumors grew more rapidly in the setting of chronic immunosuppression. Five patients were described with rapid disease progression possibly suggesting accelerated tumor growth.[59, 62, 63]

**Stage of Disease.** Stage of disease was not routinely reported in these studies. One patient with a 6 x 6 cm mass in the body and tail of the pancreas died within 5 months of foregut resection and OLT from tumor recurrence.[59]

**Adjuvant and Neoadjuvant Therapies.** Use of adjuvant of neoadjuvant therapies for liver metastases was not described in any of the published reports.

Results Published in 1995 or Later. Because the reports were primarily cases of heterogeneous disease states, no conclusions can be made regarding disease-free survival before and after 1995.

**Extended Transplantation.** Two studies reported outcomes following extended transplantation.[24, 62] These studies did not distinguish outcomes for patients following OLT from those following extended transplantation.

**Graft Survival**. One report of 8 patients described graft survival following OLT for metastatic disease.[61] This report described two deaths from lymphoma recurrence in the allograft at 2 weeks and 2 months following OLT, respectively.[61]

**Quality of Life** following OLT for metastatic disease was not addressed. Given poor survival outcomes with a mean time to tumor related mortality of 8.3 months, quality of life is expected to be poor.[61]

Comparison to Other Treatment Modalities. Liver transplantation has not been directly compared to other therapies for patients with nonresectable metastatic tumors.

**Summary.** The exact number of liver transplantations performed in the United States for metastatic tumors is unclear. At least three transplants have been reported for "Meta Disease – lung ca", "metastatic carcinoma", and "sigmoid carcinoma 12/89." Our search revealed 7 reports of liver transplantation for metastatic disease from 4 transplant centers describing outcomes for 26 patients (Table 40). All studies were individual case reports or case series. One study included 10 patients. Studies varied widely regarding length of follow-up and details of reported outcomes. Nevertheless, the available data support the following general conclusions:

- Median patient survival ranged from 5 to 31 months. The study that included 10 patients reported no survivors beyond 3 years.
- Recurrence was reported in 75 to 100% of patients. Mean time to tumor related mortality was 8.3 months. Time to tumor related death in all studies ranged from 2 weeks to 31 months.
- Graft survival was reported in one study of eight patients. Two patients experienced recurrence of lymphoma in the allograft at 2 weeks and 2 months following OLT.

- Quality of life following OLT for metastatic disease was not addressed in any report.
- There were insufficient data to make firm conclusions regarding patient, tumor, or transplant characteristics that were associated with a favorable prognosis.

## GALLBLADDER CANCER

Gallbladder carcinoma is the fifth most common gastrointestinal malignancy. In the United States there are an estimated 4000 new cases of gallbladder carcinoma diagnosed each year.[64] It occurs more commonly in women (2.5-3 to 1 F:M) and peaks in incidence during the seventh decade of life.[65]

Over 80 percent of gallbladder carcinomas are adenocarcinomas, with the remaining cases being adenosquamous carcinomas, anaplastic carcinomas, and rarely carcinoid tumors or embryonal rhabdomyosarcoma. Advanced local and regional disease usually is present at the time of diagnosis. Direct extension of the carcinoma into the gallbladder fossa is present in 69 to 83 percent of patients. The staging systems used for gallbladder carcinoma are based on the pathologic characteristics of local invasion by the tumor and lymph node metastases as developed by the American Joint Cancer Committee (AJCC) in the tumor-node-metastasis (TNM) staging schema.

Prognosis and outcome of gallbladder cancer is usually poor. Median survival is 11 months or less despite therapeutic intervention.[66] The principal treatment of gallbladder cancer is the removal of the primary tumor and the areas of local extension, although the majority of patients are not candidates for curative resection because of location of disease. Chemotherapy, external beam radiation, and intra-arterial chemotherapy have also been used to treat gallbladder cancer, but at best, response rates are 10 to 20%.[66] Complete remission is rare.

UNOS reports two transplants have been performed in the United States for gallbladder cancer in the last decade. Published reports of the world experience with transplant for those with gallbladder cancer are also limited. A total of four patients with gallbladder cancer have been discussed in three case reports (Table 43). All three reports discussed patient survival and disease-free survival. One study addressed quality of life, and none of the studies discussed graft survival following OLT. Study follow-up ranged from 11 to 30 months. Mean age was 49 years. Thirty-three percent were male.

**Patient Survival.** All three patients undergoing orthotopic liver transplant for gallbladder cancer were alive 24 to 30 months following transplantation. Studies are summarized in Table 43. One patient undergoing cluster transplantation including the liver, pancreas, and duodenum died at 11 months.[29] Limited information regarding the

stage of disease at time of transplantation limits comparison of patient survival within these patients, as well as to those undergoing OLT for other hepatobiliary tumors.

**Disease-Free Survival.** Of three patients undergoing OLT, all were alive without recurrence of disease 24 to 30 months following transplantation.[67, 68] The patient undergoing cluster transplant died with recurrence at 11 months.[29]

**Quality of life.** Of the four patients reported in the literature undergoing transplantation for gallbladder carcinoma, reference was made to the quality of life in one patient who returned to work and was hoping for a pregnancy.[67] This same patient was noted to "feel well" and "has not lost weight" 24 months following transplantation.

**Comparison to other treatments.** No study directly compared transplantation to other treatments for gallbladder cancer.

**Summary.** Two transplants have been performed in the United States since 1990 for gallbladder cancer. Our search revealed a total of four patients with gallbladder cancer reported from 3 transplant centers (Table 43). All four patients were discussed in three individual case series. Thus, no general conclusions can be made.

## LIVER TRANSPLANTATION IN THE SETTING OF PREEXISTING EXTRAHEPATIC MALIGNANCY

Liver transplant candidates with a preexisting extrahepatic malignancy are thought to pose special problems with OLT. Because of the long-term immunosuppression that accompanies OLT, there is increased concern about the risk for recurrent or de novo tumors as well as accelerated tumor growth. In addition, these patients may have a different profile of rejection-related complications compared with transplant recipients without a history of malignancy.

For these reasons, the presence of preexisting malignancy is often considered a relative contraindication to OLT.[69] The American Association for the Study of Liver Disease currently recommends that OLT for patients with extrahepatic malignancies other than squamous cell skin carcinoma be deferred for at least 2 years after completion of curative therapy before transplantation is attempted.[63, 70]

The natural history and prognosis of end-stage liver disease in the setting of preexisting malignancy varies according to both the underlying liver disease process and the specific malignancy. Available treatments for end-stage liver disease in the setting of preexisting malignancy are limited, and depend on the etiology of the underlying liver disease process.

The UNOS Database provides limited information regarding transplantation for end-stage liver disease in the setting of preexisting malignancy. Patients are categorized by etiology of liver disease without identifying preexisting extrahepatic malignancy. In 1994 UNOS began asking a yes/no/unknown question regarding previous malignancy on transplant candidate registration forms. Although this information is now routinely obtained, it does not provide details regarding tumor type, timing, or previous treatment. In 1999 UNOS began routine interval follow-up reporting of de novo tumors or recurrence of pre-transplant malignancy.

Eleven published reports document a total of 76 patients with preexisting extrahepatic malignancy (Table 44). Fifty-one transplants were performed in the United States and 25 were performed in Europe. The majority of studies described only one or two patients. Two studies reported outcomes for more than 10 patients; the largest included 44 patients from a tumor registry with a median OLT follow-up of 11 months.[63] Follow-up ranged from 2.5 months to 102 months. Mean age was 46 years. Forty-two percent were male.

**Patient Survival.** Patient survival following transplantation varied (Table 45). The largest series reported that 81% of cancer related deaths occurred within 2 years in a series of 44 patients.[63] However, the smaller reports described patient survival between 24 and 102 months.

**Incidental Tumors.** Four patients were diagnosed with malignancy incidentally at time of OLT.[69] Two patients had renal carcinoma, 1 had colon cancer, and 1 had bladder carcinoma.[69] Three of these 4 patients were alive at time of follow-up without tumor recurrence. However, the patient who also underwent resection of a renal cell carcinoma during OLT died in the early post-operative period of sepsis and multi-organ failure.

**Extended Transplantation.** One cluster transplant was performed for Budd-Chiari syndrome.[39] This patient was never discharged from the hospital and died of respiratory failure 8 months following OLT.

**Disease-Free Survival**. Disease-free survival or recurrence was described in 10 reports (Table 46). Recurrence or persistence of a preexisting malignancy was described in 24% of 44 OLT recipients 1.5 to 42.5 months following OLT (median 7.5 months).[63] Patients had been treated from 6.5 to 41 months prior to OLT.

**Incidental Tumors.** Four patients had a malignancy diagnosed incidentally at time of OLT; two patients had renal carcinoma, 1 had colon cancer, and 1 had bladder carcinoma.[69] The patient who underwent resection of a renal cell carcinoma during OLT died in the early post-operative period of sepsis and multi-organ failure.

**Graft Survival.** One study of 5 patients reported a 20% 1-year graft survival rate (Table 47). This patient required regrafting at 6 months for recurrent Budd-Chiari disease.

**Quality of life.** Five case reports addressed quality of life following OLT (Table 48). All reports described improvements "alive and well" or "well." One patient was identified as regaining pre-bone marrow weight and having a Karnofsky score of 90%.[71] One patient returned to baseline functional status[72] and another returned to 100% performance status[73]. Although a patient required mechanical ventilation for nearly the entire postoperative period, OLT offered "improved mental status" prior to death.[74]

**Summary.** The number of liver transplantations performed in the United States since 1990 for candidates with preexisting extrahepatic malignancy is not known because UNOS only recently began inquiring about previous malignancy. Our search revealed 11 reports of liver transplantation from 11 transplant centers describing outcomes for 76 patients with preexisting extrahepatic malignancy (Table 44). All studies were individual case reports or case series. Two studies included a minimum of 10 patients (total 62 patients). Studies varied widely regarding etiology of liver disease, location of previous malignancy, length of follow-up, and details of reported outcomes. Nevertheless, the available data support the following general conclusions:Median patient survival ranged from 24 to 102 months. The largest series reported that 81% of cancer related deaths occurred within 2 years.

- Recurrence or persistence of a preexisting malignancy was described in 24% of patients with a median follow-up of 7.5 months (range 1.5 to 42.5 months)(total 44 patients). These preexisting malignancies had been treated 6.5 to 41 months prior to OLT.

- Graft survival was reported in one study. One of six patients required regrafting at 6 months.

- Five reports include details describing quality of life following OLT. All reports described patients as "alive and well" or "well". One patient returned to pre-bone marrow transplant weight, one returned to "baseline functional status", and one returned to "100% performance status". One patient who required mechanical ventilation during almost the entire post-operative period had reported "improved mental status" prior to death.

- There were insufficient data to make firm conclusions regarding patient, tumor, adjuvant or neoadjuvant chemotherapy, or transplant characteristics that were associated with a favorable prognosis.

# TRANSPLANTATION FOR OTHER TUMORS

UNOS data identified 7 transplants for lymphoma and 15 for other secondary hepatic malignancies not otherwise specified. The published literature described 6 patients with rare liver malignancies undergoing liver transplantation (Table 49). Tumors include primary liver lymphoma, hemangiopericytoma, liver adenomatosis, lymphangioma, cystadenocarcinoma, and Caroli's disease with unresectable adenocarcinoma of the intrahepatic bile ducts.

**Patient Survival.** Four patients were described as being alive 31 to 192 months following transplantation (Table 50). The longest reported survivor underwent OLT for "massive" liver adenomatosis.[75] Another patient survived 72 months following OLT for cystadenocarcinoma.[11] One patient died of disease recurrence within 30 days following OLT.[76]

**Incidental Tumors.** The only report of an incidentally diagnosed tumor was a patient with lymphoma diagnosed at time of OLT for fulminant hepatic failure.[76] The patient died 30 days later from recurrence.

**Disease-Free Survival.** Disease-free survival or recurrence was described in 5 studies (Table 51). One patient died of recurrence disease in the allograft within 30 days of OLT.[76] This patient was diagnosed with peripheral T-cell Non-Hodgkin's Lymphoma involving the liver and spleen without lymphadenopathy at the time of OLT for fulminant hepatic failure. Four other patients are described as alive without recurrence at 31 to 192 months following transplantation.

**Graft Survival**. One report described recurrence of peripheral T-cell Non-Hodgkin's lymphoma in the allograft.[76] The patient's diagnosis was established at time of transplantation.

**Quality of Life**. Quality of life was described in three reports (Table 52). One patient with hemangiopericytoma treated with several cycles of chemotherapy was "symptom free" 48 months following OLT.[77] A patient OLT for Caroli's disease with unresectable adenocarcinoma of the intrahepatic bile ducts was "alive and well" at 2 years.[78] A patient with cystadenocarcinoma treated with OLT was "alive and well" over 6 years following OLT.[11]

**Summary.** Seven liver transplants for lymphoma and 15 liver transplants for secondary hepatic malignancies have been performed in the United States since 1990. Our search revealed six reports of liver transplantation for other tumors from five transplant centers describing outcomes for 6 patients (Table 49). All studies were individual case reports or

case series. The heterogeneity of the described patients limits the formulation of general conclusions.

**Table 1**. United Network of Organ Sharing Registry for Transplantations Performed by Tumor Diagnosis 1990-2001

| Tumor | 90 | 91 | 92 | 93 | 94 | 95 | 96 | 97 | 98 | 99 | 00 | 03/01 | TOTAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cholangiocarcinoma | | | | | | | | | | | | | |
| Secondary | 14 | 10 | 5 | 11 | 4 | 4 | 7 | 6 | 3 | 6 | 4 | 1 | 75 |
| PSC | 1 | 3 | 3 | 2 | | | 1 | | 1 | | | | 11 |
| NOS | | | | | 1 | | | | | | | | 1 |
| Klatskin | 2 | | | | 1 | | | | | 1 | | | 4 |
| Cholangiocarcinoma & HCC | 1 | | | | | 1 | | | | | | | 2 |
| Bile duct cancer – NOS | 6 | 2 | 1 | 0 | 2 | 1 | 3 | 0 | 0 | 1 | 1 | 0 | 17 |
| PSC | 1 | 1 | | | | | | | | | | | 2 |
| GB carcinoma – NOS | 1 | | | | | | | | | | | | 1 |
| PSC | | | | | 1 | | | | | | | | 1 |
| Biliary Cystadenocarcinoma | | 2 | | | | | | | | | | | 2 |
| Carcinoid | 4 | 2 | 2 | 1 | | | | 2 | 3 | | 3 | 1 | 18 |
| Neuroendocrine | 2 | 5 | 2 | 1 | 1 | 1 | 3 | | | 2 | 1 | | 18 |
| VIPoma | | 3 | 1 | | | | | | | 1 | | | 5 |
| Gastrinoma/ZE syndrome | | 2 | 1 | 1 | 1 | | | 2 | | | | | 7 |
| Islet Cell Tumor | 2 | 2 | 1 | 1 | | | | 1 | | 1 | | | 8 |
| Glucagonoma | | | | 1 | | | | | | | | | 1 |
| Insulinoma | | | | | 1 | 1 | | | | | | | 2 |
| Adenoca of Vater | 1 | | | | | | | | | | | | 1 |
| Epithelioid Hemangioendothelioma | | | | | | | | 1 | | | | | 1 |
| Hemangioendothelioma-hemangiosarcoma | 7 | 1 | 3 | 5 | 1 | 3 | 6 | 5 | 5 | 6 | 3 | 0 | 45 |
| Hemangiosarcoma – Hepangiosarcoma - Hemangioendothelioma | 1 | | | | | | | | | | | | 1 |
| Leiomyosarcoma | 4 | 2 | 4 | 3 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 15 |
| Sarcoma – with mets | 1 | | | | | | | | | | | | 1 |
| Metastatic GIST | | | | | | | | | 1 | | 1 | | 2 |
| Spindle Cell tumor | | | | | | | | | | 1 | | | 1 |
| Meta Disease – lung ca | | | | | 1 | | | | | | | | 1 |
| Metastatic carcinoma | | | | | | | | | | | | 1 | 1 |
| Unk Chemo:Breast ca | | | 1 | | | | | | | | | | 1 |
| Sigmoid carcinoma 12/89 | | | 1 | | | | | | | | | | 1 |
| Lymphoma | | | 1 | | 2 | | | 2 | | 2 | | | 7 |
| 2nd hepatic malig – NOS | 4 | | | 1 | 2 | 1 | 4 | 1 | 2 | 3 | | | 18 |
| $2^{nd}$ - Recurrent disease | | | 1 | | | | | | | | | | 1 |
| NonHCC TUMOR TOTAL | 52 | 35 | 27 | 27 | 19 | 12 | 24 | 22 | 16 | 24 | 13 | 3 | 273 |
| TOTAL TRANSPLANTS | 2177 | 2452 | 2569 | 2918 | 3097 | 3428 | 3551 | 3617 | 3920 | 4183 | 4384 | 1060 | 37356 |

**Figure 1**. Total Number of Liver Transplants Performed in the United States, by Year 1990 through May 2001, as recorded by the United Network of Organ Sharing (UNOS).

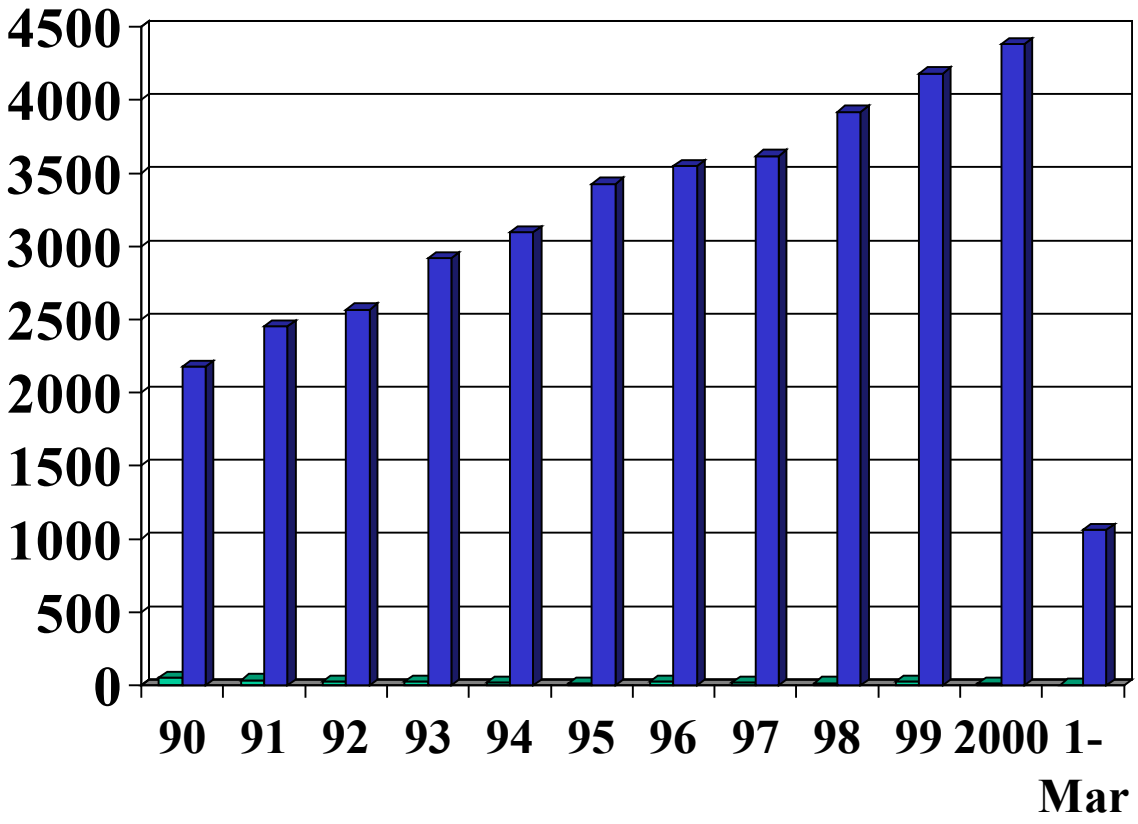
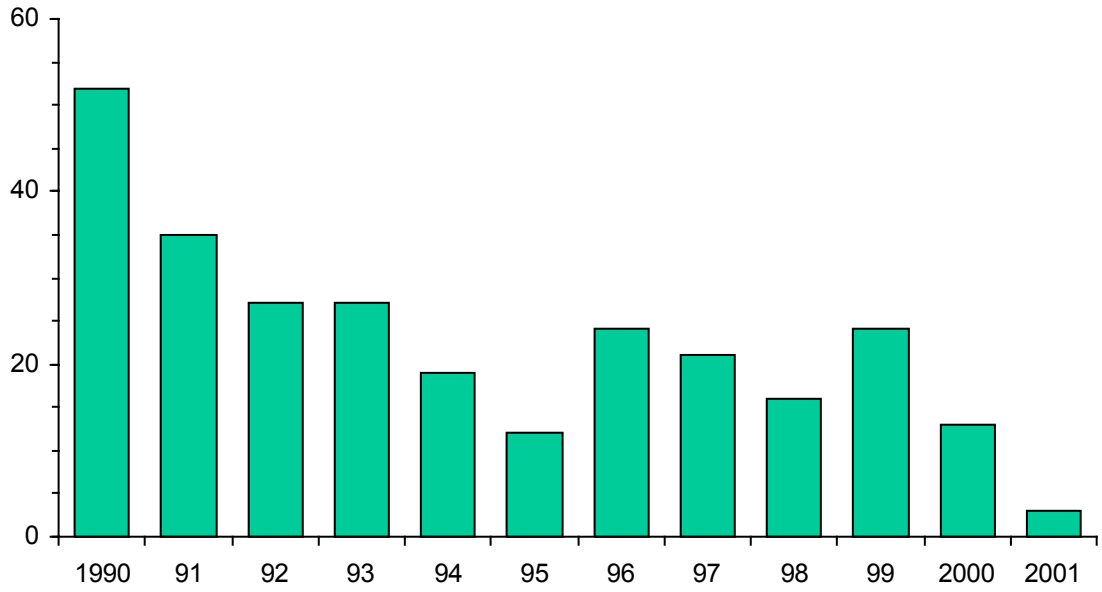


**Figure 2**. Number of Liver Transplants Performed in the United States for Malignancies Other Than Hepatocellular Carcinoma, by Year 1990 Through March 2001 as recorded by the United Network of Organ Sharing (UNOS).



| Reference | Location (Years of transplants reported) | # Patients in Report | Follow-up (months) | % Male | Age at Transplant (years) | Patient disease features | Procedure |
|---|---|---|---|---|---|---|---|
| Meyer 2000[1] | Cincinati (68-97) | 207 | 23 | 62 | 47 | 43 incidental tumors (23 with PSC), 164 known or suspected cancers (25 with PSC); 27 multifocal tumors; 21 treated with 5-FU and XRT; 12 patients with concurrent HCC | OLT |
| Pichlmayr 1998[11] Pichlmayr 1996[8] Klempnauer 1997[13] Nashan 1996[17] | Hannover, Germany (72-96) Hannover, Germany (75-93) Hannover, Germany (71-95) Hannover, Germany (72-94) | 50 25 32 10 | ND ND 5.3-11 64 | ND ND ND ND | ND ND ND ND | 20 Intrahepatic tumors; 30 proximal tumors of which 13 were stage I&II, 4 stage III, 12 stage IV Proximal bile duct cancer; 7 patients had PSC – all 7 had incidental diagnoses; 18 did not have PSC; Of incidental cancers UICC tumors stage: 1 II and 5 IVa & IVb ; Of all patients UICC tumor stage 1 I, 8 II, 4 III, 10 IVa, 2 IVb; Hilar cholangiocarcinoma All patients with PSC; 1 known tumor, 9 incidental tumors; 7 extrahepatic bile duct (1 I, 2 II, 3 IVa, 1 IVb), 2 Gallbladder cancers (II, IVb), 1 intrahepatic tumor (II); | OLT OLT OLT OLT |
| Abu-Elmagd 1993[6] Flickinger 1991[12] Iwatsuki 1998[5] Urego 1999[20] | Pittsburgh (81-90) Pittsburgh (76-88) Pittsburgh (81-96) Pittsburgh (90-95) | 18 12 38 9 | 43 ± 29 ND Median 76.7±5 22 | ND ND ND ND | ND ND ND ND | All patients had PSC; 2 intrahepatic, 13 hilar, 3 gallbladder/cystic duct tumors; 11/18 tumors incidentally diagnosed; 11 patients received radiation and chemotherapy before and/or after OLT Extrahepatic and gallbladder cancers; 8 patients received postoperative radiation therapy; 1 patient received preoperative radiation therapy; Hilar cholangiocarcinoma; 21 known tumors, 17 incidental tumors; 27/38 with cirrhosis; TNM stage of 27 undergoing OLT: 3 0, 1 I, 9 II, 13 IVa, 1 IVb; Of the 11 undergoing cluster OLT: 1 O, 6 IVa, 4 IVb Biliary duct adenocarcinoma; 6 Klatskin tumors, 1 with conventional resection of distal biliary duct tumor combined with chemotherapy and radiation. Concurrent chemotherapy with 2 cycles of 5-FU/leucovorin/interferon alpha; No maintenance chemotherapy; | 17 OLT; 1 OLT with abdominal exenteration OLT 27 OLT; 11 OLT with upper abdominal exenteration and cluster organ transplant OLT |
| Alessiani 1995[24] Mieles 1990[27] | Pittsburgh (88-92) Pittsburgh (88-89) | 20 9 | ND 14-46 | 50 ND | ND ND | 12 extrahepatic tumors, 8 intrahepatic tumors 2 cholangiocarcinoma (one recurrent); 7 bile duct cell carcinoma (3 with PSC, 1 recurrent bile duct carcinoma) | OLT, modified OLT, OLT with islet cells, OLT-pancreas-duodenum – results report a combination of procedures Cluster transplant including liver, stomach, pancreas, spleen, duodenum, proximal jejunum, and ascending plus transverse colon |
| Neuhaus 1999[25] Neuhaus 1994[35] Neuhaus 2000[26] | Berlin, Germany (1988-1998) Berlin, Germany Berlin, Germany | 15 7 (1 did not have cancer) 14 | 22.7±24.9 6-18 48 | ND 50 ND | 58.2±11.1 33-55 ND | 15 Hilar tumors; UICC Stage 1/II in 5, stage IVa in 8, stage IVb in 2, NO in 10, N1/2 5; Bismuth type IIIa in 2, IIIb in 2, IV in 11; No adjuvant radiation or chemotherapy; 7-day course of postoperative octreotide used in last 8 OLT 1 adenocarcinoma of hepatic bifurcation with positive lymph nodes and noted right ovary and paraaortal lymph node distant metastases, 3 tubular adenocarcinoma of hepatic bifurcation, 1 tubular/alveolar adenocarcinoma of hepatic bifurcation, 1 undifferentiated anaplastic adenocarcinoma of hepatic ducts; One patient with PSC did not have tumor on explant; 4 with IUCC I/II tumors, 9 IUCC IVa, 1 IVb | OLT and partial pancreatoduodenectomy OLT with Kausch-Whipple Operation OLT and partial pancreatoduodenectomy |

