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Review

Liver Transplantation for Cholangiocarcinoma: An Update and Review

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Abstract

Cholangiocarcinoma (CCA) is an aggressive malignancy of the biliary epithelium. Its management is significantly challenging, as most cases are diagnosed at an advanced stage and treatment options are limited. Surgical resection is the standard treatment approach. However, approximately 70% of patients are diagnosed with unresectable disease due to distant metastases, extensive local disease, or poor hepatic reserve. Liver transplantation (LT) has gained attention as an alternative for select cases of unresectable perihilar (pCCA) and intrahepatic (iCCA) CCA.

This review aims to evaluate the role of LT in the management of CCA.

Earlier studies assessing the use of LT in treating CCA reported poor outcomes. However, the development of new neoadjuvant chemoradiotherapy protocols has led to remarkable improvements in post-transplant outcomes, with five-year survival rates exceeding 80% in selected pCCA patients. As for early-stage iCCA, limited data suggest that LT combined with neoadjuvant therapy yields more favorable outcomes than surgical resection, suggesting its potential benefit.

LT combined with neoadjuvant chemoradiotherapy appears to be a promising treatment option for unresectable CCA, especially in select cases of pCCA. Yet, there is still a significant gap in the literature, and further studies are needed to address this issue.

Keywords: Cholangiocarcinoma, liver transplantation, living-donor liver transplantation, peri-hilar cholangiocarcinoma

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Cholangiocarcinoma (CCA) is an aggressive malignancy of the biliary epithelium, being adenocarcinoma histologically.[1,2] It is the second most common primary malignancy of the liver after hepatocellular carcinoma, with an estimated prevalence of around 6 persons per 100,000 population.[2,3] CCA occurs more frequently in certain areas around the world, such as Chile, South Korea, and Thailand.[3] CCAs are categorized into three primary subtypes according to their anatomical site of origin: intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA) CCA.[2,4] Primary

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sclerosing cholangitis (PSC) is one of the most common risk factors for the development of CCA. Among patients with PSC, the annual risk of developing CCA ranges from 0.5% to 1.5%.[5] Other risk factors implicated in the development of CCA include liver fluke infection, congenital biliary cystic disorders, intrahepatic gallstones, and cirrhosis.[6] CCA is associated with a generally poor prognosis with a 5-year overall survival rate of less than 10%.[7–9] In addition, CCA has a high rate of recurrence treatment (>75%).[10,11]

The standard treatment for CCA has been radical surgical resection due to its potentially curative nature. However, surgical resection is often not feasible due to either local advancement and metastasis of the tumor at presentation or inadequate hepatic functional reserve secondary to underlying liver disease. It is estimated that up to 70% of cases of CCA are not amenable to resection, which underscores the challenges associated with the treatment of CCA.[12] Patients with unresectable CCA have a survival of only 12-16 months after development of symptoms.[13] The dearth of feasible treatment options is especially clinically relevant given the generally poor prognostic outcomes associated with CCA.[10,11]

In recent years, liver transplant (LT) has increasingly been explored as a potentially curative treatment option for locally advanced iCCA and pCCA without distant metastasis. LT for CCA was first performed in the 1980s with poor treatment outcomes due to a high incidence of recurrence (~50%) and mortality (5-year survival ~15%).14 These early studies showed LT alone was associated with poor overall outcomes in patients with CCA. However, in 1987, the transplant team at the University of Nebraska devised a protocol of high-dose neoadjuvant brachytherapy and 5-fluorouracil (5-FU) preceding LT. Early results reporting survival were encouraging.[15] In 1993, the Mayo Clinic developed its own neoadjuvant chemoradiation protocol for LT along with strict patient selection criteria. Preliminary results reported in 2000 showed promising results, and a 2004 update by the Mayo Clinic reported a 5-year survival rate of 82% for 28 patients.[16,17] Results from the Mayo Clinic and other retrospective studies have led to the acceptance and adoption of LT as a treatment option for pCCA in carefully selected patients. A standard model for end-stage liver disease (MELD) exception was also introduced in 2009 to facilitate patients with pCCA listed for LT.[18] While earlier research indicated that liver transplantation was not recommended for iCCA because of poor outcomes, more recent studies have shown better outcomes, particularly in patients with very early or early-stage iCCA.[19] This may reflect the importance of improved neoadjuvant therapy, stricter patient selection criteria, and increased center experience in patients undergoing LT for CCA.