45 **Table 2**. Cholangiocarcinoma: Unique Study Population Descriptions By Study Size

| Reference | Location (Years of transplants reported) | # Patients in Report | Follow-up (months) | % Male | Age at Transplant (years) | Patient disease features | Procedure |
|---|---|---|---|---|---|---|---|
| | (1988-) | | | | | | |
| Gores 2000[33] | Mayo (ND) | 13 | 42 | 77 | 46 | 8 patients with PSC, 2 with cirrhosis; Adjuvant protocol using external-beam irradiation plus bolus 5-FU followed by brachytherapy plus protracted venous includions 5-FU and subsequent OLT for early-stage CCA | OLT |
| De Vreede 2000[23] | Mayo (93-98) | 11 | 44 | 72 | 56 | 6 patients had PSC, 2 had cirrhosis; Unresectable cholangiocarcinoma above the cystic duct without intrahepatic or extrahepatic metastases initially received external-beam irradiation plus bolus 5-FU, followed by brachytherapy with iridium and infusion of 5-FU; OLT occurred after exploratory laparotomy to exclude metastases; 3 with stage I, 7 with stage II disease, 1 with stage IVa; No patients had frank vascular invasion; | OLT |
| Goss 1997[7] | UCLA (84-96) | 14 | 36 | ND | ND | All patients with PSC; 10 incidental tumors, 4 known tumors | OLT |
| Farmer 1993[59] | UCLA (84-92) | 3 | 6-15 | ND | ND | 1 stage IVA distal common bile duct cancer in patient with PSC; 1 IVA intrahepatic tumor; 1 stage 1 common hepatic duct tumor in patient with concurrent biliary papillomatosis; No preoperative treatment; 1 patient received 5-FU and cisplatin post-operatively | OLT with oancreatico-duodenectomy + hepatectomy |
| Olthoff 1990[53] | UCLA (84-89) | 3 | 22 | ND | ND | 2 patients with PSC, 1 without PSC | OLT |
| Shaked 1992[79] | UCLA (85-90) | 2 | 48 | 22/36 | 42.7±9.2 | 2 patients with PSC incidentally diagnosed with hilar tumors <2cm; resection margins free of tumor; | OLT with resection of CBD and Roux-en-Y |
| Casavilla 1997[10] | Pittsburgh (81-94) | 20 | 81.6 (15.6-178.8) | 39 | 54.3±11.4 | 20 intrahepatic tumors; 8 in the setting of cirrhosis; TNM classification I+II 3; III 4; IVA 10; IVB 3 | OLT and Cluster OLT<br>Cluster transplant |
| Madariaga 1998[31] | Pittsburgh (81-94) | 1 | 48 | ND | ND | Patient with peripheral cholangiocarcinoma who developed recurrent disease 7m following resection | |
| Liden 2000[9] | Gothenburg, Sweden (85-96) | 4 | 16 | ND | ND | Incidental cholangiocarcinoma found in 4 patients with PSC | OLT |
| Saldeen 1999[80] | Goteberg, Sweden (86-96) | 6 | 28 | ND | ND | All patients with PSC; 5 cholangiocarcinoma, 1 gallbladder ca; | OLT |
| Soderdahl 1992[81] | Sweden (Since 1984) | 9 | ND | ND | ND | Cholangiocarcinoma | OLT |
| Goldstein 1993[16] | Baylor, Texas (84-92) | 17 | 30 | 53 | ND | All PSC. 17 in report (3 often excluded from results from “operative mortality”) Of 17, 12 known tumors, 5 incidental tumors; Of 14, 11 known tumors, 3 incidental tumors; Location: 6 hilar, 6 peripheral, 2 hilar and peripheral; Lesions: 9 unilocal, 5 multifocal; TNM Staging: Stage I – 1, Stage II – 5, Stage III – 7, Stage IVa – 1; 12 Moderately differentiated, 2 well-differentiated; All patients received radiation therapy and 5-FU 8 weeks before OLT | OLT in 12 patients; OLT with extended resection in 2 patients |
| Gruenberger 1996[22] | Austria, Vienna (82-95) | 15 | 60(4-108) | 60 | 50 | Cholangiocarcinoma | OLT |
| Calne 1993[82] | Cambridge, U.K. (80-91) | 13 | ND | ND | ND | Peripheral or central cholangiocarcinoma | OLT |
| Sansalone 1994[83] | Milan, Italy (85-93) | 11 | 42 | 91 | 49(38-55) | 6 central cholangiocarcinoma, 5 peripheral cholangiocarcinoma; 4 cholangiocarcinomas associated with liver cirrhosis and in 2 of them concurrent hepatocellular carcinoma; 2 patients with solitary lesions, 1 bifocal, 2 with more than 3 lesions; Median diameter of peripheral cholangiocarcinoma was 5.2cm; Grading G1 in 6 patients, G2 in 2 patients, G3 in 3 patients. No tumors had a capsule. All peripheral cholangiocarcinomas were T4 by TNM classification. All central cholangiocarcinomas were B4 by Bismuth classification. All patients had tumor-free resection margins; 3 patients had lymph node involvement, 3 had | OLT |

| Reference | Location (Years of transplants reported) | # Patients in Report | Follow-up (months) | % Male | Age at Transplant (years) | Patient disease features | Procedure |
|---|---|---|---|---|---|---|---|
| | | | | | | vascular infiltration, and all Klatskin tumors had perineural infiltration. | |
| Haug 1992[84] | Mass General, Boston (83-90) | 9 | 25.7 (3-80) | 44 | 44.1(22-69) | 3 received radiation and chemotherapy in the perioperative period | OLT and Roux-en-Y with wide margins |
| Figueras 2000[15] | Barcelona, Spain (89-99) | 8 | ND | ND | 64±11 | Hilar cholangiocarcinoma; 1 incidental diagnosis, 7 unresectable tumors; 1 Type III, 7 type IV; All patients received adjuvant therapy 4 weeks after surgical resection with 5-FU and external beam radiation. | OLT |
| Knechtle 1995[19] | Madison, WI | 7 | At least 6 months | ND | ND | All with PSC; 2 with known tumors, 5 incidental tumors | OLT |
| Chung 1997[85] | Toronto (85-94) | 6 | ND | ND | 45±12 | | OLT |
| Graziadei 1999[86] | Mayo (85-96) | 6 | 33 | ND | ND | 4 known tumors<br>2 incidental tumors | OLT with Roux-en-Y |
| Oldhafer 2000[60] | Hannover, Germany (88-98) | 6 | 40 | 77 | 51.3±7.3(30-71) | 2 cholangiocarcinomas and 3 Klatskin tumors | OLT following ex situ liver surgery; One patient with cholangiocarcinoma did not undergo ex situ surgery; |
| Robles 1999[87] | Murcia, Spain (88-98) | 6 | ND | ND | ND | 6 Bismuth type IV Klatkin's tumors | OLT with Roux-en-Y |
| Ahrendt 1999[18] | Johns Hopkins (84-97) | 4 | 10-53 | ND | ND | Cholangiocarcinoma in PSC; Known tumor in 1, incidental tumors in 3; | OLT |
| Launois 1999[88] | Rennes, France (68-93) | 4 | 84 | ND | ND | Proximal tumors; All Type IV, T3. Two are IVa and two IVb; | 2 OLT with extensive lymph node dissection & Roux-en-Y; 1 OLT with porta hepatis resection and total pancreatectomy; 1 OLT with porta hepatis resection, total pancreatectomy, stomach and right colon: |
| Miros 1991[89] | Queensland, Australia (85-89) | 4 | 14-39 | 36 | 40(17-48) | All incidental tumors; 1 common hepatic duct, 1 common bile duct, 1 common bile duct/right and left hepatic ducts, 1 common bile duct/common hepatic duct/adjacent liver; 2 patients with Stage III cirrhosis, 2 patients with Stage IV cirrhosis. 3 well or moderately differentiated tumors. 1 intraductal papillary carcinoma; | OLT with Roux-en-Y |
| Strasser 1993[90] | Sydney, Australia (86-92) | 4 | 25.4±21.8 | ND | ND | Incidental cholangiocarcinoma in patients with PSC | OLT |
| Washburn 1995[21] | Boston, MA Deaconess (85-94) | 4 | 5.5y | ND | ND | 1 patient with PSC and extensive intrahepatic cholangiocarcinoma; 3 patients with PSC – 1 N1 hilar, 1 N1 intrahepatic, 1 intrahepatic without nodal involvement | OLT |
| Ismail 1990[55] | Birmingham, UK (82-89) | 3 | 7-12 | 33 | 40-53 | 2 known tumors in patients with PSC; 1 incidental tumor in patient with PSC; All stage III disease, all multifocal. | OLT |
| Berdah 1996[91] | Marseille, France (88-95) | 2 | 16 | ND | 56 | Stage IVa peripheral cholangiocarcinoma stage in both patients; 1 tumor 13cm and the other 15cm | OLT |
| Cherqui 1995[34] | Creteil, France (89-93) | 2 | 25-31 | ND | ND | Intrahepatic cholangiocarcinoma;1 patient underwent OLT for recurrence after initial resection, 1 underwent OLT after initial exploratory laparotomy | OLT |
| Cherqui 1995[92] | Creteil, France | 2 | 18-28 | 50 | 39-54 | 1 patient had PSC; Both patients had hilar tumors; Patient with PSC received adjuvant external radiation therapy | OLT with hepaticojejunostomy; OLT with pancreaticogastrostomy and gastrojejunostomy |
| Knechtle 1993[29] | Madison, WI | 2 | 11-21 | 50 | 36-43 | 1 cholangiocarcinoma, 1 gallbladder cancer | Cluster transplant with liver, pancreas, spleen, stomach, duodenum with transplant of liver, pancreas, and duodenum |
| Muiesan 1994[93] | King's College, London (89-94) | 2 | 32 | ND | ND | 2 patients with PSC and cholangiocarcinoma – 1 known tumor and 1 incidental tumor measuring 3cm with a single lymph node metastasis found in the porta hepatitis | OLT with Roux-en-Y |
| Petrassi 1999[82] | Cosenza, Italy | 2 | ND | ND | ND | | OLT following abdominal exenteration; 1 patient received visceral transplant with hepatoduodenal ligament, duodenum, pancreas; 1 patient received cluster transplant of stomach, duodenum, ileum, |

| Reference | Location (Years of transplants reported) | # Patients in Report | Follow-up (months) | % Male | Age at Transplant (years) | Patient disease features | Procedure |
|---|---|---|---|---|---|---|---|
| | | | | | | | pancreas, liver, right colon, and transverse colon |
| Loinaz –Moreno-1998[4] | Madrid, Spain (86-96) | 1 | 58 | 0 | 26 | Hilar cholangiocarcinoma, TNM III. No cirrhosis. | OLT with Roux-en-Y |
| Farges 1995[94] | Villejuif, France (76-92) | 1 | 96 | ND | ND | Incidental cholangiocarcinoma in patient with PSC | OLT with subtotal duodenopancreatectomy |
| Moreno Gonzalez 1993[56] | Madrid, Spain (86-92) | 1 | 44 | ND | ND | Stage III Klatskin tumor, well differentiated, underlying cirrhosis | OLT with Roux-en-Y |
| Masada 1994[3] | Nebraska | 1 | 3 | 0 | 45 | Poorly differentiated, incidentally diagnosed hilar cholangiocarcinoma measuring 6.5x3x3cm | OLT |
| Foo 1997[28] | Mayo (80-91) | Total # transplants not reported, results include 1 outcome | 60 | ND | ND | PSC with extrahepatic bile duct carcinoma; no malignancy in liver explant; Treated with external beam irradiation +/- 5-FU followed by transcatheter Ir boost | OLT |

ND = not discussed, OLT=orthotopic liver transplantation, PSC = primary sclerosing cholangitis

**Table 3.** Patient Survival Following OLT: Overall Summary of Results for Studies Reporting a Minimum of 10 Patients.

| | No. studies | No. patients | Median Patient Survival (months) | Operative Mortality (%) | Patient Survival* | | |
|---|---|---|---|---|---|---|---|
| | | | | | 1-yr | 3-yr | 5-yr |
| **CHOLANGIOCARCINOMA** | | | | | | | |
| All Tumors | 15 | 503 | 11.8 | 14 | 63 | 46 | 22 |
| Incidental Tumors | 3 | 28 | 23 | ND[$] | 86 | ND | 52 |
| Peripheral Tumors | 2 | 40 | 5.5 | ND | 45 | 18 | 10 |
| Central Tumors | 5 | 127 | 19.4 | 18 | 63 | 28 | 12 |
| Patients with PSC[$] | 3 | 38 | 11.1 | 30 | 71 | 57 | 54 |
| Includes Stage of Disease Details | 4 | 210 | | | | | |
| Adjuvant & Neoadjuvant Therapies | 3 | 47 | 17.6 | 14 | 68 | 25 | 24 |
| Transplants Reported in 1995 or Later | 13 | 471 | 11.5 | 15 | 66 | 29 | 23 |
| Transplants Reported before 1995 | 2 | 38 | 19.2 | ND | 58 | 24 | 27[#] |
| Extended Transplant | 2 | 21 | ND | 18 | 55 | 9 | 9 |
| | | | | | | | |
| **NEUROENDOCRINE TUMORS** | | | | | | | |
| All Tumors | 5 | 81 | 30.7 | 15 | 64 | 60 | 53 |
| Includes Stage of Disease Details | ND | ND | ND | ND | ND | ND | ND |
| Adjuvant and Neoadjuvant Therapies | 2 | 33 | ND | ND | ND | ND | ND |
| Extended Transplant | 1 | 14 | ND | ND | ND | ND | ND |
| | | | | | | | |
| **EPITHELIOID HEMANGIOENDOTHELIOMA** | 1 | 16 | ND | ND | 100 | 86 | 71 |
| | | | | | | | |
| **SOFT TISSUE SARCOMAS OTHER THAN HEMANGIOENDOTHELIOMA** | 0 | 0 | | | | | |
| | | | | | | | |
| **METASTATIC DISEASE** | 1 | 10 | ND | ND | ND | 0% | 0% |
| | | | | | | | |
| **GALLBLADDER CANCER** | 0 | 0 | | | | | |
| | | | | | | | |
| **PREEXISTING EXTRAHEPATIC MALIGNANCY** | 2 | 62 | ND | ND | ND | ND | ND |

$ ND = not described, PSC = primary sclerosing cholangitis

*Estimates of 1-, 3-, and 5-year survival were obtained by dividing the total number of patients reaching and endpoint by the total number of patients transplanted.

# One study reported 5-year survival while the other did not have long enough follow-up

**Table 4**. Disease-Free Survival Following OLT: Overall Summary of Results for Studies Reporting a Minimum of 10 Patients

| | No. studies | No. patients | Recurrence Rate (%) | Disease-Free Survival* | | |
|---|---|---|---|---|---|---|
| | | | | 1-yr | 3-yr | 5-yr |
| **CHOLANGIOCARCINOMA** | | | | | | |
| All Tumors | 18 | 543 | 52 | 58 | 22 | 13 |
| Incidental Tumors | 2 | 61 | 61 | ND$ | 10 | 5 |
| Peripheral Tumors | 1 | 20 | 55 | 67 | 31 | 31 |
| Central Tumors | 5 | 140 | 53 | ND | ND | 18 |
| Patients with PSC$ | 4 | 59 | 53 | 40 | ND | ND |
| Includes Stage of Disease Details | 6 | 326 | | | | |
| Adjuvant & Neoadjuvant Therapies | 2 | 38 | 63 | 40 | 10 | 5 |
| Transplants Reported in 1995 or Later | 13 | 471 | 52 | 69 | 16 | 11 |
| Transplants Reported before 1995 | 5 | 72 | 51 | 65 | 75 (2 studies report) | 55 (1 study reports) |
| Extended Transplant | 1 | 20 | 57 | ND | ND | ND |
| | | | | | | |
| **NEUROENDOCRINE TUMORS** | | | | | | |
| All Tumors | 5 | 81 | 52 | ND | ND | ND |
| Adjuvant and Neoadjuvant Therapies | 2 | 33 | ND | ND | ND | ND |
| Extended Transplant | 1 | 14 | ND | ND | ND | ND |
| | | | | | | |
| **EPITHELIOID HEMANGIOENDOTHELIOMA** | 1 | 16 | 55 | 81 | 69 | 60 |
| | | | | | | |
| **SOFT TISSUE TUMORS OTHER THAN HEMANGIOENDOTHELIOMA** | 0 | 0 | | | | |
| | | | | | | |
| **METASTATIC DISEASE** | 0 | 0 | | | | |
| | | | | | | |
| **GALLBLADDER CANCER** | 0 | 0 | | | | |
| | | | | | | |
| **PREEXISTING EXTRAHEPATIC MALIGNANCY** | 1 | 44 | 24 | ND | ND | ND |

$ ND = not described, PSC = primary sclerosing cholangitis

*Estimates of 1-, 3-, and 5-year disease-free survival were obtained by dividing the total number of patients reaching and endpoint by the total number of patients transplanted.

**Table 5**. Graft-Survival Following OLT: Overall Summary of Results for Studies Reporting a Minimum of 10 Patients

| | No. studies | No. patients | No. patients with graft failure | 1-year Graft Survival |
|---|---|---|---|---|
| CHOLANGIOCARCINOMA | 2 | 24 | 2 | 91 |
| | | | | |
| NEUORENDOCRINE TUMORS | 0 | 0 | | |
| | | | | |
| EPITHELIOID HEMANGIOENDOTHELIOMA | 1 | 16 | 3 | ND |
| | | | | |
| SOFT TISSUE TUMORS OTHER THAN HEMANGIOENDOTHELIOMA | 0 | 0 | | |
| | | | | |
| METASTATIC TUMORS | 0 | 0 | | |
| | | | | |
| GALLBLADDER CANCER | 0 | 0 | | |
| | | | | |
| PREEXISTING EXTRAHEPATIC MALIGNANCY | 0 | 0 | | |

52 **Table 6** Cholangiocarcinoma: Studies Reporting Extended Transplantation by Center

| Reference | Location (Years oftransplantreported) | Number of Patients | Follow-up(months) | % Male | Age atTransplant(years) | Patient cancer features | Procedure |
|---|---|---|---|---|---|---|---|
| Abu-Elmagd 1993[6] Iwatsuki 1998[5] Alessiani 1995[24] Mieles 1990[27] Casavilla 1997[10] Madariaga 1998[31] | Pittsburgh (81-90) Pittsburgh (81-96) Pittsburgh (88-92) Pittsburgh (88-89) Pittsburgh (81-94) Pittsburgh (81-94) | 18 38 20 9 20 1 | 43 ± 29 Median 76.7±5 ND 14-46 81.6 (15.6-178.8) 48 | ND 43/72 50 ND 39 ND | ND 51 (19-81) ND ND 54.3±11.4 ND | All patients had PSC; 2 intrahepatic, 13 hilar, 3 gallbladder/cystic duct tumors; 11/18 incidental tumors; 11 patients received radiation and chemotherapy before and/or after OLT Hilar cholangiocarcinoma; 21 known tumors, 17 incidental tumors; 27/38 with cirrhosis; TNM stage of 27 undergoing OLT: 3 0, 1 I, 9 II, 13 IVa, 1 IVb; Of the 11 undergoing cluster OLT: 1 O, 6 IVa, 4 IVb 12 extrahepatic tumors, 8 intrahepatic tumors 2 cholangiocarcinoma (one recurrent); 7 bile duct cell carcinoma (3 with PSC, 1 recurrent bile duct carcinoma) 20 intrahepatic tumors; 8 in the setting of cirrhosis; TNM classification: I+II 3; III 4; IVA 10; IVB 3 Peripheral cholangiocarcinoma | 17 OLT; 1 OLT with abdominal exenteration 27 OLT; 11 OLT with upper abdominal exenteration and cluster organ transplant OLT, modified OLT, OLT with islet cells, OLT-pancreas-duodenum – results are a combination of all procedures Cluster transplant including liver, stomach, pancreas, spleen, duodenum, proximal jejunum, and ascending plus transverse colon OLT and Cluster OLT Cluster transplant |
| Cherqui 1995[34] | Creteil, France | 2 | 18-28 | 50 | 39-54 | 1 patient had PSC; Both patients had hilar tumors; Patient with PSC received adjuvant external radiation therapy | OLT with hepaticojejunostomy; OLT with pancreaticogastrostomy and gastrojejunostomy |
| Farges 1995[94] | Villejuif, France (76-92) | 1 | 96 | 64 (patients with PSC andtransplant) | 36±1.6 | Incidental tumor in patient with PSC | OLT with subtotal duodenopancreatectomy |
| Goldstein 1993[16] | Baylor, Texas (84-92) | 17 | 30 | 53 | ND | All PSC. 17 in report (3 often excluded from results from “operative mortality”) Of 17, 12 known tumors, 5 incidental tumors; Of 14, 11 known, 3 incidental tumors; Location: 6 hilar, 6 peripheral, 2 hilar and peripheral; Lesions: 9 unilocal, 5 multifocal; TNM Staging: Stage I – 1, Stage II – 5, Stage III – 7, Stage IVa – 1; 12 Moderately differentiated, 2 well-differentiated; All patients received radiation and 5-FU 8 weeks before OLT | OLT in 12; OLT with extended resection in 2 |
| Farmer 1993[59] | UCLA (84-92) | 3 | 6-15 | 3/6 | 39±12 | 1 stage IVA distal common bile duct tumor in patient with PSC; 1 IVA intrahepatic tumor; 1 stage 1 common hepatic duct tumor in patient with concurrent biliary papillomatosis; No preoperative treatment; 1 patient received 5-FU and cisplatin post-operatively | OLT and pancreatico-duodenectomy |
| Knechtle 1993[29] | Madison, WI | 2 | 11-21 | 50 | 36-43 | 1 cholangiocarcinoma, 1 gallbladder cancer | Cluster transplant with liver, pancreas, spleen, stomach, duodenum with transplant of liver, pancreas, and duodenum |
| Launois 1999[88] | Rennes, France (68-93) | 4 | 84 | ND | ND | Proximal tumors; All Type IV, T3. Two were IVa and two IVb; | 2 OLT with extensive LN & Roux-en-Y; 1 OLT with porta hepatis resection and total pancreatectomy; 1 OLT with porta hepatis resection, total pancreatectomy, stomach and right colon: |
| Neuhaus 1999 [25] Neuhaus 1994[25] | Berlin, Germany (1988-1998) Berlin, Germany | 15 7 (1 did not have | 22.7±24.9 6-18 | ND 50 | 58.2±11.1 33-55 | 15 Hilar tumors UICC Stage 1/II in 5, stage IVa in 8, stage IVb in 2, NO in 10, N1/2 5; Bismuth type IIIa in 2, IIIb in 2, IV in 11; No adjuvant radiation or chemotherapy; 7-day course of postoperative octreotide used in last 8 OLT 1 adenocarcinoma of hepatic bifurcation with positive lymph nodes and noted right ovary and paraaortal lymph node distant metastases, 3 tubular adenocarcinoma of | OLT and partial pancreatoduodenectomy OLT with Kausch-Whipple Operation |

| Reference | Location (Years of transplant reported) | Number of Patients | Follow-up (months) | % Male | Age at Transplant (years) | Patient cancer features | Procedure |
|---|---|---|---|---|---|---|---|
| | | cancer) | | | | hepatic bifurcation, 1 tubular/alveolar adenocarcinoma of hepatic bifurcation, 1 undifferentiated anaplastic adenocarcinoma of hepatic ducts; Patient with PSC did not have tumor on explant; | |
| Neuhaus 2000[26] | Berlin, Germany (1988-) | 14 | 48 | ND | ND | 4 patients with IUCC I/II tumors, 9 IUCC IVa, 1 IVb | OLT and partial pancreatoduodenectomy |
| Petrassi 1999[62] | Cosenza, Italy | 2 | ND | ND | ND | | OLT following abdominal exenteration; 1 patient received visceral transplant with hepatoduodenal ligament, duodenum, pancreas; 1 patient received cluster transplant with stomach, duodenum, ileum, pancreas, liver, right colon, and transverse colon |

ND = not discussed, OLT = orthotopic liver transplantation, PSC = primary sclerosing cholangitis

**Table 7.** Cholangiocarcinoma: Patient Survival Outcomes For all Studies

| Reference | Operative mortality (%) | Median survival (months) | Patient Survival year (%) 1 | 2 | 3 | 5 | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| Abu-Elmagd 1993[6] | ND | 23 (incidental tumors)<br>14 (known tumors) | 72 | 54.6 (incidental tumors)<br>28.6m (known tumors) | | 26.7 | 1-year and 5-year patient survival for those with PSC without cholangiocarcinoma: 85% and 75.8%, respectively. |
| Ahrendt 1999[18] | 25 | 21 +/-1 | 75 | | 38 | 0 | 2 patients alive without evidence of recurrence at 10 months and 53 months; Survival compared to survival rates for all 25 patients with cholangiocarcinoma and PSC: 1-, 3-, and 5-year survival of 28%, 9%, and 0%, respectibely; The actuarial survival of patients with cholangiocarcinoma managed with OLT was significantly lower than in the 26 PSC patients without cholangiocarcinoma managed since 1990; |
| Alessiani 1995[24] | Excluded operative mortality | 19 | 50 | | 20 | | 3 patients alive at 52 ,54, and 59 months without recurrence |
| Berdah 1996[91] | 50 | | 50 | | | | Survival of 16 months in patient with 13cm tumor; |
| Calne 1993[82] | ND | | | | | 23.8 | 7 patients – including the longest survivor of 125 months - were still alive |
| Casavilla 1997[10] | ND | | 70 | | 29 | 18 | Did not distinguish OLT from cluster transplant; 16/20 patients dead at time of follow-up; Compared to resected patients who had 1-, 3-, and 5-year survival of 60%, 37%, and 31%, respectively. |
| Chergui 1995[92] | ND | | 100 | 100 | | | Alive and disease free at 25 months and 32 months, including patient with recurrence following resection as indication for transplant |
| Chung 1997[85] | ND | | 83 | | 21 | 21 | 1/6 patients alive and free of disease<br>Compared to other “high risk” transplant indications where 3year survival was 80% |
| De Vreede 2000[23] | ND | | | | | | All 11 were alive; 3 patients were “at risk” at <12m; remaining 8 had median follow-up of 44 months |
| Farges 1995[94] | ND | | 100 | 100 | 100 | 100 | Alive without recurrence at 8 years |
| Farmer 1993[59] | No operative deaths | | 100 | | | | Alive at 6 months, 13 months, and 15 months; Survival results compared to tumor control group (54 patients with other malignancies) and total OLT group; |
| Figueras 2000[15] | ND | | 100 | | 92 | 36 | Patients with OLT had better 5-year survival rate than those treated with tumor resection (36% v. 21%); |
| Flickinger 1991[12] | ND | | 68 (OLT and radiation treatment) | 27 (OLT and radiation treatment) | 22 (OLT and radiation treatment) | 17 (2 patients disease free at 50 months)<br>22 (OLT and radiation treatment) | Survival rates compared to conservative therapy where 1-, 3-, and 5-year patient survival was 28%, 8%, and 0%, respectively. |
| Foo 1997[28] | ND | | | | | | 1 patient alive without recurrence 5 years following OLT |
| Goldstein 1993[16] | 3 patients intermittently excluded from results: 1 with bony mets at OLT, 2 with early postoperative deaths from sepsis and lymphoproliferative disorder | 11.1 | 53 | 30month survival 41 | | | 7 patients alive, 4 with recurrence, 3 without recurrence at 28 months, 31 months, and 44 months. Of patients undergoing extended resection one was alive with recurrent disease, the other was alive without recurrence; |

| Reference | Operative mortality (%) | Median survival (months) | Patient Survival year (%) 1 | 2 | 3 | 5 | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| Goss 1997[7] | ND | | 33 (known tumor)<br><br>100 (incidental tumor) | 33 (known tumors)<br><br>83 (incidental tumors) | | 0 (known tumors)<br><br>83 (incidental tumors) | Compared to survival for all OLT patients with PSC (127) at 1-, 2-, and 5-year survival rates of 90%, 86%, and 85%, respectively. Compared survival to all PSC patients without cholangiocarcinoma (n=113): 1-, 2-, and 5-year survival rates of 90%, 88%, and 87%, respectively. 9 covariates evaluated in regression model. Cholangiocarcinoma on frozen section only predictor of "survival disadvantage" |
| Gruenberger 1996[22] | 7 | 14 | 53 | | 33<br><br>grade I: 82<br><br>grade II: 68<br><br>grade III: 50 | 33 | No statistical benefit observed in cirrhotic patients; Significantly better overall survival observed in patients without vascular invasion; Differentiation of tumor significant in multivariate analysis – comparing grade I and II tumors with grade III tumors revealed a better disease-free survival in the more differentiated tumor group (p=.009); |
| Haug 1992[84] | ND | | 56 | 36 | | | 5 patients alive. 4 alive without recurrence at 10 months, 29.87months, 52.97 months, 79.23 months; 4/5 with recurrent disease died 3.2-8 months following OLT; 1 alive 3 years post OLT following chest well resection at 20 months for recurrence; No deaths within 3 months of transplant; "Actuarial survival of patients with benign disease was not significantly different than in patients with cholangiocarcinoma" |
| Ismail 1990[55] | ND | 11 | 0 | | | | Compared to actuarial survival for primary hepatic malignancy at 6 m, 1y, 2y – 75%, 45%, 28%, respectively. Compared to actuarial survival for acute and chronic parenchymal disease 6m, 1y, 2y: 62%, 60%, 60%, respectively. |
| Iwatsuki 1998[5] | 6/27 OLT<br>2/11 OLT-cluster | | 60 (OLT and OLT-Cl)<br><br>59.3 (OLT)<br><br>54.6 (OLT-Cl) | | 32 (OLT and OLT-Cl)<br><br>36.2 (OLT)<br><br>9.1 (OLT-Cl) | 25 (OLT and OLT-Cl)<br><br>36.2 (OLT)<br><br>9.1 (OLT-Cl) | Univariate analysis of transplant and partial hepatectomy: tumor tis 1,2 <.008, lymph node negative <.025, TNM stage 0,I,II <.007, negative margins <0.024, adjuvant therapy <0.043; Compared to hepatic resection with 1y, 3y and 5y survivals: 73.5%, 33.9%, 9.1%; Difference in survival between groups not statistically significant; After OLT patients with T-is, T-1 and T-2 had significantly better survival than T-3; 7 patients receiving OLT and 1 receiving OLT-CL lived free of tumor >5 years; One 5-year survivor patient died with tumor recurrence at 8 years 3 months; After OLT positive surgical margins were associated with a significantly reduced survival; Of those living longer than 5 years, they are known to be alive and free of tumor at 8, 15, 11, 7y, 7, 7, and 6 years. |
| Klempnauer 1997[13] | 15.6 | 19.68 +/- .33 | | | | 21 | Follow-up of long-term survivors 11, 5.3, 10.8, and 9.3 years. Prognosis after OLT was not significantly different from resection, although the procedure was reserved for patients with conventionally unresectable tumors. |
| Knechtle 1995[19] | ND | | 70 | 0 | | | 1 patient with incidental tumor alive at 11 months without recurrence and 1 known tumor alive at 20months without recurrence; Compared to results for those without cholangiocarcinoma who had 1y, 3y, and 5y survival rates of 88%, 85%, and 62%, respectively. |
| Knechtle 1993[29] | ND | | 0 | | | | Cholangiocarcinoma death with recurrence at 21 months; Gallbladder cancer death with recurrence at 11 months. |
| Launois 1999[88] | ND | | 75 | | 25 | 25 | 1 patient alive without recurrence at 7 years. One patient with cluster died secondary to ileocolic leakage, one cluster patient without stomach and right colon resection is still alive; Compared results to those with report of 40 tumor resections for proximal tumors with 1y, 3y, and 5y survival rates of 57.1%, 28.6%, and 0%, respectively. |
| Liden 2000[9] | 50 | | 25 | 0 | | | 100% dead; 2 in early postoperative period from portal vein thrombosis and multisystem organ failure. 2 from disseminated cancer at 10 months and 16 months |
| Loinaz – Moreno 1998[4] | ND | 58 | 100 | 100 | 100 | 0 | Retransplanted at 37 months for chronic rejection. Disease recurrence and death at 58 months |
| Madariaga 1998[31] | ND | 48 | 100 | 100 | 100 | 0 | Died 4 years later with recurrent disease |
| Masada 1994[3] | ND | 3 | 0 | | | | Recurrence 2.6 months following OLT with death at 3 months with multifocal cholangiocarcinoma present in hepatic allograft, lungs, and adrenals |

| Reference | Operative mortality (%) | Median survival (months) | Patient Survival year (%) 1 | 2 | 3 | 5 | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| Mieles 1990[27] | ND | | | | | | 1 patient with cholangiocarcinoma and 4 patients with bile duct cell carcinoma (3 whom had PSC) died at 57, 72, 112, 304, and 197days; 3 patients with duct cell cancer are still living at 296, ,290, and 247days; Patient with recurrent cholangiocarcinoma alive at 205days. |
| Meyer 2000[1] | 10 | 8.4<br><br>22 (21 patients treated with 5-FU and radiation) | 72 | 48 | | 23 | 34% alive; 20 patients survived >3 years without recurrence, 11 >5 years; 95 patients died secondary to recurrent tumor; 20 patients with known tumors <5cm – 8 had recurrence with median time to recurrence 6.5 months, 12 without recurrence (4 died of sepsis, 8 alive). 19 patients with known tumors >5cm – 16 had recurrence with a median of 4 months, 3 without recurrence (1 died of sepsis 1 month, 2 survived 64 months and 78months) |
| Miros 1991[89] | 25 | | 75 | 25 | 0 | | One patient alive without tumor at 14 months; One patient with recurrence dead at 23 months; I with recurrence alive at 39 months; Death at 30days secondary to sepsis. |
| Moreno Gonzalez 1993[56] | ND | | 100 | 100 | 100 | | Alive at 44 months; required retransplant at 15 months for chronic rejection without recurrence. |
| Muiesan 1994[93] | ND | | 50 | 50 | | | Known tumor died 2 months following OLT with recurrence; Incidental tumor alive and disease-free 32 months following transplantation; |
| Nashan 1996[17] | 50 | | | | | | No survival beyond 6 years; 1 graft failure at 13 months; 2 recurrence of bile duct carcinoma at 6 months and 64 months leading to death; 1 recurrence of central cholangiocarcinoma at 5 months; Of 7 bile duct carcinoma 4 died from sepsis, 1 chronic graft failure, and 2 local recurrences; Of 2 gallbladder carcinomas both dead at 13 days from sepsis; 1 with intrahepatic disease died 14 months with recurrence |
| Neuhaus 1994[35] | 17 | | 76 | | | | 5 Alive; 1 died after 6 months from diffuse metastasis, 1 died of hemorrhage day 15 |
| Neuhaus 1999[25] | 13 | | | | | | |
| Neuhaus 2000[26] | 14 | | | | | | 4-year survival including postoperative mortality 30%; ½ of patients with recurrence had graft metastases; Compared to patients undergoing right trisegmentectomy with 4-year survival 59% |
| Oldhafer 2000[60] | ND | | 20 | 20 | 20 | | Klatskin tumor survival time – unclear if from transplant or other ex situ procedure: death at 50, 113, and 35days – all from sepsis; One cholangiocarcinoma died day 43 from sepsis; One cholangiocarcinoma alive after 3 years 4 months without known recurrence in the patient without ex situ surgery; |
| Olthoff 1990[53] | 33 | | 35 | 0 | | | Patient without PSC died from multi-organ failure 1month following OLT without recurrence; 2 PSC patients had recurrence at 22 months and 6 months; Compared to survival for all malignancies at UCLA (16 hepatocellular carcinoma, 3 cholangiocarcinomas, 6 other primariers, 3 metastatic disease) with 6m, 1y, and 3y survivals – 67.3%, 51%, 31%, respectively. |
| Petrassi 1999[62] | ND | 7 | 0 | | | | Most data combined with 2 hepatocellular carcinoma cases. Patient with visceral transplant died day 45 of sepsis, patient undergoing cluster transplant died day 97 of sepsis; |
| Pichlmayr 1998[11] | ND | 5.5 (intrahepatic)<br><br>19.2 (proximal) | 20.8 (intrahepatic)<br><br>65.5 (proximal) | | 6.3 (intrahepatic)<br><br>23.6 (proximal) | 0 (intrahepatic)<br><br>18.9 (proximal) | Prognosis for proximal tumors strongly correlated with tumor stage - Survival for stages of proximal bile duct cancer shown in table, but unable to identify numbers; Proximal tumors with survivors at 10, 11, and 12 years without recurrence; Longest intrahepatic survivor 4.5 years without recurrence on follow-up. |
| Pichlmayr 1996[8] | 12 | 15.5<br><br>I/II 37.8<br><br>III 19.6<br><br>IV 5.8 | 60<br><br>I/II 88.9<br><br>III 75<br><br>IV 33.3 | | 21.4<br><br>I/II 55.6<br><br>III 0<br><br>IV 0 | 17.1<br><br>I/II 44.4<br><br>III 0<br><br>IV 0 | 4 of 25 patients survived over 5 years; Patients alive at 8,9,and 10 years without recurrence. Stage II incidental tumor death at 5 years with recurrence; Survival for transplant of early tumor stage 1year 88.9% and 5 year 44.4%; Univariate/multivariate analysis for resection and OLT; survival correlates with UICC tumor stage. No difference when compared to resected group (1year survival 65%, 5 year survival 27.1%). Longest survival in patients with positive lymph nodes was only 16 months. |

| Reference | Operative mortality (%) | Median survival (months) | Patient Survival year (%) 1 | 2 | 3 | 5 | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| Robles 1999[87] | ND | | | | | | 2 alive and tumor free at 26months and 27months; 4 died from recurrence |
| Saldeen 1999[80] | 33 | | | 17 | | | One surviving patient with gallbladder cancer at 28months without signs of recurrence; 3 deaths “directly linked to cholangiocarcinoma”; One early death related to multiple organ failure; One early death related to liver failure |
| Sansalone 1994[83] | ND | | 89 | | 53 | 53 | 5 patients alive without disease at 25, 37, 42, 84, and 86 months; 4 patients died of recurrence at 7, 5, 20, and 31 months; Overall disease-free survival was not statistically different but survival decreased if there was lymph node or vascular invasion |
| Shaked 1992[79] | ND | | 100 | 50 | 50 | | One died with recurrence at 20months; One alive without recurrence at 48months; |
| Soderdahl 1995[81] | ND | | | | 17 | | 1/6 patients has survived >3years (although 9 reported in series?) |
| Strasser 1993[90] | 25 | | | | | | |
| Urego 1999[20] | ND | | 90 (for those with lymph node negative, hilar biliary cancers) | | 64.8 (for those with lymph node negative, hilar biliary cancers) | 64.8 (for those with lymph node negative, hilar biliary cancers) | Most results include transplant combined with resection data; The OLT patients had a significantly longer survival than the 16 who did not undergo OLT (64.8% v. 0% at 5 years) |
| Washburn 1995[21] | ND | | 25 | 25 | 25 | 25 | PSC with extensive intrahepatic cholangiocarcinoma died from recurrence at 5.3m. N1 hilar cholangiocarcinoma died with recurrence at 3months; N1 intrahepatic cholangiocarcinoma died with recurrence at 6.4months; intrahepatic without nodal involvement disease-free at 5.5years |

ND = not discussed, OLT = orthotopic liver transplantation, OLT-Cl = cluster orthotopic liver transplantation, PSC = primary sclerosing cholangitis

**Table 8**. Cholangiocarcinoma: Patient Survival for Incidental Tumors

| Reference | Operative mortality% | Median survival (months) | Patient Survival year (%) | | | | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 5 | |
| Abu-Elmagd 1993[6] | | 23 (incidental tumors)<br>14 (known tumors) | 72 | 54.6 (Incidental tumors)<br>28.6 (known tumors) | | 26.7 | Patient survival for PSC without cholangiocarcinoma reported as 1- and 5-years: 85% and 75.8%, respectively |
| Farges 1995[94] | | | 100 | 100 | 100 | 100 | Alive without recurrence at 8 years |
| Goss 1997[7] | | | 33 (known tumors)<br>100 (incidental tumor) | 33 (known tumors)<br>83 (incidental tumors) | | Known tumors (4): 0 (known tumors)<br>83 (incidental tumors) | Compared to survival for all OLT patients with PSC (127) at 1-, 2-, and 5-years: 90%, 86%, and 85%, respectively. Compared to all PSC patients without cholangiocarcinoma (n=113) at 1y, 2y and 5y – 90%, 88%, 87%, respectively. 9 covariates evaluated in regression model. Colangiocarcinoma on frozen section only predictor of "survival disadvantage" |
| Knechtle 1995[19] | | | 70 | 0 | | | 1 patient with incidental tumor alive at 11months without recurrence and 1 known tumor alive at 20months without survival; |
| Liden 2000[9] | 50 | | 25 | 0 | | | 100% dead; 2 in early postoperative period from portal vein thrombosis and multi-organ system failure. 2 from disseminated cancer at 10months and 16months |
| Masada 1994[3] | | 3 | 0 | | | | Recurrence 2.6months following OLT with death at 3months with multifocal cholangiocarcinoma present in hepatic allograft, lungs, and adrenals |
| Miros 1991[89] | 25 | | 75 | 25 | 0 | | One patient alive without tumor at 14 months; One patient with recurrence dead at 23months; I with recurrence alive at 39 months; 1 death at 30days secondary to sepsis. |
| Muiesan 1994[93] | | | 50 | 50 | | | Preoperatively diagnosed cholangiocarcinoma died 2 months following OLT with recurrence; The incidental diagnosis is alive and disease-free 32 months following transplantation; |
| Pichlmayr 1996[8] | 12 | 15.5<br>I/II 37.8<br>III 19.6<br>IV 5.8 | 60<br>I/II 88.9<br>III 75<br>IV 33.3 | | 21.4<br>I/II 55.6<br>III 0<br>IV 0 | 17.1<br>I/II 44.4<br>III 0<br>IV 0 | Stage II incidental tumor death at 5 years with recurrence; Survival for transplant of early tumor stage 1 and 5 years: 88.9% and 44.4%, respectively; Univariate/multivariate analysis for resection and OLT; survival correlates with UICC tumor stage. |
| Shaked 1992[79] | | | 100 | 50 | 50 | | One died with recurrence at 20 months; One alive without recurrence at 48 months; |
| Strasser 1993[90] | 25 | | | | | | |

ND = not discussed, OLT = orthotopic liver transplantation, PSC = primary sclerosing cholangitis

**Table 9**. Cholangiocarcinoma: Patient Survival for Reports Specific to Peripheral Tumors

| Reference | Operative mortality% | Median survival (months) | Patient Survival year (%) | | | | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 5 | |
| Berdah 1996[91] | 50 | | 50 | | | | Survival of 16 months in patient with 13cm tumor; |
| Casavilla 1997[10] | ND | | 70 | | 29 | 18 | Do not distinguish OLT from cluster transplant; 16/20 patients dead at time of follow-up; Compared to resected patients who had 1-, 3-, and 5-years survival rates of 60%, 37%, and 31%, respectively. |
| Cherqui 1995[92] | ND | | 100 | 100 | | | Alive and disease free at 25 months and 32 months (patient with recurrence following resection as indication for transplant) |
| Madariaga 1998[31] | ND | 48 | 100 | 100 | 100 | 0 | Died 4 years later with recurrent disease |
| Pichlmayr 1998[11] | ND | 5.5 (intrahepatic)<br>19.2 (proximal) | 20.8 (intrahepatic)<br>65.5 (proximal) | | 6.3 (intrahepatic)<br>23.6 (proximal) | 0 (intrahepatic)<br>18.9 (proximal) | "Prognosis for proximal tumors strongly correlated with tumor stage" - Survival for stages of proximal bile duct carcinomas shown in table, but unable to identify numbers; |

ND = not discussed; OLT = orthotopic liver transplantation

**Table 10**. Cholangiocarcinoma: Patient Survival for Reports Specific to Central Tumors

| Reference | Operative mortality% | Median survival (months) | Patient Survival year (%) 1 | 2 | 3 | 5 | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| Figueras 2000[15] | ND | | 100 | | 92 | 36 | Most results combine OLT with resection; Patients with OLT had better 5-year survival rate than those treated with tumor resection (36% v. 21%); |
| Flickinger 1991[12] | ND | | 68 (OLT and radiation therapy) | 27 (OLT and radiation therapy) | 22 (OLT and radiation therapy) | 17 (2 patients disease free at 50 months)<br>22 (OLT and radiation therapy) | Compared to survival rates for conservative therapy: 1-, 3-, and 5-year survival rates: 28, 8, and 0%, respectively. |
| Foo 1997[28] | ND | | | | | | 1 patient alive without recurrence 5years following OLT |
| Iwatsuk 1998[5] | 6/27 OLT<br>2/11 OLT-cluster | | 60 (OLT and OLT-CI)<br>59.3 (OLT)<br>54.6 (OLT-CI) | | 32 (OLT and OLT-CI)<br>36.2 (OLT)<br>9.1 (OLT-CI) | 25 (OLT and OLT-CI)<br>36.2 (OLT)<br>9.1 (OLT-CI) | Univariate analysis of transplant and partial hepatectomy: tumor tis 1,2 <.008, lymph node negative <.025, TNM stage 0,I,II <.007, negative margins <0.024, adjuvant therapy <0.043; Compared to hepatic resection with 1y, 3y and 5y survivals: 73.5%, 33.9%, 9.1%; Difference in survival between groups not statistically significant; After OLT patients with T-is, T-1 and T-2 had significantly better survival than T-3; 7 patients receiving OLT and 1 receiving OLT-CL lived free of tumor >5 years; One 5-year survivor pt died with tumor recurrence at 8y3m; After OLT positive surgical margins were associated with a significantly reduced survival; Of those living longer than 5 years, they are known to be alive and free of tumor at 8, 15, 11, 7, 7, 7, and 6 years. |
| Klempnauer 1997[13] | 15.6 | 19.68 +/- .33 | | | | 21 | Follow-up of long-term survivors 11, 5.3, 10.8, and 9.3 years. Prognosis after OLT was not significantly different from resection, although the procedure was reserved for patients with conventionally unresectable tumors. |
| Launois 1999[88] | ND | | 75 | | 25 | 25 | 1 patient alive without recurrence at 7 years. One patient with cluster died secondary to ileocolic leakage, one cluster patient without stomach and right colon resection is still alive; Compared results to those with report of 40 tumor resections for proximal tumors with 1y, 3y, and 5y survival rates of 57.1%, 28.6%, and 0%, respectively. |
| Loinaz – Moreno 1998[4] | ND | 58 | 100 | 100 | 100 | 0 | |
| Masada 1994[3] | ND | 3 | 0 | | | | |
| Moreno Gonzalez 1993[[56] | ND | | 100 | 100 | 100 | | Alive at 44 months |
| Neuhaus 1999[25] | 13 | | | | | | |
| Pichlmayr 1996[8] | 12 | 15.5<br>I/II 37.8<br>III 19.6<br>IV 5.8 | 60<br>I/II 88.9<br>III 75<br>IV 33.3 | | 21.4<br>I/II 55.6<br>III 0<br>IV 0 | 17.1<br>I/II 44.4<br>III 0<br>IV 0 | 4 of 25 patients survived over 5 years; Stage II incidental tumor death at 5 years with recurrence; Survival for transplant of early tumor stage 1- and 5-year: 88.9% and 44.4%, respectively; Univariate/multivariate analysis for resection and OLT; Survival correlates with UICC tumor stage. No difference when compared to resected group (1y survival 65%, 5y 27.1%). Longest survival in patients with positive lymph nodes was only 16m. |
| Pichlmayr 1998[11] | ND | 5.5 (intrahepatic)<br>19.2 (proximal) | 20.8 (intrahepatic)<br>65.5 (proximal) | | 6.3 (intrahepatic)<br>23.6 (proximal) | 0 (intrahepatic)<br>18.9 (proximal) | "Prognosis for proximal tumors strongly correlated with tumor stage" - Survival for stages of proximal bile duct carcinomas shown in table, but unable to identify numbers; |
| Robles 1999[87] | ND | | | | | | 2 alive and tumor free at 26 and 27 months; 4 died from recurrence |
| Shaked 1992[79] | ND | | 100 | 50 | 50 | | One died with recurrence at 20 months; One alive without recurrence at 48 months; |

| Reference | Operative mortality% | Median survival (months) | Patient Survival year (%) | | | | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 5 | |
| Urego 1999[20] | ND | | 90 (for those with lymph node negative, hilar biliary cancers) | | 64.8 (for those with lymph node negative, hilar biliary cancers) | 64.8 (for those with lymph node negative, hilar biliary cancers) | Most results include transplant combined with resection data; The OLT patients had a significantly longer survival than the 16 who did not undergo OLT (64.8% v. 0% at 5 years) |