In this review, we will discuss the existing literature on LT for CCA, focusing on pCCA and iCCA, explore outcomes and complications associated with LT for CCA, and compare LT outcomes with surgical resection for CCA. Additionally, we also aim to highlight any differences in outcomes between LT from living donors versus deceased donors. Given surgical resection is precluded in up to 70% of pCCA cases due to advanced disease at presentation, it is important to assess the feasibility of other treatment options with acceptable survival and recurrence rates.[20,21]

Classification of Cholangiocarcinoma

CCAs are categorized into three primary subtypes according to their anatomical origin: intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA) CCA.[2,4] iCCA arises proximal to the second-order bile ducts; pCCA develops in the region extending from the right and left hepatic ducts to the confluence of the cystic duct and common bile duct; and dCCA occurs distal to this confluence.[2] pCCA is the predominant subtype of CCA, representing approximately 50% of cases. dCCA and iCCA follow with a prevalence of approximately 42% and 8%, respectively.[22]

The reported incidence of iCCA has shown an upward trend across the US (0.44 cases per 100,000 in 1973 to 1.18 cases per 100,000 in 2012), whereas the incidence of extrahepatic CCA has been relatively stable.[23,24] It remains unclear whether the observed rise in iCCA cases reflects a true increase in incidence or is a result of improvements in diagnostic accuracy.

Surgical Resection

Surgical resection remains the primary treatment option for CCA with curative intent. The affected lobe or segments containing the tumor are typically removed in cases of iCCA. dCCA is usually treated with a pancreatoduodenectomy, while for pCCA, the surgical approach often involves resecting the affected intrahepatic and extrahepatic bile ducts, along with the ipsilateral liver, gallbladder, and regional lymph nodes, depending on tumor extent.[12]

Recommendations for surgical resection must take into account the patient's suitability for surgery, the size of the tumor, any metastatic spread, biochemical characteristics, and vascular and/or lymphatic involvement.[25] Survival after surgical resection varies by CCA subtype; 5-year survival rates following surgical resection vary depending on the CCA subtype, ranging from 22% to 44% for iCCA, 11% to 41% for pCCA, and 27% to 37% for dCCA.[12] R0 resection is key for long-term survival.[22] Positive tumor margins, cirrhosis, portal hypertension, and lymph node metastases are all associated with worse outcomes in patients who undergo surgical resection for CCA.[22,26,27] Neither neoadjuvant nor adjuvant therapy seems to favorably impact survival in patients who undergo resection for CCA.[28]

Notably, most patients are diagnosed with tumors that are not amenable to surgical resection — up to 70% of CCA tumors are classified as inoperable due to locally advanced tumors, distant metastases, lack of functional hepatic reserve secondary to underlying liver disease, etc.[12,29] This has contributed to the growing use LT as a treatment option for unresectable CCA.

Liver Transplantation

History of LT for CCA

The success of LT as a curative treatment for hepatocellular carcinoma encouraged the consideration of LT as a treatment option for CCA. Since LT achieves radical resection and often results in clean/R0 resection margins, it was thought that LT could be an ideal operation for CCA, especially in cases of underlying PSC. However, early studies reported poor survival outcomes and high recurrence rates. The Cincinnati Transplant Tumor Registry, which included data until 1997, reported a 5-year survival rate of 23% and a recurrence rate of 51%.[14] In those with recurrence, the median time from LT until recurrence was only 10 months. Another study, which included data from 1984 up to 1992, reported results from a center after the development of a protocol involving adjuvant chemotherapy and radiotherapy following LT for CCA.[30] Although the adjuvant therapy was well-tolerated, they found that their adjuvant therapy protocol failed to demonstrate a significant benefit. They reported 1-year survival to be 53% and the disease-free survival after 1-year to be 40%.[30] A study from Japan reported an overall survival rate of 35% at 3 years.[31] A multicenter Canadian study examined data from 1996 to 2003 of patients undergoing LT with incidental CCA found in the explant and reported a 3-year survival rate of 30% and a median recurrence time of 26 months.[32] A Spanish retrospective study of 36 patients with pCCA reported similar results with a 30% 5-year survival rate and a 53% tumor recurrence rate.[33]

The poor outcomes reported in the early studies may be due to poor patient selection criteria, lack of neoadjuvant therapy use, and lack of differentiation between tumor subtypes.

Neoadjuvant chemoradiotherapy

In 1987, the University of Nebraska introduced a neoadjuvant treatment protocol prior to LT involving the use of 5-fluorouracil (5-FU) combined with high-dose biliary brachytherapy. The rationale behind this approach was to curb and potentially downstage the tumor.[15] Although complications developed in some patients, survival outcomes were encouraging — long-term, tumor-free survival was 45% in transplanted patients. In 1993, the Mayo Clinic developed its own neoadjuvant protocol that included three weeks of continuous infusion of 5-FU and a subsequent two weeks of brachytherapy.[16] Capecitabine was then given until LT. For staging purposes, patients underwent abdominal exploration a few days before deceased donor transplantation and one day before living donor transplantation. Details of this protocol are outlined in Table 1, including strict patient selection criteria (Table 2 and Table 3).[16]

Table 1. Criteria for neoadjuvant therapy and liver transplantation for pCCA

Transcatheter biopsy or brush cytology
CA19-9 >100 mg/ml and/or mass on cross-sectional imaging with a malignant-appearing stricture on cholangiography
Biliary ploidy by FSH with a malignant-appearing stricture on cholangiography
Unresectable tumor above cystic duct
Pancreatoduodenectomy for microscopic involvement of CBD
Resectable CCA arising in PSC
Radial tumour diameter <-3 cm
Absense of intra- and extrahepatic metastases
Candidate for liver transplantation.

Table 2. Mayo Clinic protocol for neoadjuvant therapy and liver transplantation

External beam radiation therapy (45 Gy in 30 fractions, 1.5 Gy twice daily) and continuous infusion 5-FU - administered over 3 weeks
→ Brachytherapy (20 Gy at 1 cm in approximately 20-25 hours) – administered 2 weeks following completion of external beam radiation therapy
→ Capecitabine – administered until time of transplantation, held during perioperative period for staging
→ Abdominal exploration for staging – as time nears for deceased donor transplantation or day prior to living donor transplantation
→ liver transplantation

Table 3. Exclusion criteria

Intrahepatic cholangiocarcinoma
Uncontrolled infection
Prior radiation or chemotherapy
Prior biliary resection or attempted resection
Intrahepatic metastases
Evidence of extrahepatic disease
History of other malignancy in the past 5 years
Transperitoneal biopsy (including percutaneous and EUS-guided FNA)

Although most of the existing literature reports experience with a neoadjuvant protocol consisting of external beam radiotherapy combined with brachytherapy, continuous intravenous 5-FU, and subsequent oral capecitabine administration prior to LT, as described previously, there are some publications that have reported the use of different neoadjuvant protocols. A 2018 study by Loveday et al. reported the use of concurrent administration of conformal radiotherapy and capecitabine followed by maintenance cisplatin and gemcitabine after surgical staging.[34] Another study reported use of gemcitabine alone or combined with cisplatin.[35] No comparative studies have been carried out to evaluate any difference in outcomes between different neoadjuvant regimens.

Neoadjuvant therapy increases the risk of radiation-related injury, which can pose challenges to surgery. Portal vein and hepatic artery stenosis, with or without thrombosis, occurs in up to 20% of transplanted patients after undergoing neoadjuvant therapy.[29] However, these vascular complications are amenable to treatment with stents and vascular grafts with an excellent success rate.[36]