ND = not discussed; OLT = orthotopic liver transplantation; OLT-Cl = Cluster orthotopic liver transplantation

**Table 11**. Cholangiocarcinoma: Patient Survival for Patients with Concurrent Primary Sclerosing Cholangitis

| Reference | Operative mortality% | Median survival (months) | Patient Survival year (%) | | | | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 5 | |
| Ahrendt 1999[18] | 25 | Mean 21 +/-1 | 75 | | 38 | 0 | Survival compared to 1-, 3-, 5-year rates for all 25 patients with cholangiocarcinoma and PSC: 28%, 9%, 0%, respectively; The actuarial survival of patients with cholangiocarcinoma managed with OLT was significantly lower than in the 26 PSC patients without cholangiocarcinoma managed since 1990; |
| Farges 1995[94] | ND | | 100 | 100 | 100 | 100 | Alive without recurrence at 8 years |
| Foo 1997[28] | ND | | | | | | 1 patient was alive without recurrence 5 years following OLT |
| Goldstein 1993[16] | 3 patients intermittently excluded from results: 1 with bony metastases at OLT, 2 with early postoperative deaths from sepsis and lymphoproliferative disorder | 11.1 | 53 (all 17 patients) | 30 month survival 41 (all 17 patients) | | | 7 patients alive, 4 with recurrence, 3 without recurrence at 28, 31, and 44 months. Of patients undergoing extended resection one was alive with recurrent disease, the other was alive without recurrence. |
| Goss 1997[7] | ND | | 33 (known tumors)<br>100 (incidental tumors) | 33 (known tumors)<br>83 (incidental tumors) | | 0 (known tumors)<br>83 (incidental tumors) | Compared to survival for all OLT patients with PSC (127) who had 1y, 2y and 5y survivals of 90%, 86%, and 85%, respectively. Compared to all PSC patients without cholangiocarcinoma (n=113) who had 1y, 2y and 5y survival rates of 90%, 88%, and 87%, respectively. 9 covariates evaluated in regression model. Cholangiocarcinoma on frozen section only predictor of "survival disadvantage" |
| Ismail 1990[55] | ND | 11 | 0 | | | | Compared to actuarial survival for primary hepatic malignancy at 6m, 1y, 2y survivals: 75%, 45%, 28%, respectively. Compared to actuarial survival for acute and chronic parenchymal disease at 6m, 1y, 2y: 62%, 60%, 60%, respectively. |
| Knechtle 1995[19] | ND | | 70 | 0 | | | 1 incidental tumor alive at 11 months without recurrence and 1 known tumor alive at 20 months without recurrence; Compared to results for those without cholangiocarcinoma: 1y, 3y, and 5y survival of 88%, 85%, and 62%, respectively. |
| Liden 2000[9] | 50 | | 25 | 0 | | | 100% dead; 2 in early postoperative period from portal vein thrombosis and multi-system organ failure. 2 from disseminated cancer at 10 months and 16 months |
| Muiesan 1994[93] | ND | | 50 | 50 | | | Preoperatively diagnosed cholangiocarcinoma died 2 months following OLT with recurrence; The incidental diagnosis was alive and disease-free 32 months following transplantation; |
| Nashan 1996[17] | 50 | | | | | | No survival beyond 6 years; 1 graft failure at 13 months; 2 recurrence of bile duct cancer at 6 months and 64 months leading to death; 1 recurrence of central cholangiocarcinoma at 5 months; Of 7 bile duct cancer 4 died from sepsis, 1 chronic graft failure, and 2 local recurrences; Of 2 gallbladder cancers both dead at day 13 from sepsis; 1 with intrahepatic disease died 14 months with recurrence |
| Olthoff 1990[53] | 33 | | 35 | 0 | | | 2 PSC patients had recurrence at 22 months and 6 months; Compared to survival for all malignancies at UCLA (16 hepatocellular carcinoma, 3 cholangiocarcinoma, 6 other primary tumors, 3 metastatic disease) with 6m, 1y, and 3y survivals: 67.3%, 51%, 31%, respectively. |
| Pichlmayr 1996[95] | 12 | 15.5<br>I/II 37.8<br>III 19.6<br>IV 5.8 | 60<br>I/II 88.9<br>III 75<br>IV 33.3 | | 21.4<br>I/II 55.6<br>III 0<br>IV 0 | 17.1<br>I/II 44.4<br>III 0<br>IV 0 | 4 of 25 patients survived over 5 years; Patients alive at 8, 9,and 10 years without recurrence. Stage II incidental tumor death at 5 year with recurrence; Survival for transplant of early tumor stage 1year 88.9% and 5year 44.4%; Univariate/multivariate analysis for resection and OLT ; survival correlates with UICC tumor stage. No difference when compared to resected group (1y survival 65%, 5y 27.1%). |
| Saldeen 1999[80] | 33 | | | 17 | | | One surviving patient with gallbladder cancer at 28 months without signs of recurrence; 3 deaths "directly linked to cholangiocarcinoma"; One early death related to multiple organ failure; One early death related to liver failure |
| Shaked 1992[79] | ND | | 100 | 50 | 50 | | One died with recurrence at 20 months; One alive without recurrence at 48 months; |

| Reference | Operative mortality% | Median survival (months) | Patient Survival year (%) | | | | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 5 | |
| Washburn 1995[68] | ND | | 25 | 25 | 25 | 25 | PSC with extensive intrahepatic cholangiocarcinoma died from recurrence at 5.3 months. N1 hilar cholangiocarcinoma died with recurrence at 3 months; N1 intrahepatic cholangiocarcinoma died recurrence at 6.4 months; intrahepatic without nodal involvement disease free at 5.5 years. |

ND = not discussed; OLT = orthotopic liver transplantation; PSC = primary sclerosing cholangitis

**Table 12**. Cholangiocarcinoma: Patient Survival with Specific Outcomes for Stage of Disease

| Reference | Disease features | Operative mortality% | Median survival (months) | Patient Survival year (%) | | | | Outcomes Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 5 | |
| Berdah 1996[91] | Location: Peripheral cholangiocarcinoma<br><br>Stage: stage IVa in both patients;<br><br>Size: 1 tumor 13cm and the other 15cm | 50 | | 50 | | | | Survival of 16 months in patient with 13cm tumor |
| Chung 1997[85] | | ND | | 83 | | 21 | 21 | 2 patients had tumors <2cm and both developed recurrent cholangiocarcinoma within 1 year and died |
| Gruenberger 1996[22] | 15 cholangiocarcinoma; 71% with multicentric lesions; Median tumor diameter 11.5 cm; 7% with associated cirrhosis;<br><br>Differentiation: grade I good 23%; grade II moderate 55%, grade III 22% poor;<br><br>Transplants after 1995 received neoadjuvant chemotherapy with 5 cycles of doxorubicin preoperatively, intraoperative doxorubicin before manipulation of liver, and doxorubicin postoperative, and thereafter every 2 weeks to total dose of 300 mg/m2 | 7 | 14 | 53 | | 33<br><br>grade I: 82<br><br>grade II: 68<br><br>grade III: 50 | 33 | Differentiation of tumor significant in multivariate analysis – comparing grade I and II tumors with grade III tumors revealed a better disease-free survival in the more differentiated tumor group (p=.009); |
| Ismail 1990[55] | 2 known tumors in patients with PSC; 1 incidental tumor diagnosed in patient with PSC;<br><br>All stage III disease, all multifocal; | ND | 11 | 0 | | | | Compared to actuarial survival for primary hepatic malignancy at 6m, 1y, 2y – 75%, 45%, 28%, respectively. Compared to actuarial survival for acute and chronic parenchymal disease at 6m, 1y, 2y: 62%, 60%, 60%, respectively. |
| Iwatsuki 1998[5] | Hilar cholangiocarcinoma; 21 known tumors, 17 incidental tumors; 27/38 with cirrhosis;<br><br>TNM stage of 27 undergoing OLT: 3 0, 1 I, 9 II, 13 IVa, 1 IVb; Of the 11 undergoing cluster OLT: 1 O, 6 IVa, 4 IVb | 6/27 OLT<br>2/11 OLT-cluster | | 60 (OLT and OLT-CI)<br><br>59.3 (OLT)<br><br>54.6 (OLT-CI) | | 32 (OLT and OLT-CI)<br><br>36.2 (OLT)<br><br>9.1 (OLT-CI) | 25 (OLT and OLT-CI)<br><br>36.2 (OLT)<br><br>9.1 (OLT-CI) | Univariate analysis of transplant and partial hepatectomy: tumor tis 1,2 <.008, lymph node negative <.025, TNM stage 0,I,II <.007, negative margins <0.024, adjuvant therapy <0.043; Compared to hepatic resection with 1y, 3y and 5y survivals: 73.5%, 33.9%, 9.1%; Difference in survival between groups not statistically significant; After OLT patients with T-is, T-1 and T-2 had significantly better survival than T-3; 7 patients receiving OLT and 1 receiving OLT-CL lived free of tumor >5 years; One 5-year survivor pt died with tumor recurrence at 8y3m; After OLT positive surgical margins were associated with a significantly reduced survival; Of those living longer than 5 years, they are known to be alive and free of tumor at 8y, 15y, 11y, 7y, 7y, 7y, 6y; |
| Loinaz –Moreno 1998[4] | Hilar cholangiocarcinoma, TNM III. No cirrhosis. | ND | 58 | 100 | 100 | 100 | 0 | Retransplanted at 37 months for chronic rejection. Disease recurrence and death at 58 months |
| Masada 1994[3] | Poorly differentiated, incidentally diagnosed hilar cholangiocarcinoma measuring 6.5x3x3cm | ND | 3 | 0 | | | | Recurrence 2.6 months following OLT with death at 3 months with multifocal cholangiocarcinoma present in hepatic allograft, lungs, adrenals |
| Moreno Gonzalez 1993[56] | Stage III Klatskin tumor, well differentiated, underlying cirrhosis | ND | | 100 | 100 | 100 | | Alive at 44 months; required retransplant at 15 months for chronic rejection without recurrence. |
| Pichlmayr 1998[11] | 30 proximal tumors of which 13 stage I&II, 4 stage III, 12 stage IV | ND | 19.2 | 65.5 | | 23.6 | 18.9 | "Prognosis for proximal tumors strongly correlated with tumor stage" - Survival for stages of proximal bile duct cancer shown in table, but unable to identify numbers; |

| Reference | Disease features | Operative mortality% | Median survival (months) | Patient Survival year (%) | | | | Outcomes Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 5 | |
| Pichlmayr 1996[8] | Proximal bile duct cancer; 7 patients had PSC – all 7 had incidental tumors; 18 did not have PSC.<br><br>Of incidental tumors 1 II and 5 IVa & IVb ; Of total transplanted patients UICC tumor stage: 1 I, 8 II, 4 III, 10 IVa, 2 IVb; | 12 | 15.5<br><br>I/II 37.8<br><br>III 19.6<br><br>IV 5.8 | 60<br><br>I/II 88.9<br><br>III 75<br><br>IV 33.3 | | 21.4<br><br>I/II 55.6<br><br>III 0<br><br>IV 0 | 17.1<br><br>I/II 44.4<br><br>III 0<br><br>IV 0 | Stage II incidental tumor death at 5 years with recurrence; Survival for transplant of early tumor stage 1y , 5y 88.9% and 44.4%; Univariate/multivariate analysis for resection and OLT; survival correlates with UICC tumor stage. No difference when compared to resected group (1y survival 65%, 5y 27.1%). Longest survival in patients with positive lymph nodes was only 16 months. |
| Sansalone 1994[[83] | 6 central cholangiocarcinoma, 5 peripheral cholangiocarcinoma, 4 cholangiocarcinoma associated with liver cirrhosis and in 2 of them hepatocellular carcinoma concurrently; 2 patients with solitary lesions, 1 bifocal, 2 had more than 3 lesions; Median diameter of peripheral cholangiocarcinoma was 5.2cm; Grading G1 in 6 patients, G2 in 2 patients, G3 in 3 patients.<br><br>All peripheral cholangiocarcinomas were T4 by TNM. All central cholangiocarcinomas were B4 by Bismuth.<br><br>In all patients resection margin was tumor-free, 3 with lymph-node involvement, 3 with vascular infiltration, and all Klatskin tumors had perineural infiltration | ND | | 89 | | 53 | 53 | Overall disease-free survival was not statistically different but survival decreased if there was lymph node or vascular invasion |
| Urego 1999[20] | Biliary duct adenocarcinoma; 6 Klatskin tumors, 1 with conventional resection of distal biliary duct tumor combined with chemotherapy and radiation although unclear if the outcomes reported are for these patients. | ND | | 90 (in those with lymph node negative, hilar biliary cancers) | | 64.8 (in those with lymph node negative, hilar biliary cancers) | 64.8 (in those with lymph node negative, hilar biliary cancers) | Most results include transplant combined with resection data; The OLT patients had a significantly longer survival than the 16 who did not undergo OLT (64.8% v. 0% at 5 years) |
| Washburn 1995[68] | 1 patient with sclerosing cholangitis and extensive intrahepatic cholangiocarcinoma; 3 patients with PSC – 1 N1 hilar, 1 N1 intrahepatic, 1 intrahepatic without nodal involvement | ND | | 25 | 25 | 25 | 25 | PSC with extensive intrahepatic cholangiocarcinoma died from recurrence at 5.3 months. N1 hilar cholangiocarcinoma died with recurrence at 3 months; N1 intrahepatic cholangiocarcinoma died recurrence at 6.4months; intrahepatic without nodal involvement disease free at 5.5 years |

ND = not discussed, OLT = orthotopic liver transplantation, OLT-Cl = cluster orthotopic liver transplantation; PSC = primary sclerosing cholangitis

**Table 13**. Cholangiocarcinoma: Patient Survival in Reports Describing Adjuvant and Neoadjuvant Therapies

| Reference | Operative mortality % | Median survival (months) | Patient Survival year (%) | | | | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 5 | |
| Figueras 2000[15] | ND | | 100 | | 92 | 36 | Many results combine OLT with resection; Patients with OLT had better 5-year survival rate than those treated with tumor resection (36% v. 21%); |
| Flickinger 1991[12] | ND | | 68 (OLT and radiation therapy) | 27 (OLT and radiation therapy) | 22 (OLT and radiation therapy) | 22 (OLT and radiation therapy) | Compared to conservative therapy patient survivals of 1year 28%, 3year 8%, and 5year 0%. |
| Foo 1997[28] | ND | | | | | | 1 patient alive without recurrence 5 years following OLT |
| Goldstein 1993[16] | 3 patients intermittently excluded from results: 1 with bony metastases at OLT, 2 with early postoperative deaths from sepsis and lymphoproliferative disorder | 11.1 | 53 (all 17 patients) | 30 month survival 41 (all 17 patients) | | | 7 patients alive. Of patients undergoing extended resection one was alive with recurrent disease, the other was alive without recurrence; Average time of recurrence to death 1.4 months; |
| Meyer 2000[1] | ND | 22 (in 21 patients treated with 5-FU and radiation therapy) | | | | | |
| Urego 1999[20] | ND | | 90 (in those with lymph node negative, hilar biliary cancers) | | 64.8 (in those with lymph node negative, hilar biliary cancers) | 64.8 (in those with lymph node negative, hilar biliary cancers) | Most results include transplant combined with resection data; The OLT patients had a significantly longer survival than the 16 who did not undergo OLT (64.8% v. 0% at 5 years) |

ND = not discussed, OLT = orthotopic liver transplantation

**Table 14**. Cholangiocarcinoma: Patient Survival for Reports Published in 1995 or Later

| Reference | Operative mortality % | Median survival (months) | Patient Survival year (%) 1 | 2 | 3 | 5 | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| Ahrendt 1999[18] | 25 | Mean 21 +/-1 | 75 | | 38 | 0 | Two patients alive without evidence of recurrence at 10 months and 53 months; Survival compared to 1, 3, 5y rates for all 25 patients with cholangiocarcinoma and PSC: 28%, 9%, 0%, respectively; The actuarial survival of patients with cholangiocarcinoma managed with OLT was significantly lower than in the 26 PSC patients without cholangiocarcinoma managed since 1990 |
| Alessiani 1995[24] | Excluded operative mortality | 19 | 50 | | 20 | | 3 patients alive at 52, 54, 59 months without recurrence |
| Berdah 1996[91] | 50 | | 50 | | | | Survival of 16 months in patient with 13cm tumor |
| Casavilla 1997[10] | ND | | 70 | | 29 | 18 | Do not distinguish OLT from cluster transplant; 16/20 patients dead at time of follow-up; Compared to resected patients who had survival rates at 1-,3-, and 5-years of 60%, 37%, and 31%, respectively. |
| Cherqui 1995[34] | ND | | 100 | 100 | | | Alive and disease free at 25 months and 32 months |
| Chung 1997[85] | ND | | 83 | | 21 | 21 | 1/6 patients alive and free of disease. Compared to other "high risk" transplant indications where 3year survival was80% |
| De Vreede 2000[23] | ND | | | | | | All 11 were alive |
| Farges 1995[94] | ND | | 100 | 100 | 100 | 100 | Alive without recurrence at 8 years |
| Figueras 2000[15] | ND | | 100 | | 92 | 36 | Many results combine OLT with resection; Patients with OLT had better 5-year survival rates than those treated with tumor resection (36% v. 21%); |
| Foo 1997[28] | ND | | | | | | 1 patient alive without recurrence 5 years following OLT |
| Goss 1997[7] | ND | | 33 (known tumors)<br>100 (incidental tumors) | 33 (known tumors)<br>83 (incidental tumors) | | 0 (known tumors)<br>83 (incidental tumors) | Compared to survival for all OLT patients with PSC (127) at 1y, 2y and 5y – 90%, 86%, and 85%, respectively. Compared to all PSC patients without cholangiocarcinoma (n=113) at 1y, 2y and 5y: – 90%, 88%, 87%, respectively. 9 covariates evaluated in regression model. Cholangiocarcinoma on frozen section only predictor of "survival disadvantage" |
| Gruenberger 1996[22] | 7 | 14 | 53 | | 33<br>grade I: 82<br>grade II: 68<br>grade III: 50 | 33 | No statistical benefit observed in cirrhotic patients; Significantly better overall survival observed in patients without vascular invasion; Differentiation of tumor significant in multivariate analysis – comparing grade I and II tumors with grade III tumors revealed a better disease-free survival in the more differentiated tumor group (p=.009); |
| Iwatsuki 1998[5] | 6/27 OLT 2/11 OLT-CI | | 60 (OLT and OLT-CI)<br>59.3 (OLT)<br>54.6 (OLT-CI) | | 32 (OLT and OLT-CI)<br>36.2 (OLT)<br>9.1 (OLT-CI) | 25 (OLT and OLT-CI)<br>36.2 (OLT)<br>9.1 (OLT-CI) | Univariate analysis of transplant and partial hepatectomy: tumor tis 1,2 <.008, lymph node negative <.025, TNM stage 0,I,II <.007, negative margins <0.024, adjuvant therapy <0.043; Compared to hepatic resection with 1y, 3y and 5y survivals: 73.5%, 33.9%, 9.1%; Difference in survival between groups not statistically significant; After OLT patients with T-is, T-1 and T-2 had significantly better survival than T-3; 7 patients receiving OLT and 1 receiving OLT-CL lived free of tumor >5 years; One 5-year survivor pt died with tumor recurrence at 8y3m; After OLT positive surgical margins were associated with a significantly reduced survival; Of those living longer than 5 years, they are known to be alive and free of tumor at 8y, 15y, 11y, 7y, 7y, 7y, 6y; |
| Klempnauer 1997[13] | 15.6 | 19.68 +/- .33 | | | | 21 | Follow-up of long-term survivors 11, 5.3, 10.8, and 9.3 years. Prognosis after OLT was not significantly different from resection, although the procedure was reserved for patients with conventionally unresectable tumors. |
| Knechtle [19]1995[19] | ND | | 70 | 0 | | | 1 incidental tumor alive at 11months without recurrence and 1 known tumor alive at 20 months without survival; Compared to results for those without cholangiocarcinoma: 1y, 3y, and 5y survival of 88%, 85%, and 62%, respectively. |

| Reference | Operative mortality % | Median survival (months) | Patient Survival year (%) 1 | 2 | 3 | 5 | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| Launois 1999[88] | ND | | 75 | | 25 | 25 | 1 patient alive without recurrence at 7 years. One patient with cluster transplant died secondary to ileocolic leakage, one cluster patient without stomach and right colon resection was still alive; Compared results to those with report of 40 tumor resections for proximal tumors with 1y, 3y, and 5y survival rates of 57.1%, 28.6%, and 0%, respectively. |
| Liden 2000[9] | 50 | | 25 | 0 | | | 100% dead; 2 in early postoperative period from portal vein thrombosis and multi-system organ failure, 2 from disseminated cancer at 10 months and 16months |
| Loinaz – Moreno 1998[4] | ND | 58 | 100 | 100 | 100 | 0 | Disease recurrence and death at 58 months |
| Madariaga 1998[31] | ND | 48 | 100 | 100 | 100 | 0 | Died 4 years later with recurrent disease |
| Meyer 2000[1] | 10 | 8.4<br><br>22 (In 21 patients treated with 5-FU and XRT) | 72 | 48 | | 23 | 34% alive; 20 patients survived >3 years without recurrence, 11 >5 years; 95 patients died secondary to recurrent tumor; |
| Nashan 1996[17] | 50 | | | | | | No survival beyond 6 years; 2 recurrence of bile duct cancer at 6 months and 64 months leading to death; 1 recurrence of central cholangiocarcinoma at 5 months; Of 7 bile duct cancer 4 died from sepsis, 1 chronic graft failure, and 2 local recurrences; Of 2 gallbladder carcinomas both dead at 13 days from sepsis; 1 with intrahepatic disease died 14 months with recurrence |
| Neuhaus 1999[25] | 13 | | | | | | |
| Neuhaus 2000[26] | 14 | | | | | | 4-year survival including postoperative mortality 30%; Compared to patients undergoing right trisegmentectomy with 4-year survival 59% |
| Oldhafer 2000[60] | ND | | 20 | 20 | 20 | | Klatskin tumor survival time – unclear if from transplant or other ex situ procedur: death at 50 days, 113 days, 35 days – all from sepsis; One cholangiocarcinoma died 43 days from sepsis; One cholangiocarcinoma alive after 3 years 4 months without known recurrence in the patient without ex situ surgery; |
| Petrassi 1999[62] | ND | 7 | 0 | | | | Patient with visceral transplant died 45 days of sepsis, patient undergoing cluster trasplant died 97days of sepsis; |
| Pichlmayr 1998[11] | ND | 5.5 (intrahepatic)<br><br>19.2 (proximal) | 20.8 (intrahepatic)<br><br>65.5 (proximal) | | 6.3 (intrahepatic)<br><br>23.6 (proximal) | 0 (intrahepatic)<br><br>18.9 (proximal) | Proximal tumors with survivors at 10, 11, and 12 years without recurrence; Longest intrahepatic survivor 4.5 years without recurrence on follow-up |
| Pichlmayr 1996[8] | 12 | 15.5<br><br>I/II 37.8<br><br>III 19.6<br><br>IV 5.8 | 60<br><br>I/II 88.9<br><br>III 75<br><br>IV 33.3 | | 21.4<br><br>I/II 55.6<br><br>III 0<br><br>IV 0 | 17.1<br><br>I/II 44.4<br><br>III 0<br><br>IV 0 | 4 of 25 patients survived over 5 years; Patients alive at 8,9,and 10 years without recurrence; Stage II incidental tumor death at 5 years with recurrence; Survival for transplant of early tumor stage 1 year 88.9% and 5 year 44.4%; Univariate/multivariate analysis for resection and OLT; Survival correlates with UICC tumor stage. No difference when compared to resected group (1year survival 65%, 5yar 27.1%). Longest survival in patients with positive lymph nodes was only 16 months. |
| Robles 1999[87] | ND | | | | | | 2 alive and tumor free at 26months and 27months; 4 died from recurrence |
| Saldeen 1999[80] | 33 | | | 17 | | | One surviving patient with gallbladder cancer at 28 months without signs of recurrence; 3 deaths “directly linked to cholangiocarcinoma”; One early death related to multiple organ failure; One early death related to liver failure |
| Soderdahl 1995[81] | ND | | | | 17 | | 1/6 patients has survived >3years (although 9 reported in series?) |

| Reference | Operative mortality % | Median survival (months) | Patient Survival year (%) | | | | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 5 | |
| Urego 1999[20] | ND | | 90 – (in those with lymph node negative, hilar biliary cancers) | | 64.8 (in those with lymph node negative, hilar biliary cancers) | 64.8 (in those with lymph node negative, hilar biliary cancers) | OLT patients had a significantly longer survival than the 16 who did not undergo OLT (64.8% v. 0% at 5 years) |
| Washburn 1995[21] | ND | | 25 | 25 | 25 | 25 | PSC with extensive intrahepatic cholangiocarcinoma died from recurrence at 5.3 months. N1 hilar cholangiocarcinoma died with recurrence at 3months; N1 intrahepatic cholangiocarcinoma died recurrence at 6.4 months; intrahepatic without nodal involvement disease free at 5.5 years |

ND = not discussed, OLT = orthotopic liver transplantation, OLT-CI = cluster orthotopic liver transplantation, PSC = primary sclerosing cholangitis

**Table 15**. Cholangiocarcinoma: Patient Survival Following Extended Transplantation

| Reference | Operative mortality% | Median survival (months) | Patient Survival year (%) 1 | 2 | 3 | 5 | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| Iwatsuki 1998[5] | 6/27 OLT 2/11 OLT-cluster | | 60 (OLT and OLT-Cl)<br>59.3 (OLT)<br>54.6 (OLT-Cl) | | 32 (OLT and OLT-Cl)<br>36.2 (OLT)<br>9.1 (OLT-Cl) | 25 (OLT and OLT-Cl)<br>36.2 (OLT)<br>9.1 (OLT-Cl) | Univariate analysis of transplant and partial hepatectomy: tumor tis 1,2 <.008, lymph node negative <.025, TNM stage 0,I,II <.007, negative margins <0.024, adjuvant therapy <0.043; Compared to hepatic resection with 1y, 3y and 5y survivals: 73.5%, 33.9%, 9.1%; Difference in survival between groups not statistically significant; After OLT patients with T-is, T-1 and T-2 had significantly better survival than T-3; 7 patients receiving OLT and 1 receiving OLT-CL lived free of tumor >5 years; One 5-year survivor pt died with tumor recurrence at 8y3m; After OLT positive surgical margins were associated with a significantly reduced survival; Of those living longer than 5 years, they are known to be alive and free of tumor at 8y, 15y, 11y, 7y, 7y, 7y, 6y; |
| Knechtle 1993[29] | ND | | 0 | | | | Cholangiocarcinoma death with recurrence at 21 months; Gallbladder cancer death with recurrence at 11 months |
| Launois 1999[88] | ND | | 75 | | 25 | 25 | 1 patient alive without recurrence at 7 years. One patient with cluster died secondary to ileocolic leakage, one cluster patient without stomach and right colon resection was still alive; Compared results to those with report of 40 tumor resections for proximal tumors with 1y, 3y, and 5y survival rates 57.1%, 28.6%, and 0%, respectively. |
| Madariaga 1998[31] | ND | 48 | 100 | 100 | 100 | 0 | Died 4 years later with recurrent disease |
| Mieles 1990[27] | ND | | | | | | 1 patient with cholangiocarcinoma and 4 patients with bile duct cell carcinoma (3 whom had PSC) died at 57, 72, 112, 304, and 197days; 3 patients with duct cell cancer were still living at 296,290, and 247days; Patient with recurrent cholangiocarcinoma alive at 205days. |
| Oldhafer 2000[60] | ND | | 20 | 20 | 20 | | Klatskin tumor survival time – unclear if from transplant or other ex situ procedure: death at 50, 113, and 35 days – all from sepsis; One cholangiocarcinoma died 43 days from sepsis; One cholangiocarcinoma alive after 3 years 4 months without known recurrence in the patient without ex situ surgery; |
| Petrassi 1999[62] | ND | 7 | 0 | | | | Patient with visceral transplant died 45 days of sepsis, patient undergoing cluster transplant died 97days of sepsis; |

ND = not discussed, OLT = orthotopic liver transplantation, OLT-Cl = cluster transplantation, PSC = primary sclerosing cholangitis

**Table 16**. Cholangiocarcinoma: Recurrence and Disease-Free Survival for All Studies

| Reference | Disease features | Procedure | Recurrence (%) | Years of disease free survival (%) | | | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| | | | | 1 | 3 | 5 | |
| Abu-Elmagd 1993[6] | All 18 patients had PSC; 2 intrahepatic, 13 hilar, 3 gallbladder/cystic duct tumors; 11/18 incidental tumors; 11 patients received radiation and chemotherapy before and/or after OLT | 17 OLT;<br>1 OLT with abdominal exenteration | 55 (incidental tumors)<br><br>86 (known tumors) | | | | 5 (45%) Incidental tumor patients alive without recurrent 23-73 months; 1 (17%) known tumor alive at 26 months without recurrence |
| Ahrendt 1999[18] | Cholangiocarcinoma in PSC; Known diagnosis in 1, incidental diagnosis in 3; | OLT | 25 | | | | Two patients alive without evidence of recurrence at 10 months and 53 months |
| Alessiani 1995[24] | 12 extrahepatic tumors, 8 intrahepatic tumors | OLT, modified OLT, OLT with islet cells, OLT-pancreas-duodenum | 57 (in patients with at least 3 months follow-up) | | | | 3 patients alive at 52, 54, and 59 months without recurrence |
| Calne 1993[82] | 13 peripheral or central cholangiocarcinoma | OLT | | | | | 7 patients – including the longest survivor of 10 years 3 months - were still alive<br><br>46 died from recurrence |
| Casavilla 1997[10] | 20 intrahepatic tumors; 8 in the setting of cirrhosis; TNM classification: I+II 3; III 4; IVA 10; IVB 3 | OLT and Cluster OLT | 55 overall (44 in OLT-CI) | 67 | 31 | 31 | |
| Cherqui 1995[92] | Intrahepatic cholangiocarcinoma; 1 patient underwent OLT for recurrence after initial resection, 1 underwent OLT after initial exploratory laparotomy | OLT | 0 | 100 | | | Alive and disease free at 25 months and 32 months (in patient who underwent OLT for recurrence after initial resection) |
| Cherqui 1995[34] | 1 patient had PSC; 2 hilar tumors; Patient with PSC received adjuvant external radiation therapy | OLT with hepaticojejunostomy; OLT with pancreaticogastrostomy and gastrojejunostomy | 0 | | | | |
| Chung 1997[85] | ND | OLT | 83 | | | | 1/6 patients alive and free of disease<br>2 patients had tumors <2cm and both developed recurrent cholangiocarcinoma within 1 year and died |
| De Vreede 2000[23] | Unresectable cholangiocarcinoma above the cystic duct without intrahepatic or extrahepatic metastases initially received external-beam irradiation plus bolus 5-FU, followed by brachytherapy with iridium and infusion of 5-FU; OLT after exploratory laparotomy to rule out metastatic disease; 3 with stage I, 7 with stage II disease, 1 | OLT | 9 | | | | 10/11 disease free; Patient that developed recurrence was stage IVa, and developed asymptomatic elevation of CA 19-9 at 40 months. |

| Reference | Disease features | Procedure | Recurrence (%) | Years of disease free survival (%) | | | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| | | | | 1 | 3 | 5 | |
| | with stage IVa; 6 patients had PSC, 2 had cirrhosis; No frank vascular invasion; | | | | | | |
| Farges 1995[94] | Incidental cholangiocarcinoma in patient with PSC | OLT with subtotal duodenopancreatectomy | 0 | 100 | 100 | 100 | Alive without recurrence at 8 years |
| Farmer 1993[59] | 1 stage IVA distal common bile duct in patient with PSC; 1 IVA intrahepatic tumor; 1 stage 1 common hepatic duct in patient with concurrent biliary papillomatosis; No preoperative treatment; 1 patient received 5-FU and cisplatin post-operatively | OLT with pancreatico-duodenectomy | 0 | | | | |
| Foo 1997[28] | PSC with extrahepatic bile duct carcinoma; no malignancy in liver explant; Treated with external beam irradiation +/- 5-FU followed by transcatheter Ir boost | OLT | | | | | 1 patient alive without recurrence 5 years following OLT |
| Goldstein 1993[16] | All PSC. 17 in report (3 often excluded from results from "operative mortality") Of 17, 12 known tumors, 5 incidental tumors; Of 14, 11 known tumors, 3 incidental tumors; Location: 6 hilar, 6 peripheral, 2 hilar and peripheral; Lesions: 9 unilocal, 5 multifocal; TNM Staging: Stage I – 1, Stage II – 5, Stage III – 7, Stage IVa – 1; 12 Moderately differentiated, 2 well-differentiated; All patients received radiation therapy and 5-FU 8 weeks before OLT | OLT 12; OLT with extended resection 2 | 79 | 40 | | | 7 patients alive, 4 with recurrence, 3 without recurrence at 28, 31, and 44 months. Both well differentiated tumors recurred at 8months and 29 months; Recurrence occurred in 1 Stage I, 3 Stage II, 6 Stage III, and 1 Stage IVa; Sites of recurrence bone 4, lung 4, liver 3, pancreas 1; Of patients undergoing extended resection one is alive with recurrent disease, the other is alive without recurrence;<br><br>Average time of recurrence to death 1.4 months;<br>Death due to recurrence: 50 (n=7)<br>Mean time to recurrence 14.3 months |
| Gores 1993[32] | 8 patients with PSC, 2 with cirrhosis; Adjuvant protocol using external-beam irradiation plus bolus 5-FU followed by brachytherapy plus protracted venous includions 5-FU and subsequent OLT for early-stage cholangiocarcinoma | OLT | 8 | | | | 12/13 patients disease free; Patient who developed recurrence was stage IVa at OLT and developed asymptomatic, elevated CA 19-9 at 40months |
| Goss 1997[7] | All with PSC; 10 | OLT | 100 | | | | |

| Reference | Disease features | Procedure | Recurrence (%) | Years of disease free survival (%) | | | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| | | | | 1 | 3 | 5 | |
| | incidental tumors, 4 known tumors | | (within 6 months for known tumors) | | | | |
| Graziadei 1999[86] | 4 known tumors, 2 incidental tumors | OLT with Roux-en-Y | | | | | No recurrence in incidental tumors at 8 months and 6 years follow-up. In those with known tumor, 1 patient without chemotherapy but radiation died from recurrence "shortly after transplant", 3 patients underwent chemotherapy and radiation therapy before transplant without evidence of recurrence at mean follow-up 33 months |
| Gruenberger 1996[22] | 15 cholangiocarcinoma; 71% with multicentric lesions; Median tumor diameter 11.5 cm; 7% with associated cirrhosis; Differentiation: grade I good 23%; grade II moderate 55%, grade III 22% poor; Transplants after 1995 received neoadjuvant chemotherapy with 5 cycles of doxorubicin preop, intraoperative doxorubicin before manipulation of liver, and doxorubicin postoperative, and thereafter every 2 weeks to total dose of 300 mg/m2 | OLT | | 72 | | 39 | Differentiation of tumor significant in multivariate analysis – comparing grade I and II tumors with grade III tumors revealed a better disease-free survival in the more differentiated tumor group (p=.009);<br><br>Death due to recurrence: 55 |
| Haug 1992[84] | 3 received radiation and chemotherapy in perioperative period | OLT and Roux-en-Y with wide margins | 55 | | | | 5 patients alive. 4 alive without recurrence at 10, 29.87, 52.97, and 79.23m; 4/5 with recurrent disease died 3.2-8 months following OLT; 1 alive 3 years post OLT following chest well resection at 20 months for recurrence;<br><br>Most recurrences appearing in 1 year of OLT<br>Death due to recurrence: 56 (4/9) |
| Ismail 1990[55] | 2 known tumors in patients with PSC; 1 incidental tumor in patient with PSC; All stage III disease, all multifocal; | OLT | 100 | | | | Recurrence at 7 months, 11 months, and 12 months |
| Iwatsuk 1998[5] | Hilar cholangiocarcinoma; 21 known tumors, 17 incidental tumors; 27/38 with cirrhosis; TNM stage of 27 undergoing OLT: 3 0, 1 I, 9 II, 13 IVa, 1 IVb; Of the 11 undergoing OLT-CI: 1 O, 6 IVa, 4 IVb | 27 OLT; 11 OLT with upper abdominal exenteration and cluster organ transplant | | | | | One 5-year survivor died with recurrence at 8 years 3 months; Of those living longer than 5 years, they are known to be alive and free of tumor at 8, 15, 11, 7, 7, 7, and 6 years. |
| Klempnauer 1997[13] | Hilar cholangiocarcinoma | OLT | | | | 19 (4/21) | No 5 year disease free survivors had lymph node involvement at time of OLT. Of these 5 patients, stages at time of OLT were: 1 IIIa, 1 IIIb, and 2 IV |
| Knechtle 1995[19] | All with PSC; 2 with known tumors, 5 incidental tumors | OLT | | | | | 1 incidental tumor patient alive at 11months without recurrence and 1 known alive at 20 months without recurrence; |
| Knechtle 1993[29] | 1 cholangiocarcinoma, 1 gallbladder cancer | Cluster transplant with liver, pancreas, spleen, stomach, duodenum with transplant of liver, | 100 | 0 | | | Cholangiocarcinoma death with recurrence at 21 months; Gallbladder cancer death with recurrence at 11months |

| Reference | Disease features | Procedure | Recurrence (%) | Years of disease free survival (%) | | | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| | | | | 1 | 3 | 5 | |
| | | pancreas, and duodenum | | | | | |
| Launois 1999[88] | Proximal tumors; All Type IV, T3. Two were IVa and two IVb; | 2 OLT with extensive lymph node & Roux-en-Y; 1 OLT with porta hepatis resection and total pancreatectomy; 1 OLT with porta hepatis resection, total pancreatectomy, stomach and right colon: | | | | | 1 patient alive without recurrence at 7 years. One patient with cluster died secondary to ileocolic leakage, one cluster patient without stomach and right colon resection is still alive; |
| Liden 2000[9] | Incidental cholangiocarcinoma found in 4 patients with PSC | OLT | 50 | | | | 100% dead - 2 from disseminated cancer at 10 months and 16 months |
| Loinaz –Moreno 1998[4] | Hilar cholangiocarcinoma, TNM III. No cirrhosis. | OLT with Roux-en-Y | 100 | 100 | 100 | 0 | Disease recurrence and death at 58 months |
| Madariaga 1998[31] | Peripheral cholangiocarcinoma developed recurrent disease 7months following resection | OLT-CI | 100 | 100 | 100 | 0 | Died 4 years later with recurrent disease |
| Masada 1994[3] | Poorly differentiated, incidentally diagnosed hilar cholangiocarcinoma measuring 6.5x3x3cm | OLT | 100 | 0 | | | Recurrence 2.6 months following OLT with death at 3 months with multifocal cholangiocarcinoma present in hepatic allograft, lungs, and adrenals |
| Meyer 2000[1] | 43 incidental tumors (23 with PSC), 164 known or suspected cancers (25 with PSC); 27 multifocal tumors; 21 treated with 5-FU and radiation therapy; 12 patients with concurrent hepatocellular carcinoma | OLT | 51 (105/207)<br><br>40 (known tumors <5cm)<br><br>84 (known tumors >5cm)<br><br>63 (incidental tumors)<br><br>52 (those treated with 5-FU and radiation therapy) | | 10 | 5 | 34% alive; 20 patients survived >3 years without recurrence, 11 >5 years; 95 patients died secondary to recurrent tumor; 20 patients with known tumors <5cm – 8 had recurrence with median time to recurrence 6.5m, 12 without recurrence (4 died of sepsis, 8 alive). 19 patients with known tumors >5cm – 16 had recurrence with a median of 4 months, 3 without recurrence (1 died of sepsis 1 month, 2 survived 64 months and 78months)<br><br>Median time to recurrence 9.7months<br>Median time between recurrence and death 2 months<br>65% of recurrences occurred within 1 year of OLT<br>85% of recurrences occurred within 2 year of OLT<br><br>Median time to recurrence for known tumors <5cm 6.5 months<br>Mean time to recurrence for known tumors >5cm 4 months |
| Miros 1991[89] | All incidental tumors; 1 common hepatic duct, 1 common bile duct, 1 common bile duct/right and left hepatic ducts, 1 common bile duct/common hepatic duct/adjacent liver; 2 patients with Stage III cirrhosis, 2 patients with Stage IV cirrhosis. 3 well or moderately differentiated tumors, 1 intraductal papillary carcinoma; | OLT with Roux-en-Y | 50 | 75 | 50 | | One patient alive without tumor at 14 months; One patient with recurrence dead at 23 months; l with recurrence alive at 39 months; |
| Moreno Gonzalez 1993[Moreno- | Stage III Klatskin tumor, well differentiated, | OLT with Roux-en-Y | 0 | | | | |

| Reference | Disease features | Procedure | Recurrence (%) | Years of disease free survival (%) | | | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| | | | | 1 | 3 | 5 | |
| Gonzalez, 1993 #34 | underlying cirrhosis | | | | | | |
| Muiesan 1994[93] | 2 patients with PSC found to have cholangiocarcinoma – 1 known tumor and 1 incidental tumor measuring 3cm with a single lymph node metastasis found in the porta hepatitis | OLT with Roux-en-Y | 50 | 50 | 50 | | Preoperatively diagnosed cholangiocarcinoma died 2 months following OLT with recurrence; The incidental diagnosis is alive and disease-free 32 months following transplantation; |
| Nashan 1996 [17] | All patients with PSC; 1 known tumor, 9 incidental tumors; 7 extrahepatic bile duct tumor (1 I, 2 II, 3 IVa, 1 IVb), 2 gallbladder cancer (II, IVb), 1 intrahepatic tumor (II); | OLT | 60 | | | | 2 recurrence of bile duct cancer at 6 months and 64 months leading to death; 1 recurrence of central cholangiocarcinoma at 5 months; Of 7 gallbladder cancer 2 died from local recurrences; 1 with intrahepatic disease died 14 months with recurrence |
| Neuhaus 1994[35] | One patient with PSC did not have tumor on explant; 1 adenocarcinoma of hepatic bifurcation with positive lymph nodes and noted right ovary and paraaortal lymph node distant metastases, 3 tubular adenocarcinoma of hepatic bifurcation, 1 tubular/alveolar adenocarcinoma of hepatic bifurcation, 1 undifferentiated anaplastic adenocarcinoma of hepatic ducts | OLT with Kausch-Whipple Operation | 17 (1/6) | | | | 1 died after 6 months from diffuse metastases. |
| Neuhaus 1999 [25] | 15 Hilar tumors UICC Stage 1/II in 5, stage IVa in 8, stage IVb in 2, NO in 10, N1/2 5; Bismuth type IIIa in 2, IIIb in 2, IV in 11; No adjuvant radiation therapy or chemotherapy; 7-day course of postoperative octreotide used in last 8 OLT | OLT and partial pancreatoduodenectomy | 53 (8/15) | | | | |
| Neuhaus 2000[26] | 4 with IUCC I/II tumors, 9 IUCC IVa, 1 IVb | OLT and partial pancreatoduodenectomy | | | | | ½ of patients with recurrence had graft metastases |
| Oldhafer 2000 [60] | 2 cholangiocarcinoma and 3 Klatskin tumors | OLT following ex situ liver surgery; One patient with cholangiocarcinoma did not undergo ex situ surgery; | 0 | | 20 | | |
| Olthoff 1990 [53] | 2 with PSC, 1 without PSC | OLT | 67 | 0 | | | 2 PSC patients had recurrence at 22 months and 6 months |
| Petrassi 1999[62] | | OLT following abdominal | 0 | | | | Patient with visceral transplant died 45 days of sepsis, patient undergoing cluster transplant |

| Reference | Disease features | Procedure | Recurrence (%) | Years of disease free survival (%) | | | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| | | | | 1 | 3 | 5 | |
| | | exenteration; 1 patient received visceral transplant with hepatoduodenal ligament, duodenum, pancreas; 1 patient received cluster transplant of stomach, duodenum, ileum, pancreas, liver, right colon, and transverse colon | | | | | died 97days of sepsis; |
| Pichlmayr 1998 [11] | 20 Intrahepatic; 30 proximal of which 13 stage I&II, 4 stage III, 12 stage IV | OLT | | | | | Proximal tumors with survivors at 10, 11, and 12 years without recurrence; Longest intrahepatic survivor 4.5 years without recurrence on follow-up. |
| Pichlmayr 1996 [8] | Proximal bile duct cancer; 7 patients had PSC – all 7 had incidental tumors; 18 did not have PSC; Of incidental tumors. 1 II and 5 IVa & IVb ; Of total transplanted patients UICC tumor stage 1 I, 8 II, 4 III, 10 IVa, 2 IVb; | OLT | | | | | 4 of 25 patients survived over 5 years; Patients alive at 8, 9,and 10 years without recurrence. Stage II incidental tumor death at 5 years with recurrence; |
| Robles 1999[87] | 6 Bismuth type IV Klatkin's tumors | OLT with Roux-en-Y | 67 | | | | 2 alive and tumor free at 26 months and 27 months; 4 died from recurrence – 3 with local recurrence at 46, 43, and 19 months, another with pulmonary metastases as 12 months |
| Saldeen 1999[80] | All patients with PSC; 5 cholangiocarcinomas, 1 gallbladder carcinoma; | OLT | 50 | | | | One surviving patient with gallbladder cancer at 28 months without signs of recurrence; 3 deaths "directly linked to cholangiocarcinoma"; One early death related to multiple organ failure; One early death related to liver failure |
| Sansalone 1994[83] | 6 central cholangiocarcinoma, 5 peripheral cholangiocarcinoma 4 cholangiocarcinoma associated with liver cirrhosis and in 2 of them hepatocellular carcinoma concurrently; 2 patients with solitary lesions, 1 bifocal, 2 had more than 3 lesions; Median diameter of peripheral cholangiocarcinoma was 5.2cm; Grading G1 in 6 patients, G2 in 2 patients, G3 in 3 patientsAll peripheral cholangiocarcinoma were T4 by TNM. All central cholangiocarcinoma were B4 by Bismuth. In all patients resection margins were tumor-free, 3 with lymph node involvement, 3 vascular infiltration, and | OLT | 36 | 67 | 53 | 53 | 5 patients alive without disease at 25, 37, 42, 86, and 84 months. 4 patients with recurrence at 5, 9, 9, and 27months; 4 patients died of recurrence at 7, 5, 20, and 31months; Overall disease-free survival were not statistically different but survival decreased if there was lymph node or vascular invasion |

| Reference | Disease features | Procedure | Recurrence (%) | Years of disease free survival (%) | | | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| | | | | 1 | 3 | 5 | |
| | perineural infiltration in all Klatskin tumors. | | | | | | |
| Shaked 1992[79] | Two patients with PSC incidentally diagnosed with hilar tumors <2cm; resected margins free of tumor; | OLT with resection of common bile duct and Roux-en-Y | 50 | 50 | 50 | | One died with recurrence at 20 months; One alive without recurrence at 48months; |
| Washburn 1995[21] | 1 patient with sclerosing cholangitis and extensive intrahepatic cholangiocarcinoma; 3 patients with PSC – 1 N1 hilar, 1 N1 intrahepatic, 1 intrahepatic without nodal involvement | OLT | 75 | 25 | 25 | 25 | PSC with extensive intrahepatic cholangiocarcinoma died from recurrence at 5.3 months. N1 hilar cholangiocarcinoma died with recurrence at 3 months; N1 intrahepatic cholangiocarcinoma died recurrence at 6.4 months; intrahepatic without nodal involvement disease free at 5.5 years |

OLT = orthotopic liver transplantation, OLT-CI = cluster trasplantation, PSC = primary sclerosing cholangitis

**Table 17**. Cholangiocarcinoma: Recurrence and Disease-Free Survival for Incidental Tumors

| Reference | Recurrence (%) | Years of disease free survival (%) | | | Outcomes Comments |
|---|---|---|---|---|---|
| | | 1 | 3 | 5 | |
| Abu-Elmagd 1993[6] | 55 (incidental tumors)<br><br>86 (known tumors) | | | | 5 (45%) incidental tumor patients alive without recurrent 23-73 months |
| Farges 1995[94] | 0 | 100 | 100 | 100 | Alive without recurrence at 8 years |
| Graziadei 1999[86] | | | | | No recurrence in incidental tumors at 8 months and 6 years follow-up |
| Knechtle 1995[19] | | | | | 1 incidental tumor patient alive at 11 months without recurrence and 1 known tumor patient alive at 20 months without recurrence |
| Liden 2000[9] | 50 | | | | 100% dead - 2 from disseminated cancer at 10 months and 16 months |
| Meyer 2000[1] | 51 (105/207)<br><br>40 (known tumors <5cm)<br><br>84 (known tumors >5cm)<br><br>63 (incidental tumors)<br><br>52 (those treated with 5-FU and radiation therapy) | | 10 | 5 | |
| Pichlmayr 1996 [8] | | | | | Stage II incidental tumor death at 5 years with recurrence |
| Shaked 1992[79] | 50 | 50 | 50 | | One died with recurrence at 20 months; One alive without recurrence at 48 months |

**Table 18**. Cholangiocarcinoma: Recurrence and Disease-Free Survival for Peripheral Tumors

| Reference | Recurrence (%) | Years of disease free survival (%) | | | Outcomes Comments |
|---|---|---|---|---|---|
| | | 1 | 3 | 5 | |
| Casavilla 1997[10] | 55 (overall)<br>44 (OLT-CI) | 67 | 31 | 31 | |
| Cherqui 1995[92] | 0 | 100 | | | Alive and disease free at 25 months and 32 months (in patient who underwent OLT for recurrence after initial resection) |
| Madariaga 1998[31] | 100 | 100 | 100 | 0 | Died 4 years later with recurrent disease |

OLT = orthotopic liver transplantation, OLT-CI = cluster transplantation

**Table 19**. Cholangiocarcinoma: Recurrence and Disease-free Survival for Central Tumors

| Reference | Recurrence (%) | Years of disease free survival (%) | | | Outcomes Comments |
|---|---|---|---|---|---|
| | | 1 | 3 | 5 | |
| Foo 1997[28] | | | | | 1 patient alive without recurrence 5 years following OLT |
| Iwatsuki 1998[5] | | | | | One 5-year survivor died with recurrence at 8 years 3months; Of those living longer than 5 years, recipients are known to be alive and free of tumor at 8, 15, 11, 7, 7, 7, and 6 years; |
| Klempnauer 1997[13] | | | | 19 (4/21) | No 5 year disease free survivors had lymph node involvement at time of OLT. Of these 5 patients, stages at time of OLT were: 1 IIIa, 1 IIIb, and 2 IV |
| Launois 1999[88] | | | | | 1 patient alive without recurrence at 7 years. |
| Loinaz –Moreno 1998[4] | 100 | 100 | 100 | 0 | Disease recurrence and death at 58 months |
| Masada 1994[3] | 100 | 0 | | | Recurrence 2.6 months following OLT with death at 3 months with multifocal cholangiocarcinoma present in hepatic allograft, lungs, and adrenals |
| Moreno Gonzalez 1993 | 0 | | | | |
| Neuhaus 1999 [25] | 53 (8/15) | | | | |
| Pichlmayr 1998 [11] | | | | | Proximal tumors with survivors at 10 years, 11 years, and 12 years without recurrence; Longest intrahepatic survivor 4.5 years without recurrence on follow-up |
| Pichlmayr 1996 [8] | | | | | Patients alive at 8, 9,and 10 years without recurrence. Stage II incidental tumor death at 5 years with recurrence; |
| Robles 1999[87] | 67 | | | | 2 alive and tumor free at 26 months and 27 months; 4 died from recurrence – 3 with local recurrence at 46, 43, and 19 months, another with pulmonary metastases as 12months |
| Shaked 1992[79] | 50 | 50 | 50 | | One died with recurrence at 20 months; One alive without recurrence at 48 months; |

OLT = orthotopic liver transplantation

**Table 20.** Cholangiocarcinoma: Recurrence and Disease-Free Survival for Patients with Primary Sclerosing Cholangitis

| Reference | Recurrence (%) | Years of disease free survival (%) | | | Outcomes Comments |
|---|---|---|---|---|---|
| | | 1 | 3 | 5 | |
| Abu-Elmagd 1993[6] | 55 (incidental tumors)<br><br>86 (known tumors) | | | | 5 (45%) incidental tumor patients alive without recurrent 23-73 months; 1 (17%) known tumor alive at 26 months without recurrence |
| Ahrendt 1999[18] | 25 | | | | Two patients alive without evidence of recurrence at 10 months and 53 months |
| Cherqui 1995[34] | 0 | | | | |
| Farges 1995[94] | 0 | 100 | 100 | 100 | Alive without recurrence at 8 years |
| Foo 1997[28] | | | | | 1 patient alive without recurrence 5 years following OLT |
| Goldstein 1993[16] | 79 | 40 | | | 7 patients alive, 4 with recurrence, 3 without recurrence at 28 months, 31 months, and 44 months. Both well differentiated tumors recurred at 8months and 29 months; Recurrence occurred in 1 Stage I, 3 Stage II, 6 Stage III, and 1 Stage IVa; Sites of recurrence: bone 4, lung 4, liver 3, pancreas 1; Of patients undergoing extended resection one was alive with recurrent disease, the other was alive without recurrence;<br>Average time of recurrence to death 1.4 months;<br>Death due to recurrence: 50 (n=7)<br>Mean time to recurrence 14.3 months |
| Goss 1997[7] | 100 (within 6 months for known tumors) | | | | |
| Ismail 1990[55] | 100 | | | | Recurrence at 7 months, 11 months, 12 months |
| Knechtle 1995[19] | | | | | 1 incidental alive at 11 months without recurrence and 1 known alive at 20 months without recurrence; |
| Liden 2000[9] | 50 | | | | 100% dead - 2 from disseminated cancer at 10 months and 16 months |
| Muiesan 1994[93] | 50 | 50 | 50 | | Known cholangiocarcinoma died 2 months following OLT with recurrence; The incidental diagnosis is alive and disease-free 32 months following transplantation; |
| Nashan 1996 [17] | 60 | | | | 2 recurrence of bile duct carcinoma at 6 months and 64 months leading to death; 1 recurrence of central cholangiocarcinoma at 5 months; Of 7 gallabladder cancers 2 died from local recurrences; 1 with intrahepatic disease died 14 months with recurrence |
| Olthoff 1990 [53] | 67 | 0 | | | 2 PSC patients had recurrence at 22 months and 6 months; |
| Saldeen 1999[80] | 50 | | | | One surviving patient with gallbladder cancer at 28 months without signs of recurrence; 3 deaths “directly linked to cholangiocarcinoma”; One early death related to multiple organ failure; One early death related to liver failure |
| Shaked 1992[79] | 50 | 50 | 50 | | One died with recurrence at 20 months; One alive without recurrence at 48 months; |
| Washburn 1995[21] | 75 | 25 | 25 | 25 | PSC with extensive intrahepatic cholangiocarcinoma died from recurrence at 5.3 months. N1 hilar cholangiocarcinoma died with recurrence at 3 months; N1 intrahepatic cholangiocarcinoma died recurrence at 6.4 months; intrahepatic without nodal involvement disease-free at 5.5 years |

OLT = orthotopic liver transplantation, PSC = primary sclerosing cholangitis

**Table 21**. Cholangiocarcinoma: Recurrence and Disease-Free Survival by Stage of Disease

| Reference | Recurrence (%) | Years of disease free survival (%) | | | Outcomes Comments |
|---|---|---|---|---|---|
| | | 1 | 3 | 5 | |
| Chung 1997[85] | 83 | | | | 1/6 patients alive and free of disease<br>2 patients had tumors <2cm and both developed recurrent cholangiocarcinoma within 1 year and died |
| Gruenberger 1996[22] | | 72 | | 39 | Differentiation of tumor significant in multivariate analysis – comparing grade I and II tumors with grade III tumors revealed a better disease-free survival in the more differentiated tumor group (p=.009);<br><br>Death due to recurrence: 55 |
| Ismail 1990[55] | 100 | | | | Recurrence at 7months, 11months, and 12months |
| Iwatsuki 1998[5] | | | | | One 5-year survivor died with recurrence at 8 years 3 months; Of those living longer than 5 years, they are known to be alive and free of tumor at 8,15, 11, 7, 7, 7, and 6 years; |
| Loinaz –Moreno 1998[4] | 100 | 100 | 100 | 0 | Disease recurrence and death at 58 months |
| Masada 1994[3] | 100 | 0 | | | Recurrence 2.6 months following OLT with death at 3 months with multifocal cholangiocarcinoma present in hepatic allograft, lungs, adrenals |
| Meyer 2000[1] | 51 (105/207)<br><br>40 (known tumors <5cm)<br><br>84 (known tumors >5cm)<br><br>63 (incidental tumors)<br><br>52 (those treated with 5-FU and radiation therapy) | | 10 | 5 | 34% alive; 20 patients survived >3 years without recurrence, 11 >5 years; 95 patients died secondary to recurrent tumor; 20 patients with known tumors <5cm – 8 had recurrence with median time to recurrence 6.5months 12 without recurrence (4 died of sepsis, 8 alive). 19 patients with known tumors >5cm – 16 had recurrence with a median of 4 months, 3 without recurrence (1 died of sepsis 1m, 2 survived 64 months and 78 months)<br><br>Median time to recurrence 9.7months<br>Median time between recurrence and death 2 months<br>65% of recurrences occurred within 1 years of OLT<br>85% of recurrences occurred within 2 years of OLT<br><br>Median time to recurrence for known tumors <5cm 6.5 months<br>Mean time to recurrence for known tumors >5cm 4 months |
| Moreno Gonzalez 1993 | 0 | | | | |
| Pichlmayr 1998 [11] | | | | | Proximal tumors with survivors at 10, 11, and 12 years without recurrence; Longest intrahepatic survivor 4.5 years without recurrence on follow-up. |
| Pichlmayr 1996 [8] | | | | | 4 of 25 patients survived over 5 years; Patients alive at 8, 9,and 10 years without recurrence. Stage II incidental tumor death at 5 years with recurrence; |
| Sansalone 1994[83] | 36 | 67 | 53 | 53 | 5 patients alive without disease at 25, 37, 42, 84, and 86 months. 4 patients with recurrence at 5, 9, 9, and 27; 4 patients died of recurrence at 7, 5, 20, and 31 months; Overall disease-free survival were not statistically different but survival decreased if there was lymph node or vascular invasion |
| Shaked 1992[79] | 50 | 50 | 50 | | One died with recurrence at 20 months; One alive without recurrence at 48 months; |
| Washburn 1995[21] | 75 | 25 | 25 | 25 | PSC with extensive intrahepatic cholangiocarcinoma died from recurrence at 5.3 months. N1 hilar cholangiocarcinoma died with recurrence at 3 months; N1 intrahepatic cholangiocarcinoma died recurrence at 6.4 months; intrahepatic without nodal involvement disease free at 5.5 years |

OLT = orthotopic liver transplantation, PSC = primary sclerosing cholangitis

**Table 22.** Cholangiocarcinoma: Recurrence and Disease-Free Survival in Studies Reporting Adjuvant and Neoadjuvant Therapies.

| Reference | Recurrence (%) | Years of disease free survival (%) | | | Outcomes Comments |
|---|---|---|---|---|---|
| | | 1 | 3 | 5 | |
| Foo 1997[28] | | | | | 1 patient alive without recurrence 5 years following OLT |
| Goldstein 1993[16] | 79 | 40 | | | 7 patients alive, 4 with recurrence, 3 without recurrence at 28 months, 31 months, and 44 months. Both well differentiated tumors recurred at 8 months and 29 months; Recurrence occurred in 1 Stage I, 3 Stage II, 6 Stage III, and 1 Stage IVa; Sites of recurrence bone 4, lung 4, liver 3, pancreas 1; Of patients undergoing extended resection one was alive with recurrent disease, the other was alive without recurrence;<br>Average time of recurrence to death 1.4 months;<br>Death due to recurrence: 50 (n=7)<br>Mean time to recurrence 14.3 months |
| Meyer 2000[1] | 51 (105/207)<br><br>40 (known tumors <5cm)<br><br>84 (known tumors >5cm)<br><br>63 (incidental tumors)<br><br>52 (those treated with 5-FU and radiation) | | 10 | 5 | 34% alive; 20 patients survived >3 years without recurrence, 11 >5 years; 95 patients died secondary to recurrent tumor; 20 patients with known tumors <5cm – 8 had recurrence with median time to recurrence 6.5m, 12 without recurrence (4 died of sepsis, 8 alive). 19 patients with known tumors >5cm – 16 had recurrence with a median of 4 months, 3 without recurrence (1 died of sepsis 1 month, 2 survived 64 months and 78 months)<br><br>Median time to recurrence 9.7months<br>Median time between recurrence and death 2 months<br>65% of recurrences occurred within 1y of OLT<br>85% of recurrences occurred within 2y of OLT<br><br>Median time to recurrence for known tumors <5cm 6.5 months<br>Mean time to recurrence for known tumors >5cm 4 months |

OLT = orthotopic liver transplantation

**Table 23.** Cholangiocarcinoma: Recurrence and Disease-Free Survival for All Reports after 1995

| Reference | Recurrence (%) | Years of disease free survival (%) | | | Outcomes Comments |
|---|---|---|---|---|---|
| | | 1 | 3 | 5 | |
| Ahrendt 1999[18] | 25 | | | | Two patients alive without evidence of recurrence at 10 months and 53 months |
| Alessiani 1995[24] | 57 (in patients with at least 3 months follow-up) | | | | 3 patients alive at 52, 54, 59 months without recurrence |
| Casavilla 1997[10] | 55 (overall)<br>44 (OLT-CI) | 67 | 31 | 31 | |
| Cherqui 1995[92] | 0 | 100 | | | Alive and disease free at 25 months and 32 months (in patient who underwent OLT for recurrence after initial resection) |
| Cherqui 1995[34] | 0 | | | | |
| Chung 1997[85] | 83 | | | | 1/6 patients alive and free of disease<br>2 patients had tumors <2cm and both developed recurrent cholangiocarcinoma within 1 year and died |
| De Vreede 2000[23] | 9 | | | | 10/11 disease free; Patient that developed recurrence was stage IVa, and developed asymptomatic elevation of CA 19-9 at 40 months. |
| Farges 1995[94] | 0 | 100 | 100 | 100 | Alive without recurrence at 8 years |
| Foo 1997[28] | | | | | 1 patient alive without recurrence 5 years following OLT |
| Goss 1997[7] | 100 (within 6 months for known tumors) | | | | |
| Graziadei 1999[86] | | | | | No recurrence in incidental tumors at 8 months and 6 years follow-up. In those with known tumors, 1 patient without chemotherapy but treated with radiation died from recurrence "shortly after transplant", 3 patients underwent chemotherapy and radiation therapy before transplant without evidence of recurrence at mean follow-up of 33 months |
| Gruenberger 1996[22] | | 72 | | 39 | Differentiation of tumor significant in multivariate analysis – comparing grade I and II tumors with grade III tumors revealed a better disease-free survival in the more differentiated tumor group (p=.009);<br><br>Death due to recurrence: 55 |
| Iwatsuk 1998[5] | | | | | One 5-year survivor died with recurrence at 8 years 3 months; Of those living longer than 5 years, they are known to be alive and free of tumor at 8, 15, 11, 7, 7, 7, and 6 years; |
| Klempnauer 1997[13] | | | | 19 (4/21) | No 5 year disease free survivors had lymph node involvement at time of OLT. Of these 5 patients, stages at time of OLT were: 1 IIIa, 1 IIIb, and 2 IV |
| Knechtle 1995[19] | | | | | 1 incidental tumor alive at 11 months without recurrence and 1 known tumor alive at 20 months without recurrence; |
| Launois 1999[88] | | | | | 1 patient alive without recurrence at 7 years. One patient with OLT-CI died secondary to ileocolic leakage, one cluster patient without stomach and right colon resection was still alive; |
| Liden 2000[9] | 50 | | | | 100% dead - 2 from disseminated cancer at 10 months and 16 months |
| Loinaz –Moreno 1998[4] | 100 | 100 | 100 | 0 | Disease recurrence and death at 58 months |
| Madariaga 1998[31] | 100 | 100 | 100 | 0 | Died 4 years later with recurrent disease |
| Meyer 2000[1] | 51 (105/207)<br><br>40 (known tumors <5cm)<br><br>84 (known tumors >5cm)<br><br>63 (incidental tumors)<br><br>52 (those treated with 5-FU and radiation) | | 10 | 5 | 34% alive; 20 patients survived >3 years without recurrence, 11 >5 years; 95 patients died secondary to recurrent tumor; 20 patients with known tumors <5cm – 8 had recurrence with median time to recurrence 6.5 months, 12 without recurrence (4 died of sepsis, 8 alive). 19 patients with known tumors >5cm – 16 had recurrence with a median of 4 months, 3 without recurrence (1 died of sepsis 1m, 2 survived 64 months and 78 months)<br><br>Median time to recurrence 9.7months<br>Median time between recurrence and death 2 months<br>65% of recurrences occurred within 1 years of OLT<br>85% of recurrences occurred within 2 years of OLT<br><br>Median time to recurrence for known tumors <5cm 6.5 months<br>Mean time to recurrence for known tumors >5cm 4 months |
| Nashan 1996 [17] | 60 | | | | 2 recurrence of bile duct cancers at 6 months and 64 months leading to death; 1 recurrence of central cholangiocarcinoma at 5 months; Of 7 gallbladder cancer 2 died from local recurrences; 1 with intrahepatic disease died 14 months with recurrence |
| Neuhaus 1999 [25] | 53 (8/15) | | | | |
| Neuhaus 2000[26] | | | | | ½ of patients with recurrence had graft metastases |
| Oldhafer 2000 [60] | 0 | | 20 | | |

| Reference | Recurrence (%) | Years of disease free survival (%) 1 | 3 | 5 | Outcomes Comments |
|---|---|---|---|---|---|
| Petrassi 1999[62] | 0 | | | | Patient with visceral transplant died 45 days of sepsis, patient undergoing OLT-CI died 97 d aysof sepsis; |
| Pichlmayr 1998 [11] | | | | | Proximal tumors with survivors at 10, 11, and 12 years without recurrence; Longest intrahepatic survivor 4.5 years without recurrence on follow-up |
| Pichlmayr 1996 [8] | | | | | 4 of 25 patients survived over 5 years; Patients alive at 8, 9,and 10 years without recurrence. Stage II incidental tumor death at 5 years with recurrence; |
| Robles 1999[87] | 67 | | | | 2 alive and tumor free at 26 months and 27 months; 4 died from recurrence – 3 with local recurrence at 46, 43, and 19 months, another with pulmonary metastases at 12 months |
| Saldeen 1999[80] | 50 | | | | One surviving patient with gallbladder cancer at 28 months without signs of recurrence; 3 deaths “directly linked to cholangiocarcinoma”; One early death related to multiple organ failure; One early death related to liver failure |
| Washburn 1995[21] | 75 | 25 | 25 | 25 | PSC with extensive intrahepatic cholangiocarcinoma died from recurrence at 5.3 months. N1 hilar cholangiocarcinoma died with recurrence at 3 months; N1 intrahepatic cholangiocarcinoma died recurrence at 6.4 months; intrahepatic without nodal involvement disease free at 5.5 years |

OLT = orthotopic liver transplantation, OLT-CI = cluster transplantation, PSC = primary sclerosing cholangitis

**Table 24.** Cholangiocarcinoma: Recurrence and Disease-Free Survival Following Extended Transplantation

| Reference | Recurrence (%) | Years of disease free survival (%) | | | Outcomes Comments |
|---|---|---|---|---|---|
| | | 1 | 3 | 5 | |
| Alessiani 1995[24] | 57 (in patients with at least 3 months follow-up) | | | | 3 patients alive at 52,54, and 59 months without recurrence |
| Knechtle 1993[29] | 100 | | | | Cholangiocarcinoma death with recurrence at 21 months |
| Madariaga 1998[31] | 100 | 100 | 100 | 0 | Died 4y years later with recurrent disease |

OLT-CI = cluster transplantation

**Table 25.** Cholangiocarcinoma: Graft Survival for All Studies.

| Reference | Disease features | Procedure | 1-year graft survival | Outcomes Comments |
|---|---|---|---|---|
| De Vreede 2000[23] – | Unresectable cholangiocarcinoma above the cystic duct without intrahepatic or extrahepatic metastases initially received external-beam irradiation plus bolus 5-FU, followed by brachytherapy with iridium and infusion of 5-FU; OLT after exploratory laparotomy to rule-out metastatic disease; 3 with stage I, 7 with stage II disease, 1 with stage IVa; 6 patients had PSC, 2 had cirrhosis; No frank vascular invasion; | OLT | | All 11 are alive; 1 patient underwent retransplant from early hepatic artery thrombisis and is "well" 76 months following 2nd OLT |
| Farmer 1993[59] | 1 stage IVA distal common bile duct tumor in patient with PSC; 1 IVA intrahepatic tumor; 1 stage 1 common hepatic duct in patient with concurrent biliary papillomatosis; No preoperative treatment; 1 patient received 5-FU and cisplatin post-operatively | OLT with pancreatico-duodenectomy | 67 | 1 graft lost at 3 months requiring retransplant – diagnosis of patient not given |
| Gores 1993[32] | 8 patients with PSC, 2 with cirrhosis; Adjuvant protocol using external-beam irradiation plus bolus 5-FU followed by brachytherapy plus protracted venous includions 5-FU and subsequent OLT for early-stage cholangiocarcinoma | OLT | 91 | Original graft survival rate 91% (unable to determine time given results); One patient underwent re-transplant at 1month because of early hepatic artery thrombosis and is well 7months following 2nd OLT; |
| Loinaz –Moreno 1998[4] | Hilar cholangiocarcinoma, TNM III. No cirrhosis. | OLT with Roux-en-Y | 100 | Retransplanted at 37months for chronic rejection. Disease recurrence and death at 58 months |
| Moreno Gonzalez 1993 | Stage III Klatskin tumor, well differentiated, underlying cirrhosis | OLT with Roux-en-Y | | Alive at 44 months; required retransplant at 15 months for chronic rejection without recurrence. |

OLT = orthotopic liver transplantation, PSC = primary sclerosing cholangitis

**Table 26**. Cholangiocarcinoma: Quality of Life Outcomes for All Studies.

| Reference | Dz features | Procedure | Quality of Life |
|---|---|---|---|
| Cherqui 1995[34] | 1 patient had PSC; 2 hilar tumors; Patient with PSC received adjuvant external radiation | OLT with hepaticojejunostomy; OLT with pancreaticogastrostomy and gastrojejunostomy | "Good health" at 28 months; "Good health" at 18 months |
| Neuhaus 1994[35] | One patient with PSC did not have tumor on explant; 1 adenocarcinoma of hepatic bifurcation with positive lymph nodes and noted right ovary and paraaortal lymph node distant metastases, 3 tubular adenocarcinoma of hepatic bifurcation, 1 tubular/alveolar adenocarcinoma of hepatic bifurcation, 1 undifferentiated anaplastic adenocarcinoma of hepatic ducts | OLT with Kausch-Whipple Operation | 4 patients working; 4 "excellent" (patient with no tumor, patient who died 6 months from diffuse metastasis was "excellent for 4 months", 1 tubular/alveolar adenocarcinoma excellent and working and 1 tubular/adenocarcinoma excellent for 6 months then recurrence), 2 "good" (both are working) |

OLT = orthotopic liver transplantation, PSC = primary sclerosing cholangitis

**Table 26.** Neuroendocrine Tumors: Description of Studies by Transplant Center.

| Reference | Location (Years of transplants) | Number of patients | Follow-up (months) | % male | Age (years) | Disease features | Procedure |
|---|---|---|---|---|---|---|---|
| Alessiani 1995[24] | Pittsburgh (88-92) | 14 | ND | ND | ND | Neuroendocrine | OLT, modified OLT, OLT with islet cells, OLT-pancreas-duodenum – results reported as combination of procedures |
| Iwatsuki 1990[5] | Pittsburgh | 2 | 42-60 | ND | ND | Metastatic glucagonoma | OLT |
| Mieles 1990[27] | Pittsburgh (88-89) | 3 | .33-11 | 34 | 35 | 3 Carcinoid tumors: primary in duodenum, stomach, and pancreas.<br><br>One previously treated with adriamycin and tumor embolization | Cluster transplant including liver, stomach, pancreas, spleen, duodenum, proximal jejunum, and ascending plus transverse colon |
| Todo 1995[39] | Pittsburgh (91-93) | 1 | 1.76 | 0 | ND | Malignant neuroendocrine tumor | Abdominal multivisceral transplant including stomach, liver, pancreas, intestine, and colon |
| Alsina 1990[96] | Hartford (89-90) | 2 | 5-13 | 100 | 50 | 1 neuroendocrine with carcinoid and islet cell glucagonoma features, 1 islet cell carcinoma;<br><br>Islet cell carcinoma treated with 5-FU and streptozocin for 1 year | OLT with distal pancreatectomy & splenectomy and OLT and Whipple |
| Anthuber 1996[97] | Muchen-Grosshadern, Germany | 4 | .34-33 | 50 | 50 | 1 neuroendocrine tumor, 1 glucagonoma, 2 carcinoid tumors | OLT and OLT with upper abdominal exenteration |
| Bechstein 1994[98] | Berlin, Germany (88-93) | 1 | 42 | 0 | 50 | Carcinoid of rectum with known liver metastases at time of local resection 1985; transplant in 1990 | OLT and right-sided adrenalectomy of adenoma |
| Bramley 1990[99] | Leeds, UK | 1 | 12 | 0 | 41 | VIPoma;<br><br>Trial of treatment with indomethacin, steroids, pancreatic enzymes, somatostatin, alpha interferon | OLT with pancreatectomy and splenectomy |
| Caplin 1998[100] | London, UK (96) | 1 | 15 | 0 | 19 | Gastric carcinoid with liver metastases developing inferior vena cava compression;<br><br>Previously treated with octreotide, hepatic arterial embolization | OLT |
| Claure 2000[101] | Stanford | 1 | 6 | 0 | 51 | Carcinoid: primary jejunum;<br><br>Treated with somatostatin and jejunal resection prior to OLT | OLT |
| Coperchini 1996[102] | Victoria, Austria | 2 | 24 | 50 | 40 | Carcinoid: 1 ileocecal and 1 pancreas primary;<br><br>One patient treated with ileal tumor resection and 2 cycles of 5-FU and streptozocin without response; both patients received somatostatin | OLT; OLT with retroperitoneal lymph node dissection |
| Curtiss 1995[103] | Mt. Sinai, NY (90-93) | 3 | 12-30 | 67 | 46 | 1 VIPoma, 2 nonfunctioning neuroendocrine tumors;<br><br>One treated unsuccessfully with chemoembolization; one treated with resection, chemoembolization, chemotherapy, and somatostatin | OLT; OLT with pancreatectomy |
| Dousset 1995[104, 105] | Paris, France (89-92) | 9 | .1-24 | 67 | 47 | 4 carcinoid tumors (primary: 1 ileum, 2 pancreas, 1 stomach), 4 gastrinomas, 1 glucagonoma;<br><br>All patients received medical treatment before transplant; 7/9 received surgical resection before transplant; No postoperative chemotherapy | 8 full size OLT; 1 right half split |
| Le Treut 1997[41] | Marseilles, France (89-94) Reporting all cases in France | 31 | Median 57 (10-77) | 55 | 45(26-60) | 15 carcinoid tumors, 16 islet cell tumors, 7 gastrinomas, 1 glucagonoma, 8 nonfunctioning islet cell cancers; Location of carcinoid primary: 7 ileum, 3 lung, 2 stomach, 1 sigmoid, 1 rectum, 1 pancreas; 8 OLT performed to cure without symptoms, 11 for pain/debility, 11 hormone symptoms, 1 emergent for variceal bleeding; Resection of primary tumor prior to OLT in 17 patents, at time of OLT in 11 patients, following OLT in 2 patient; 23 with systemic or intraarterial chemotherapy, most commonly 5-FU/Streptozocin; "most" carcinoids received octreotide, "most" gastrinomas received omeprazole; 5 patients without surgery or chemotherapy prior to OLT | Total hepatectomy with lymph node dissection in all procedures; 14 with extrahepatic resection; upper abdominal exenteration in 3 cases; injection of pancreatic islet cells in 1 case |
| Farmer 1993[59] | UCLA (84-92) | 2 | 29 | ND | 39±12 | 2 nonfunctioning neuroendocrine tumors from pancreatic head<br><br>One received radiation therapy and 5-FU and streptozotocin preoperatively | OLT and foregut resection |
| Olthoff 1990[53] | UCLA (84-89) | 2 | 5-70 | ND | 36.6±18.4 | Islet cell cancer (foam cell) with positive lymph node and margins; Moderate differentiated pancreatic cancer with local invasion of diaphragm with positive lymph nodes and margins treated with fluorouracil postoperatively | OLT with foregut resection including total hepatectomy, pancreatectomy, partial gastrectomy, subtotal colectomy, splenectomy, duodenectomy |

| Reference | Location (Years of transplants) | Number of patients | Follow-up (months) | % male | Age (years) | Disease features | Procedure |
|---|---|---|---|---|---|---|---|
| Frilling 1998[106, 107] | Hamburg, Germany (92-94) | 4 | .1-48 | 75 | 54 | 3 carcinoid tumors (primary – 2 bronchial, 1 pancreas), 1 VIPoma;<br><br>One patient with bronchial carcinoid s/p lobectomy; One bronchial carcinoid treated with octreotide and 3 courses of 5-FU and streptozocin prior to OLT; Pancreatic carcinoid patient underwent subtotal pancreatectomy prior to OLT; VIPoma of pancreatic head resected at time of OLT; | OLT; VIPoma received one OLT-Small intestine cluster transplant |
| Gulanikar 1991[108] | Nova Scotia, Canada | 1 | 5 | 0 | 55 | Carcinoid – few metastatic nodules noted on anterior abdominal wall at time of transplant | OLT with Billroth II |
| Hao 1996[109] | Yale | 1 | 5 | 100 | 42 | 0.5 cm common bile duct carcinoid producing gastrin and serotonin; diagnosed incidentally | OLT |
| Knetchtle 1993[29] | Madison, WI | 3 | 13-30 | ND | ND | Low grade carcinoid of pancreas, low grade islet cell cancer, and gastrinoma | Cluster transplant with liver, pancreas, spleen, stomach, duodenum with transplant of liver, pancreas, and duodenum |
| Lang 1999[40] | Essen, Germany (89-97) | 10 | To 1/99 | 40 | 45(25-61) | Pancreas tumors | OLT with lymph node dissection of hepatic hilus; 9 full grants, 1 reduced grant including IV-VIII+I; 4 tumors removed with OLT; 5 pancreatectomies at time of OLT; 1 tumor removed 46 months following OLT |
| Martin 1996[110] | Iowa City (92-95) | 1 | 29 | ND | 50 | Diffuse Glucagonoma;<br><br>Received 3 cycles of hepatic arterial chemoembolization, streptozocin, and doxorubicin prior to OLT. | OLT and total pancreatectomy |
| Pichlmayr 1998[11] | Hannover, Germany (72-96) | 15 | ND | ND | ND | | OLT |
| Routley 1995[42] | King's College London (83-93) | 11 | Median 25(8-106) | 55 | 45(34-52) | 6 carcinoid tumors; 5 ampudomas; no extrahepatic tumor at time of OLT; primary sites: anus 1, unknown 3, ileum 2, lung 3, pancreas 2;<br><br>4 previously treated with arterial embolization, 4 with somatostatin, 2 with cytotoxic chemotherapy; 6 transplants for pain, 5 transplants for symptoms secondary to hormones; 7 had primary tumor removed at time of diagnosis, 1 resected 2 years before OLT; 3 without primaries located, 9 cases with liver metastases at time of OLT | OLT |
| Schweizer 1993[45]1988. | Hartford, CT | 3 | 10-34 | 67 | 48 | Carcinoid tumor of pancreas primary, nonfunctioning islet cell pancreatic tumor, 3 patient tumor diagnosis not stated | OLT with distal pancreatectomy and splenectomy; OLT with Whipple; OLT with tumor mesenteric lymph nodes irradiated following OLT |
| Socci 1994[111] | Milan, Italy | 1 | 7 | 100 | 47 | Neuroendocrine pancreatic tumor | Liver-islet transplantation after upper abdominal exenteration |

ND = not discussed, OLT = orthotopic liver transplantation

**Table 27.** Neuroendocrine Tumors: Patient Survival for All Studies.

| Reference | Operative mortality (%) | Median survival | Patient survival in years (%) | | | | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 5 | |
| Alessiani 1995[24] | Excluded operative mortality | ND | 65 | | 64 | 64 | 5 patients without recurrence alive at 17, 27, 32, 54, and 61 months; 3 patients alive without recurrence at 33, 50, and 56 months |
| Anthuber 1996[97] | 25 | ND | 25 | | | | Deaths at 10 days, 4 months, 8 months from recurrence, and 33 months |
| Bechstein 1994 [98] | ND | 3.9 | 100 | 100 | 100 | 0 | Died at 3.5 years from recurrence |
| Caplin 1998[112] | ND | ND | | | | | "Well" 15 months following OLT; |
| Coperchini 1996[102] | ND | ND | 100 | | | | One patient with ovarian involvement at 19 months, free of known disease following right oophrectomy |
| Curtis 1995[103] | ND | ND | 100 | | | | Alive at 12, 20 and 30 months; |
| Dousset 1995[104, 105] | 33 | ND | | | | | 2/9 Alive and disease free at 15 months and 24 months; 1 alive at 62 months with recurrence at 58 months; Patient deaths attributed to sepsis day 7, portal vein thrombosis day 12, retransplant d ay6; portal vein thrombosis day 83; recurrence for bone and graft 17 months; |
| Farmer 1993[59] | ND | ND | 100 | 50 | 0 | | One patient died 22 months secondary to gastrointestinal bleed, one patient died 29 months from sepsis |
| Frilling 1998[106, 107] | 50 | ND | 50 | 50 | 50 | | 1 patient is without known tumor following resection of bone metastases 48 months following OLT; 1 patient is alive at 36 months with recurrence. One patient died day 32 secondary to sepsis; OLT-Cluster died day 4 secondary to sepsis; |
| Gulanikar 1991[108] | ND | 5 | 0 | | | | |
| Iwatsuki 1990[5] | ND | ND | 100 | 100 | 100 | | Alive 3.5 years and 5 years with tumor recurrence |
| Knetchtle 1993[29] | ND | ND | 100 | 33 | | | Carcinoid with pulmonary metastases at 18 months and death at 19 months; gastrinoma "well" 30 months following OLT. Islet cell cancer died with bone marrow metastases at 13 months |
| Lang 1999[40] | 0 | 33 | | | | | 9/10 alive at follow-up. One patient died at 68 months with residual tumor. Of the two patients alive without recurrence, one was 13.5 months and the other 90 months post-OLT. |
| Le Treut 1997 [41] | 19 | 30 | 58 | 51 | 47 | 36 | 13 alive, 18 died; 5 patients survived more than 60 months |
| Martin 1996[110] | ND | ND | 100 | 100 | | | Alive |
| Mieles 1990[27] | 33 | ND | | | | | 1 patient died of sepsis on day 9 without evidence of residual disease; 2 patients alive at 325 days and 177 days; |
| Olthoff 1990[53] | ND | ND | | | | | Islet cell tumor alive and well at 5 months; Pancreatic cancer with pulmonary recurrence at 4 months |
| Pichlmayr 1998[11] | ND | ND | | | | 86.7 | 11/15 alive, 4/11 without tumor recurrence; Longest survival 33 months in patient with colorectal cancer |
| Routley 1995[42] | ND | 20(carcinoid)<br>18(ampudoma) | 82 | | | 57 | 6 Alive with median follow-up of 25 months, 4 without recurrence, 1 with carcinoid with 26 months recurrence, and 1 ampudoma with 22 months recurrence; 5 patients who died had median survival time of 14 months |
| Schweizer 1993[45] | ND | ND | 100 | | | | Carcinoid recurred at 14 months with bone metastases and responded to radiation and 5-FU without evidence of tumor at 34 months follow-up; islet cell cancer asymptomatic at 26 months follow-up; free of symptoms at 10 month follow-up. |
| Socci 1994[111] | ND | ND | | | | | Patient was disease free, insulin independent, with normal liver function 7 months following OLT. |
| Todo 1995[39] | | 1.67 | 0 | | | | Died on day 49 from post-transplant lymphoproliferative disease, never discharged from hospital |

ND = not discussed, OLT = orthotopic liver transplantation

**Table 28.** Neuroendocrine Tumors: Disease-Free Survival and Recurrence.

| Reference | Recurrence %(n) | Disease free survival in years (%) | | Outcomes Comments |
|---|---|---|---|---|
| | | 1 | 3 | |
| Alessiani 1995[24] | 45.5 (in patients with at least 3 months follow-up) | | | 5 patients without recurrence alive at 17, 27, 32, 54, and 61 months; 3 patients alive without recurrence at 33, 50, and 56 months |
| Alsina 1990[96] | 0 | | | Patient with islet cell carcinoma "fully recovered" |
| Anthuber 1996[97] | 100 (in patients surviving more than 10 days) | 25 | 0 | Deaths at 10days, 4 months, and 8 months from recurrence, and 33 months<br><br>Recurrence at 4 months, 8 months, 24 months |
| Bechstein 1994 [98] | 100 | 0 | | Detection of lung nodules at 3 months; local rectal recurrence following abdominoperineal excision 1991; 1992 metastases in allograft; died at 3.5y years from recurrence |
| Bramley 1990[99] | 0 | | | |
| Caplin 1998[112] | | | | "Well" 15 months following OLT; octreotide scan showed 2 small 'deposits' in right lung |
| Coperchini 1996[102] | 100 | 50 | | Symptoms recurred at 23 months for one patient with diagnosis of disseminated carcinoid in lymph nodes, bone marrow, pancreas, but not liver graft; one patient with ovarian involvement at 19 months, free of known disease following right oophrectomy |
| Dousset 1995[104, 105] | 11 | | | 2/9 Alive and disease free at 15 months and 24 months; 1 alive at 62 months with recurrence at 58 months; Patient deaths attributed to sepsis day 7, portal vein thrombosis day 12, retransplant day 6; portal vein thrombosis day 83; recurrence for bone and graft 17 months; |
| Farmer 1993[59] | 0 | 100 | | One patient died 22 months secondary to gastrointestinal bleed, one patient died 29 months from sepsis |
| Frilling 1998[106, 107] | 50 | 50 | 50 | 1 patient is without known tumor following resection of bone metastases 48 months following OLT; 1 patient is alive at 36 months with recurrence at 8months |
| Gulanikar 1991[108] | 100 | 0 | | Metastases to alograt/lung/bone with death 5months following OLT<br><br>Asymptomatic abdominal wall 6cm mass recurrence at 3 months |
| Hao 1996[109] | 0 | | | No recurrence at 5 months follow-up |
| Iwatsuki 1990[5] | 100 | | | Alive 3.5 years and 5 years with tumor recurrence |
| Knetchtle 1993[29] | 67 | 100 | 33 | Carcinoid with pulmonary metastases at 18 months and death at 19 months; gastrinoma "well" 30months following OLT. Islet cell cancer died with bone marrow metastases at 13 months |
| Lang 1999[40] | 80 | | | 9/10 alive at follow-up. One patient died at 68 months with residual tumor. Of the two patients alive without recurrence, one is 13.5 months and the other 90 months post-OLT.<br><br>Tumor free interval 48 months, 1.5 months, 11 months, 25 months, 8 months, 8 months, 3 months |
| Le Treut 1997 [41] | 39 | | | 13 alive, 18 died; 5 patients survived more than 60 months |
| Mieles 1990[27] | 0 | | | 1 patient died of sepsis on day 9 without evidence of residual disease; 2 patients alive at 325 days and 177 days; |
| Olthoff 1990[53] | 50 | | | Islet cell tumor alive and well at 5 months; Pancreatic cancer with pulmonary recurrence at 4 months |
| Pichlmayr 1998[11] | 64 | | | 11/15 alive, 4/11 without tumor recurrence; Longest survival 33 months in patient with colorectal cancer |
| Routley 1995[42] | 83 (carcinoid tumors)<br><br>20 (ampudomas) | | | 6 Alive with median follow-up of 25 months, 4 without recurrence, 1 with carcinoid with 26 months recurrence, and 1 ampudoma with 22 m onths recurrence; 5 patients who died had median survival time of 14 months<br><br>Carcinoid tumors recurred at mean of 9 months<br><br>1/5 ampudoma recurred at 22 months<br>Overall median time to recurrence 14 months (range 8-26) |
| Schweizer 1993[45] | 33 | 100 | | Carcinoid recurred at 14 months with bone metastases and responded to radiation and 5-FU without evidence of tumor at 34 months follow-up; islet cell cancer asymptomatic at 26 months follow-up; free of symptoms at 10 months follow-up. |
| Socci 1994[111] | 0 | | | Patient is disease free, insulin independent, with normal liver function 7 months following OLT. |

ND = not discussed, OLT = orthotopic liver transplantation

**Table 29.** Neuroendocrine Tumors: Graft Survival.

| Reference | Graft Survival Details |
|---|---|
| Curtis 1995[103] | One retransplant from graft failure |
| Dousset 1995[104, 105] | Retransplant on day 6 for graft failure; Retransplant on day 83 for portal vein thrombosis; Retransplant for chronic graft failure at 8months |
| Frilling 1998[106, 107] | OLT-Cluster required retransplant of small intestines 48 hours following OLT and died day 4 secondary to sepsis; |
| Socci 1994[111] | Combined liver-islet transplant performed 2 daysafter first operation due to primary graft failure |

OLT = orthotopic liver transplantation

**Table 30.** Neuroendocrine Tumors: Quality of Life.

| Reference | Quality of Life Details |
|---|---|
| Alsina 1990[96] | No symptoms for either patient, with normal follow-up hormone levels |
| Anthuber 1996[97] | One patient with “2 years of good life quality”; One patient with “4 months of full life quality” |
| Bramley 1990[99] | “Good health” 12 months following surgery with “undetectable” VIP levels and normal stool frequency |
| Claure 2000[101] | “Asymptomatic” for 6 months with normal urinary 5-HIAA levels |
| Coperchini 1996[102] | One patient with “good quality of life” “over ensuing months” |
| Curtis 1995[103] | Peptide hormone levels remain low in all 3 recipients |
| Frilling 1998[106, 107] | 1 patient is alive at 36 and is in “moderate general condition” |
| Knetchtle 1993[29] | Gastrinoma “well” 30 months following OLT |
| Lang 1999[40] | “In all patients…Complete relief of tumor-related symptoms and all preoperative increased hormone levels returned to normal” |
| Martin 1996[110] | No symptoms at 29 months |
| Routley 1995[42] | “All 11 obtained complete symptom relief initially, with urinary 5 HIAA levels falling to normal range in 6 patients with elevated levels” |
| Schweizer 1993[45] | All returned to previous work (attorney, architect, housewife) |
| Socci 1994[111] | Returned to work 7 months following OLT |
| Todo 1995[39] | Never discharged from hospital |

OLT = orthotopic liver transplantation

**Table 31.** Epithelioid Hemangioendothelioma: Unique Reports.

| Reference | Location (years of transplantation reported) | Number of patients | Mean follow-up (months) | % Male | Age (years) | Disease features | Procedure |
|---|---|---|---|---|---|---|---|
| Ben-Haim 1999[50] | Mt. Sinai, NYC (90-98) | 5 | 36 | 80 | 51 | | OLT |
| Hung 1998[49] | Taipei, Taiwan (95) | 1 | 24 | 100 | 27 | Hemangioendothelioma previously treated with devascularization surgery; multiple tiny nodules scattered throughout mesentery at time of OLT | OLT |
| Ismail 1990[55] | Birmingham, UK (82-89) | 1 | 55 | 0 | 47 | Multifocal endothelioma | OLT |
| Loinaz 1998[113] | Madrid, Spain (86-96) | 2 | 9-44 | ND | 52.1 | | OLT |
| Madariaga 1995[47]<br><br><br><br>Yokoyama 1990[114] | Pittsburgh (81-93)<br>Colorado (76-80)<br><br>Pittsburgh/Colorado (80-88) | 16<br><br><br><br>8 | 52 | 44 | 37±10.6 | 14Stage IVa,<br>2 Stage IVb;<br>5 patients received adriamycin based regimens (1 preop, 3 postop, 1 pre and postop) and 3 received XRT | OLT |
| Makhlouf 1999[48] | Armed Forces Institute of Pathology (66-97) – path review | 7 | ND | ND | ND | 6 patients underwent OLT; 1 patient underwent OLT plus chemotherapy with interferon 8 months prior to OLT; 1 patient received postoperative chemotherapy for lymph node metastases | OLT |
| Olthoff 1990[53] | UCLA (84-89) | 3 | 21-65 | ND | ND | 1 patient with positive lymph nodes, 1 patient with vascular invasion | OLT |
| Pichlmayr 1998[11] | Hannover, Germany (72-96) | 7 | ND | ND | ND | | OLT |

ND=Not described, OLT=orthotopic liver transplantation, XRT=radiation therapy

**Table 32.** Hemangioendothelioma: Patient Survival Following Transplantation.

| Reference | Survival (months) | Patient survival in years(%) | | | | Outcomes Comments |
|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 5 | |
| Ben-Haim 1999[50] | ND | ND | ND | ND | ND | 3 living, 2 deaths; 1 patient with recurrence was treated with right lobectomy and is alive and free of disease at 8 years; Another patient alive and disease free at 12 months; 1 patient alive with stable residual asymptomatic disease at 32 months; 1 patient died at 9 months with recurrence related death involving graft recurrence; One patient died at 7 years with recurrence in graft and bones |
| Hung 1998[49] | ND | 100 | 100 | ND | ND | Alive at 2 years despite metastatic nodules throughout mesentery |
| Ismail 1990[55] | ND | 100 | 100 | 20 | ND | Alive at 55 months |
| Loinaz 1998[113] | ND | ND | ND | ND | ND | Both patients are alive without recurrence at 9 months and 44 months |
| Madariaga 1995[47] | ND | 100 | ND | 85.7 | 71.3 | 9 patients alive and tumor free, 7 alive >5 years; 2 patients alive with disease – recurrence at .9 years and 4 years, with patients alive at 3 years and 5 years, respectively. 5 patients died with diffuse metastatic disease at median of 43 months. |
| Makhlouf 1999[48] | 69 | ND | ND | ND | ND | 5/7 patients alive; 1 patient undergoing OLT and chemotherapy was alive with no evidence of disease at 40 months; 2 patients were alive with disease 3 years and 10 years following OLT, 2 were alive without evidence for disease, and 2 were dead of disease at 48 months and 62 months; The patient who received interferon is alive 42 months following OLT; Patient who received post-OLT chemo given positive lymph nodes is alive and well at 40 months following OLT without recurrence |
| Olthoff 1990[53] | ND | ND | ND | ND | ND | All 3 patients alive and disease free at 21 months, 39 months, and 65 months |
| Pichlmayr 1998[11] | ND | ND | ND | ND | ND | 4/7 “still alive”; Longest survival 11 years |
| Yokoyama 1990[114] | ND | 88 | ND | 73 | 48 | |

ND=Not described, OLT=orthotopic liver transplantation, XRT=radiation therapy

**Table 33.** Hemangioendothelioma: Disease-Free Survival and Recurrence Following Transplantation.

| Reference | Recurrence % | Disease-free Survival in years (%) 1 | 3 | 5 | Outcomes Comments |
|---|---|---|---|---|---|
| Ben-Haim 1999[50] | 60<br><br>1 died of recurrence in the graft at 9months with recurrence in graft and bones with death at 7years; another with liver recurrence at 4 years treated with intraperitoneal 5-fluoruracil has been free of measurable disease | | | | 1 patient with recurrence was treated with right lobectomy and was alive and free of disease at 8 years; Another patient alive and disease free at 12 months; 1 patient alive with stable residual asymptomatic disease at 32 months; 1 patient died at 9 months with recurrence related death involving graft recurrence; One patient died at 7 years with recurrence in graft and bones |
| Hung 1998[49] | 100 | | | | Alive at 2 years despite metastatic nodules throughout mesentery |
| Ismail 1990[55] | | | | | Alive at 55 months |
| Loinaz 1998[113] | 0 | | | | Both patients are alive without recurrence at 9 months and 44 months |
| Madariaga 1995[47] | 55 | 81.3 | 68.8 | 60.2 | 9 patients alive and tumor free, 7 alive >5 years; 2 patients alive with disease – recurrence at .9 years and 4 years, with patients currently alive at 3 y ears and 5 years, respectively. 5 patients died with diffuse metastatic disease at median of 43 months. |
| Makhlouf 1999[48] | ND | ND | ND | ND | 5/7 patients alive; 1 patient undergoing OLT and chemotherapy is alive with no evidence of disease at 40 months; 2 patients are alive with disease 3 years and 10 years following OLT, 2 are alive without evidence for disease, and 2 are dead of disease at 48 months and 62 months; The patient who received interferon is alive 42months following OLT; Patient who received post-OLT chemo given positive lymph nodes is alive and well at 40 months following OLT without recurrence |
| Olthoff 1990[53] | | | | | All 3 patient alive and disease free at 21 months, 39 months, and 65 months |
| Pichlmayr 1998[11] | | | | | 4/7 “still alive”; Longest survival 11 years |

ND = not described, OLT = orthotopic liver transplantation

**Table 34.** Hemangioendothelioma: Graft Survival Following Transplantation.

| Reference | Outcomes Comments |
|---|---|
| Madariaga 1995[47] | 3 retransplants: 1 for recurrence in liver graft 4 years following orthotopic liver transplantation, 2 for nonfunctioning grafts at 2 days and 4 days postoperatively |

**Table 35.** Hemangioendothelioma: Quality of Life Outcomes Following Transplantation.

| Reference | Quality of Life |
|---|---|
| Ben-Haim 1999[50] | 1 patient alive with stable residual asymptomatic disease at 32 months |
| Loinaz 1998[113] | "Normal quality of life" at 9 months and 44 months |

**Table 36.** Soft Tissue Tumors Other Than Hemangioendothelioma: Descriptions of Reports by Study Size.

| Reference | Location (years of transplant reported) | Number of patients | Follow-up (months) | % Male | Age (years) | Disease features | Procedure |
|---|---|---|---|---|---|---|---|
| Alessiani 1995[24] | Pittsburgh (88-92) | 6 | ND | 50 | ND | ND | OLT, modified OLT, OLT with islet cells, OLT-pancreas-duodenum – results combination of procedures |
| Mieles 1990[27] | Pittsburgh (88-89) | 2 | 12-15 | 50 | 31-43 | 2 spindle cell sarcoma both of duodenum, 15cm, the other 8cm. No treatment before cluster transplantation | Cluster transplant including liver, stomach, pancreas, spleen, duodenum, proximal jejunum, and ascending plus transverse colon |
| Yokoyama 1990[114] | Pittsburgh/Colorado (80-88) | 2 | 25 | ND | ND | Hemangiosarcoma | OLT |
| Ismail 1990[55] | Birmingham, UK (82-89) | 2 | 5-55 | ND | ND | Multifocal angiosarcoma | OLT |
| Olthoff 1990[53] | UCLA (84-89) | 2 | 4-70 | ND | ND | Neurosarcoma – undifferentiated spindle cell – treated with doxorubicin and hyperthermia;<br><br>Leiomyosarcoma | OLT |
| Pichlmayr 1998[11] | Hannover, Germany (72-96) | 2 | 5 | ND | ND | Hemangiosarcoma | OLT |
| Moreno-Gonzalez 1993[56]<br><br>Loinaz 1998[113] | Madrid, Spain (86-92)<br><br>Madrid, Spain( 88-96) | 1<br><br>1 | 5 | ND | ND | Angiosarcoma, 15cm right lobe, nonencapsulated tumor | OLT<br><br>OLT |
| Rojter 1995[52] | Cedars Sinai/UCLA (92) | 1 | 6 | 100 | 59 | Incidental angiosarcoma – mass in left lobe 15cm, parenchyma diffusely replaced by angiosarcoma of both mixed multinodular and massive types; | OLT |
| Zibari 1998[54] | LSU (88-95) | 1 | 24 | ND | ND | Gastric leiomyosarcoma | OLT |

ND = not discussed, OLT = orthotopic liver transplantation

**Table 37.** Soft Tissue Tumors Other Than Hemangioendothelioma: Overall Patient Survival Following Transplantation.

| Reference | Operative mortality (%) | Survival (months) | Patient Survival by year (%) | | | | Outcomes Comments |
|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 5 | |
| Alessiani 1995[24] | Excluded operative mortality | ND | 100 | ND | 44 | 44 | 1 patient tumor free at 49 months; Median time to tumor related mortality 32 months; 66% tumor related mortality; |
| Ismail 1990[55] | ND | ND | 50 | 50 | 50 | ND | One dead at 5 months from recurrence; One patient alive at 55 months |
| Mieles 1990[27] | ND | ND | 100 | ND | ND | ND | Alive at 12 months and 15 months without early satiety or pain with meals |
| Moreno-Gonzalez 1993[56]<br><br>Loinaz 1998[113] | ND | 5 | 0<br><br>0 | ND | | ND | Death at 5 months following OLT with central nervous system recurrence<br><br>Recurrence reported |
| Otlhoff 1990[53] | ND | ND | 50 | 50 | 50 | 50 | Neurosarcoma died at 4 months following tumor recurrence at 3 months;<br><br>Leiomyosarcoma alive without recurrence at 70 months |
| Pichlmayr 1998[11] | 50 | 2.5 | 0 | ND | ND | ND | 1 died perioperative period, one died with recurrence at 5 months |
| Rojter 1995[52] | ND | 6 | 0 | ND | ND | ND | Despite 2 cycles of ifosfamide patient died 6 months following OLT |
| Yokoyama 1990[114] | ND | ND | 0 | ND | ND | ND | |
| Zibari 1998[54] | ND | 24 | 100 | 100 | 0 | ND | Recurrence 18 months following OLT, died at 24 months |

ND = not discussed, OLT = orthotopic liver transplantation

**Table 38.** Soft Tissue Tumors Other Than Hemangioendothelioma: Overall Disease-Free Survival and Recurrence Following Transplantation.

| Reference | Recurrence (%) | Disease free survival in years (%) | | | Outcomes Comments |
|---|---|---|---|---|---|
| | | 1 | 3 | 5 | |
| Alessiani 1995[24] | 83<br>in patients with at least 3 months follow-up | ND | ND | ND | 1 patient tumor free at 49 months; Median time to tumor related mortality 32 months; |
| Ismail 1990[55] | 50 | 50 | 50 | ND | One dead at 5 months from recurrence; One patient alive at 55 months |
| Mieles 1990[27] | ND | ND | ND | ND | Alive at 12 months and 15 months without early satiety or pain with meals |
| Moreno-Gonzalez 1993[56] | 100 | 0 | | | Death at 5 months following OLT with central nervous system recurrence |
| Loinaz 1998[113] | 100 | | | | Recurrence reported |
| Otlhoff 1990[53] | 50 | 50 | 50 | 50 | Neurosarcoma died at 4 months following tumor recurrence at 3 months; Leiomyosarcoma alive without recurrence at 70 months |
| Pichlmayr 1998[11] | 50 | 0 | ND | ND | 1 died with recurrence at 5 months |
| Rojter 1995[52] | 100 | 0 | ND | ND | Despite 2 cycles of ifosfamide 2 months following OLT for lung nodules, patient died 6 months following OLT with metastases to spine |
| Zibari 1998[54] | 100 | 100 | 0 | ND | Recurrence 18 months following OLT, died at 24 months |

ND = not discussed, OLT = orthotopic liver transplantation

**Table 39.** Soft Tissue Tumors Other Than Hemangioendothelioma: Quality of Life Following Liver Transplantation.

| Reference | Quality of Life |
|---|---|
| Mieles 1990[27] | Alive at 12 months and 15 months without early satiety or pain with meals |

**Table 40**. Metastatic Tumors: Description of Unique Reports of Patient Outcomes.

| Reference | Location (years of transplant reported) | Number of patients | Follow-up (months) | % Male | Age (years) | Disease features | Procedure |
|---|---|---|---|---|---|---|---|
| Alessiani 1995[24] | Pittsburgh (88-92) | 4 | ND | 50 | ND | 2 pancreas carcinoma<br>2 colon carcinoma | OLT, modified OLT, OLT with islet cells, OLT-pancreas-duodenum – results do not distinguish between procedures |
| Farmer 1993[59] | UCLA (84-92) | 1 | 5 | ND | ND | 6x6cm pancreatic mass in body and tail | Foregut resection and OLT |
| Penn 1996[63] | Pittsburgh | 8 | ND | ND | ND | Retransplants as treatment of allograft lymphoma; initially diagnoses prior to first transplant are not known | Retransplantation |
| Petrassi 1999[62] | Consenza, Italy | 1 | 4 | ND | ND | Colon carcinoma | OLT-visceral transplant following abdominal exenteration |
| Oldhafer 2000[60] | Hannover, Germany (88-98) | 1 | 31 | 0 | 53 | Colon cancer | OLT on post-operative day 1 following ex situ liver surgery |
| Pichlmayr 1998[11] | Hannover, Germany (72-96) | 10 | ND | ND | ND | 4 colorectal carcinoma<br>2 melanoma<br>2 choriocarcinoma<br>2 pancreatic cancer | |
| Vaillant 1993[115] | Paris, France (70-91) | 1 | .5 | 100 | 57 | Colon carcinoma with 10 liver metastases | OLT |

ND=not described, OLT=orthotopic liver transplantation

**Table 41.** Metastatic Tumors: Patient Survival Following Liver Transplantation

| Reference | Operative mortality% | Mean survival (months) | Patient Survival by year (%) | | | Outcomes Comments |
|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | |
| Alessiani 1995[24] | Excluded operative mortality | | 20 | | | Outcomes combined with one patient with gallbladder adenocarcinoma; 1 patient with pancreas adenocarcinoma alive 44 months following OLT without recurrence; Median time to tumor related mortality 8.3 months; 60% tumor related mortality; |
| Farmer 1993[59] | ND | 5 | 0 | | | Died 5m of tumor recurrence |
| Oldhafer 2000[60] | ND | 31 | 100 | 100 | 0 | Died of tumor recurrence at 31 months |
| Pichlmayr 1998[11] | ND | | | | 0 | No survivors beyond 3 years; Longest survival 33months in patient with colorectal cancer |
| Penn 1996[63] | 3/8 – one of hemorrhage during reoperation, one shortly after surgery, and one 2 months later | | | | | 2 died of lymphoma recurrence in second allograft at 0.5 months and 2 months; 3 alive – with 2 in complete remission at 9 months and 56.5months |
| Petrassi 1999[62] | ND | | 0 | | | Died 4 months from sepsis/rejection |
| Vaillant 1993[115] | ND | | 0 | | | Death at .5 months following OLT, etiology not stated |

ND = not described, OLT = orthotopic liver transplantation

**Table 42.** Metastatic Tumors: Disease-Free Survival and Recurrence Following Transplantation.

| Reference | Recurrence (%) | Disease-free survival in years (%) | | Outcomes Comments |
|---|---|---|---|---|
| | | 1 | 3 | |
| Alessiani 1995[24] | 75 (in patients with at least 3 months follow-up) | | | 1 patient with pancreas adenocarcinoma alive 44 months following OLT without recurrence; Median time to tumor related mortality 8.3 months; 60% tumor related mortality. |
| Farmer 1993[59] | 100 | 0 | | Died 5 months secondary recurrence |
| Oldhafer 2000[60] | 100 | 100 | 0 | Died of tumor recurrence at 31 months |
| Penn 1996[63] | | | | 2 died of lymphoma recurrence in second allograft at 0.5months and 2 months; 3 alive – with 2 in complete remission at 9 months and 56.5 months |
| Petrassi 1999[62] | | 0 | | Died 4 months from sepsis/rejection |

OLT = orthotopic liver transplantation

**Table 43.** Gallbladder Cancer: Outcomes Following Liver Transplantation.

| Reference | Location | Number of Patients | Follow-up (months) | % Male | Age (years) | Disease features | Procedure | Quality of Life | Outcomes Comments |
|---|---|---|---|---|---|---|---|---|---|
| Knechtle 1993[29] | Madison, WI | 1 | 11 | | | Gallbladder cancer | Cluster transplant with liver, pancreas, and duodenum | ND | Death with recurrence at 11 months |
| Von Schonfeld 1998[67] | Essen, Germany | 1 | 24 | 0 | 29 | 1.5cm moderately differentiated adenocarcinoma infiltrating all layers of gallbladder in patient with PSC | OLT | "the patient feels well" and has "not lost weight" ."She has gone back to work and would like to have another child." | Alive without recurrence at 24 months |
| Washburn 1994[68] | New England Deaconess | 2 | 30 | 50 | 53-65 | T1N0M0 AJCC stage 1 well differentiated adenocarcinoma in patient with PBC; T2N0M0 AJCC stage 11 adenocarcinoma of gallbladder fundus | OLT | ND | Normal graft function, no evidence of recurrence for either patient at 30 months |

ND = not discussed, OLT = orthotopic liver transplantation, PSC = primary sclerosing cholangitis

**Table 44.** Liver Transplantation in the Setting of Preexisting Extrahepatic Malignancy: Unique Reports.

| Reference | Location (years of transplants) | No. of patients | Follow-up (months) | % Male | Age (years) | Disease features | Procedure |
|---|---|---|---|---|---|---|---|
| DeMaria 1995[116] | Lexington KY | 1 | 12 | 0 | 56 | "Early" signet ring cell gastric ca treated with distal gastrectomy with Billroth 1 year before OLT; Deemed "free of gastric cancer" at time of OLT | OLT |
| Dousset 1995[43] | Paris, France (82-92) | 5 | 15-102 | 60 | 35 | 1 IgA alpha Plasmacytoma treated with 6 months of XRT in setting of PBC; 1 incidentally diagnosed renal cell carcinoma in Laennec's cirrhosis; 1 Duke C1 colon cancer treated with 13 courses of intraarterial chemotherapy with mitomycin C and 5-FU and folic acid with liver diagnosis secondary to chemotherapy; 1 polycythemia vera; 1 IgM alpha lymphoproliferative disease in complete remission following chlorambucil treatment with HCV cirrhosis | OLT; OLT with right nephrectomy |
| Marks 1992[71] | Hammersmith Hospital, London | 1 | 6 | 100 | 21 | Graft-versus-host-disease following allogenic bone marrow transplant for CML. Received condition with splenic irradiation, cyclophosphamide, cyclosporine, methotrexate. On d28 liver biopsy confirmed Grade II graft-versus-host-disease. On day 104 OLT | OLT |
| Nimer 1990[73] | UCLA | 1 | 12 | 0 | 34 | Veno-occlusive disease in 34 year old with myelodysplastic syndrome and history of non-a, non-B hepatitis; initially treated with busulfan and cyclophosphamide; Veno-occlusive disease diagnosed on day 14; No evidence for graft-versus-host-disease; | OLT |
| Penn 1996[63] | Cincinnati (98-96) | 44 | 11 | ND | ND | Lymphoma 9; nonmelanoma skin cancer 8; breast cancer 7; colon cancer 4; kidney cancer 3; cervical cancer 3; ALL 1; CLL 1; Endometrial cancer 2; ovarian cancer 1; gastric cancer 1; bladder cancer 1; vaginal cancer; vulvar cancer 1; testicular cancer 1; prostate cancer 1; soft palate cancer 1 | OLT |
| Rapoport 1991[74] | Buffalo | 1 | 2.5 | 0 | 34 | Veno-occlusive disease following allogenic bone marrow transplantation for CML, conditioning with busulfan/cyclophosphamide; day 20 developed veno-occlusive disease; day 35 underwent OLT | OLT |
| Rhodes 1990[117] | MUSC (1988) | 1 | 24 | 0 | 19 | AML treated with cytaravine and daunorubicin; Bone marrow transplant with busulfan/cyclophosphamide conditioning, 23 days developed graft-versus-host-disease – treated with high does steroids and antithymocyte globulin, methylprednisolone and azathioprine, ongoing graft-versus-host-disease further treated with steroids, azathioprine, and cyclosporine with persistent cholestasis; then developed variceal bleeding | OLT |
| Rosen 1996[118] | UCLA (88-95) | 2 | 9-29.5 | 100 | 33.5 | Post-bone marrow transplant liver failure: 1 M5 AML s/p idarubicin and cytarabine, reinduction with idaraubin and cytarabine, consolidation with cytarabine and mitoxantrone he received total body irradiation and cyclophosphamid and mesna, 1994 HLA-matched allogenic bone marrow transplant with development of veno-occlusive disease and OLT on day 43;<br><br>1 L1 ALL s/p daunorubicin, prednisone, l-asparaginase, intrathecal methotrexate – for residual ALL received total body irradiation, VP-16, and HLA-matched bone marrow transplant 1993, OLT day 330 following bone marrow transplant for pruritus, coagulopathy, ascites with end stage liver disease from graft versus host disease; | OLT |
| Saigal 2001[69] | King's College London (89-99) | 18 | 58.5 | 34 | 55 | Colon cancer 4, renal cancer 2, melanoma 1, bladder cancer 1, breast cancer 1, thyroid cancer 1, endometrial cancer 1, NHL 1, myeloproliferative disease 6; OF 12 PATIENTS WITH SOLID ORGAN/SKIN MALIGNANCIES: PBC 6, PSC 2, autoimmune 1, EtOH cirrhosis 1, HBV 1, primary hyperoxaluria with combined liver/kidney transplant – 4 of these 12 were incidentally diagnosed (2 renal cancer, 1 colon cancer, 1 bladder cancer) – 3 resected with OLT 1 3 months following OLT, 8 diagnosed a median of 24 months prior to OLT; OF 6 PATIENTS WITH MYELOPROLIFERATIVE STATE /BUDD CHIARI: 3 polycythemia rubra vera, 1 essential operative hydroxyurea and busulfan and 4 with hydroxyurea post OLT | OLT |
| Schlitt 1995[119] | Hannover, Germany (1991) | 1 | 48 | 100 | 38 | OLT for veno-occlusive disease following bone marrow transplant of AML; M5 AML following 3 courses of daunorubicin/ara-c/etoposide initial therapy and ara-c/amsidyl for consolidation; d23 OLT for veno-occlusive disease | OLT |
| Todo 1995[39] | Pittsburgh (91-93) | 1 | 6.5 | ND | 32.6 | Budd-Chiari Syndrome | Abdominal multivisceral transplant including stomach, liver, pancreas, intestine, and colon |

ND = not discussed, OLT = orthotopic liver transplantation, XRT = radiation therapy

**Table 45.** Liver Transplantation in the Setting Preexisting Extrahepatic Malignancy: Patient Survival.

| Reference | Patient survival in years (%) 1 | 2 | Outcomes Comments |
|---|---|---|---|
| DeMaria 1995[116] | 100 | ND | Alive and well; |
| Dousset 1995[43] | 100 | 80 | 4/5 Alive at 33 months, 48 months, 56 months, and 102 months; One patient died at 15 months with hepatitis C virus recurrence |
| Marks 1992[71] | ND | ND | Normal liver function tests and no evidence of graft-versus-host disease 6m following OLT |
| Nimer 1990[73] | ND | ND | Recurrence of myelodysplasia in bone marrow 4.5 months following bone marrow transplant; One year following transplant she is alive with normal liver function tests and is clinically stable without need for transfusions. |
| Penn 1996[63] | ND | ND | 81% of cancer related deaths occurring within 2 years of OLT; Vaginal cancer died 2 months following OLT; CLL died 5.5 months after OLT |
| Rapoport 1991[74] | ND | ND | Died from interstitial pneumonitis on day 42 following OLT and day 77 following bone marrow transplantation; |
| Rhodes 1990[117] | ND | ND | At 2 years all liver function tests are “normal” and patient “appeared normal” without further evidence of graft-versus-host-disease |
| Rosen 1996[118] | ND | ND | Graft-versus-host-disease alive day 880 following bone marrow transplantatation with no evidence of recurrent graft-versus-host-disease or leukeumia;<br><br>Veno-occlusive disease “excellent liver allograft function” 9m following OLT |
| Saigal 2001[69] | ND | ND | 12 SOLID ORGAN/SKIN MALIGNANCIES: 1 recurrence of NHL (8.3%) treated with mantle therapy 120 months prior to OLT for HBV, chemotherapy 23 months following OLT with relapse at 27 months; Of 4 incidental diagnoses 1 recurrence in a patient who underwent resection of renal cell carcinoma during OLT and died in early postoperative course of sepsis<br><br>6 MYELOPROLIFERATIVE STATE: 5/6 with median 79 median follow-up without transformation to leukemic states; 1/6 with acute leukemia at 72 months following OLT and death at 93 months. No de novo malignancy. |
| Schlitt 1995[119] | ND | ND | 40 months after bone marrow transplantation; No transfusion requirements, no signs of infection of graft-versus-host-disease, “clinically stable” |
| Todo 1995[39] | ND | ND | Died of respiratory failure on day 197; Never discharged from hospital following OLT. |

ND = not discussed, OLT = orthotopic liver transplantation

**Table 46.** Liver Transplantation in the Setting of Preexisting Extraheptic Malignancy: Disease-Free Survival and Recurrence Outcomes Following Transplantation.

| Reference | Recurrence % | Disease-free Survival in years (%) 1 | 3 | Outcomes Comments |
|---|---|---|---|---|
| DeMaria 1995[116] | 0 | 100 | ND | No gastric cancer noted on follow-up |
| Dousset 1995[43] | ND | ND | ND | One patient died at 15 months with hepatitis C virus recurrence |
| Marks 1992[71] | 0 | ND | ND | Normal liver function tests and no evidence of graft-versus-host-disease 6 months following OLT. Marrow is morphologically and cytogenetically normal. |
| Nimer 1990[73] | 100 | 100 | 100 | Recurrence of myelodysplasia in bone marrow 4.5 months following bone marrow transplantation; One year following transplant she is alive with normal liver function tests and is clinically stable without need for transfusions. |
| Penn 1996[63] | 25 (persistence or recurrence)<br><br>40 (primary or metastatic hepatic neoplasms) | ND | ND | 81% of cancer related deaths occurring within 2 years of OLT;<br><br>Persistent of recurrent cancers include: non-melanoma skin cancer 4, breast cancer 2, colon cancer 2, CLL 1, vaginal cancer 1; soft palate cancer 1;<br><br>Median time to recurrence 7.5 months, mean 14 months |
| Rapoport 1991[74] | 0 | 0 | ND | Died from interstitial pneumonitis on day 42 following OLT and day 77 following bone marrow transplantation; early acute rejection noted on liver biopsy; |
| Rhodes 1990[117] | 0 | 100 | ND | At 2 years all liver function tests are “normal” and patient “appeared normal” without further evidence of graft-versus-host-disease |
| Rosen 1996[118] | 0 | ND | ND | Graft-versus-host-disease alive 29 months following bone marrow transplant with no evidence of recurrent graft-versus-host-disease or leukeumia; veno-occlusive disease “excellent liver allograft function” 9 months following OLT |
| Saigal 2001[69] | ND | ND | ND | 12 SOLID ORGAN/SKIN MALIGNANCIES: 1 recurrence of NHL (8.3%) treated with mantle therapy 120 months prior to OLT for HBV, chemotherapy 23 months following OLT with relapse at 27months; Of 4 incidental diagnoses 1 recurrence in a patient who underwent resection of renal cell carcinoma during OLT and died in early postoperative course of sepsis<br><br>6 MYELOPROLIFERATIVE STATE: 5/6 with median 79 months follow-up without transformation to leukemic states; 1/6 with acute leukemia at 72 months following OLT and death at 93 months. No de novo malignancy. |
| Schlitt 1995[119] | 0 | 100 | 100 | 40 months after no signs of infection of graft-versus-host disease |

ND = not discussed, OLT = orthotopic liver transplantation

**Table 47.** Liver Transplantation in the Setting of Preexisting Extrahepatic Malignancy: Graft Survival.

| Reference | 1 year graft survival | Outcomes Comments |
|---|---|---|
| Dousset 1995[43] | 80 | One patient regrafted at 6 months for recurrent Budd-Chiari |

**Table 48.** Liver Transplantation in the Setting of Preexisting Extrahepatic Malignancy: Quality of Life.

| Reference | Quality of Life |
|---|---|
| DeMaria 1995[116] | "Alive and well" |
| Marks 1992[71] | "Well" at 6 months; regained most of pre-bone marrow transplantation weight; Karnofsky score of 90%. |
| Nimer 1990[73] | 100% performance status one year following bone marrow transplantation |
| Rapoport 1991[74] | Improved mental status; required mechanical ventilator for nearly entire postoperative care |
| Rosen 1996[118] | Graft-versus-host disease patient returned to baseline functional status |

**Table 49.** Transplantation for Other Reported Tumors: Study Descriptions.

| Reference | Location (years of transplant reported) | # Pts. | Follow-up (months) | Disease features | Procedure |
|---|---|---|---|---|---|
| Adams 1999[77] | Leeds, UK | 1 | 48 | Hemangiopericytoma of left adrenal gland; tumor weighed 5.5kg, 35 x 24 x16cm liver mass; removed following 7 cycles of cyclophosphamide/epirubicin/decarbazine, 4 cycles of vincristine/methotrexate/bleomycin/cisplatin, 12 weeks interferon, 3 cycles of cyclophosphamide/epirubicin/decorbazine/dexamethasone | OLT |
| Balsells 1993[78] | Barcelona, Spain | 1 | 24 | Caroli's disease with unresectable adenocarcinoma of the intrahepatic bile ducts | OLT with Roux-en-Y |
| Blakolmer 2000[76] | Pittsburgh | 1 | .75 | Peripheral T-cell NHL involving liver and spleen without lymphadenopathy with fulminant hepatic failure; Diagnosis established at OLT | OLT |
| Chiche 2000[75] | Caen, France (80-98) | 2 | 48-192 | Liver adenomatosis "massive" | OLT |
| Olthoff 1990[53] | UCLA (84-89) | 1 | 31 | Lymphangioma with vascular and serosal invasion; tumor weighed 35 lb | OLT |
| Pichlmayr 1998[11] | Hannover, Germany (72-96) | 1 | 72 | Cystadenocarcinoma | OLT |

OLT = orthotopic liver transplantation; PSC = primary sclerosing cholangitis

**Table 50.** Transplantation for Other Reported Tumor: Patient Survival.

| Reference | Patient Survival in years (%) | | | | Outcomes Comments |
|---|---|---|---|---|---|
| | 1 0 | 2 | 3 | 5 | |
| Blakolmer 2000[76] | | | | | Death at .75months with recurrent disease in allograft |
| Chiche 2000[75] | 100 | 100 | 100 | 100 | Alive 4 years and 16 years after OLT with "progression" of disease |
| Olthoff 1999[53] | 100 | 100 | | | Alive without recurrence at 31months follow-up |
| Pichlmayr 1998[11] | 100 | 100 | 100 | | Alive and well over 6 years following OLT |

OLT = orthotopic liver transplantation

**Table 51.** Transplantation for Other Tumors: Disease-Free Survival and Recurrence Outcomes.

| Reference | Recurrence % | 1 year disease-free survival (%) | Outcomes Comments |
|---|---|---|---|
| Balsells 1993[78] | 0 | 100 | "Alive and well" at 2 years with normal liver function and no evidence of disease |
| Blakolmer 2000[76] | 100 | 100 | Death at .75 months with recurrent disease in allograft |
| Chiche 2000[75] | | | Alive 4 years and 16 years after OLT with "progression" of disease |
| Olthoff 1990[53] | 0 | 100 | Alive without recurrence at 31 months follow-up |
| Pichlmayr 1998[11] | | | Alive and well over 6 years following OLT |

OLT = orthotopic liver transplantation

**Table 52.** Transplantation for Other Tumors: Quality of Life.

| Reference | Quality of Life |
|---|---|
| Adams 1999[77] | "Symptom free" for 48months |
| Balsells 1993[78] | "Alive and well" at 2 years with normal liver function and no evidence of disease |
| Pichlmayr 1998[11] | Alive and well" over 6 years following OLT |

OLT = orthotopic liver transplantation

# **APPENDIX 1**. Data Extraction Instrument

Author: Journal Year;Volume:Pages:

Center Name/Locations: Extractor Name/Date Page of Extraction:

Years of transplants reported Able to distinguish tumor transplant data □Yes □No

**Total Number of Patients _____**

□ Cholangiocarcinoma

□ PSC _____

□ No PSC _____

□ PSC & No PSC _____

□ NOS _____

□ GB Cancer _____

□ Neuroendocrine _____

□ Neuroendocrine _____

□ Carcinoid _____

□ Islet Cell Tumors _____

□ Insulinoma _____

□ Gastrinoma _____

□ Glucagonoma _____

□ VIPoma _____

□ Other_____

□ Hemangiosarcoma _____

□ Hemangioendothelioma _____

□ Sarcoma

□ Metastatic Disease _____

Location:

□ Other _____

**Procedure Reported**

□ Liver transplant

□ Liver-pancreas-duodenum

□ Other: _____

**Characteristics**

Age:

Length follow-up:

Tumor Size

Stage of Disease

Histologic Features

Known immunosuppression agents?

Neo/Adjuvant therapies?

Other comments

**Outcomes of Interest**

Survival Time:

Operative Mortality ☐ Excluded

☐ Included

Patient Survival

6m 1y 3y 5y

Disease-Free Survival

6m 1y 3y 5y

Graft Survival

6m 1y 3y 5y

Quality of Life

Other

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