Current Evidence and Outcomes

LT in Perihilar Cholangiocarcinoma

The success of the Mayo Clinic protocol led to a shift among centers in terms of patient selection criteria and neoadjuvant therapy preceding LT. A 2014 study detailed the experience of the Irish National Liver Transplant Programme.[37] 20 patients underwent LT, provided they were progression-free after receiving brachytherapy, external beam radiotherapy, and 5-FU. Although they found short-term mortality to be high (20% hospital mortality), they reported a 61% survival rate at 4 years for patients who successfully underwent the LT. In addition, they reported tumor residue in explant and high CA 19-9 levels to be predictors of disease recurrence, similar to a study by the Mayo Clinic.[37,38] A 2012 study included outcomes from 12 high-volume liver transplant centers across the US and aimed to assess the survival rates in patients with pCCA who underwent neoadjuvant therapy followed by LT. They found a 65% recurrence-free 5-year survival rate, indicating neoadjuvant therapy followed by LT to be a highly effective treatment option for suitable patients with pCCA.40 Additionally, they found that despite the majority of patients originating from a single center, the remaining 11 centers reported similar outcomes following treatment, suggesting that good survival outcomes can be universally achieved and reproduced provided adherence to the Mayo Clinic or Mayo-like protocol of neoadjuvant therapy followed by LT.[39] A 2005 Mayo Clinic study compared neoadjuvant therapy and LT with surgical resection in patients with pCCA.[40] They reported a 5-year survival of 82% in patients who underwent LT compared to 21% after resection. Moreover, they noted fewer recurrences in the LT patients (13% versus 27%).[40] In a multicenter study, outcomes of pCCA were compared between 41 patients who underwent LT and 191 patients who underwent surgical resection.[41] They found a significant improvement in 5-year overall survival rates in the LT group (64%) versus the resection group (18%). These findings persisted even when comparing those who underwent resection for pCCA while also meeting the criteria for LT (eg. tumor size < 3 cm, lymph node-negative disease); 5-year overall survival of 54% versus 29% (p=0.03).[41] Based on these results, it was recommended that further prospective studies continue to be conducted to compare LT with resection, particularly in those patients with resectable disease. In a 2022 multicenter benchmark study, Breuer et al. reported data from 134 patients with pCCA who underwent LT after completion of Mayo-like neoadjuvant therapy.[42] They found LT was associated with a superior 5-year disease-free survival (62%) versus a matched group of patients who underwent curative liver resection (32%). They recommended updated treatment algorithms for pCCA based on their findings. A meta-analysis comparing LT and resection outcomes for pCCA. They found a significantly increased 3-year overall survival in patients who underwent LT as opposed to resection (p=0.02).[43] In addition, patients undergoing LT had a shorter hospital stay than those who had resection, and no statistically significant difference was found between LT and resection regarding postoperative mortality. They postulated that neoadjuvant therapy and/or strict selection criteria for the patients that underwent LT may have contributed to the improved survival outcomes as compared to resection and believed no certain conclusions could be drawn from their results to support the use of LT for technically resectable early-stage pCCA due to the absence of high-quality data from randomized controlled trials (RCTs).[43]

The only RCT (NCT02232932) to directly compare radio-

chemotherapy and LT against liver resection in resectable pCCA was highly anticipated for the results due to its potential to guide future direction and management of resectable pCCA by directly comparing the two treatment modalities in this patient population.[44] However, the study was ended prematurely due to insufficient patient enrollment and a high dropout rate of 55% among the first 20 patients assigned to the LT group.[42,44] The experience of this clinical trial may underscore the difficulty and limited feasibility of conducting an RCT directly comparing LT with resection.

Since the development and success of the Mayo Clinic and Mayo-like protocols, some have questioned whether improved outcomes should be attributed to neoadjuvant therapy or strict selection criteria.[43] One retrospective study aimed to assess the role of patient selection alone on LT outcomes for pCCA. They used the European Liver Transplant Registry (ELTR), from 1990 and 2010, to identify 28 patients who fulfilled the strict eligibility requirements of the Mayo Clinic protocol and did not receive neoadjuvant chemoradiation therapy. They reported a 59% 5-year survival rate, which is similar to results published by the Mayo Clinic concerning patients who underwent LT following neoadjuvant chemoradiation therapy.[45] They suggested that strict selection alone leads to improved survival outcomes in patients with pCCA; however, they did stress caution in the interpretation of their results. It is likely that both neoadjuvant therapy and strict selection criteria have an important role in the management of patients who are suitable candidates for LT.[17]

Center experience also appears to play a role in treatment outcomes in patients with pCCA who undergo LT. Kitajima et al. aimed to assess the effect of center experience on outcomes with LT and classified included transplant centers into two groups: well-experienced (defined as ≥6 LTs; n = 7 centers) and less-experienced (defined as < 6 LTs; n = 23 centers).[45] They found post-LT outcomes were significantly better at well-experienced centers, with 1-, 3-, and 5-year survival rates of 91.8%, 56.9%, and 45.8%, respectively, compared to 65.6%, 48.8%, and 26.0% at less-experienced centers. They also found a statistically significant increased risk of tumor recurrence and all-cause mortality in the less-experienced group.[46] Based on their results, Kitajima et al. suggested the potential introduction of center approval for LT to ensure consistent and comparable treatment outcomes between centers.

Predictors of Disease Recurrence Post-transplant

A 2006 Mayo Clinic study studied data from 65 patients with pCCA who underwent deceased-donor LT with the aim of assessing predictors of disease recurrence after neoadjuvant chemoradiotherapy and LT.[38] They identified several predictors, including advanced age; a pretransplant CA 19-9 level exceeding 100 U/ml; presence of > 2 cm residual tumor in the explant on cross-sectional imaging; prior cholecystectomy; and tumor grade and perineural invasion in the explant.[38] Updates to this study reported that age and prior cholecystectomy are not predictors of disease recurrence, but perineural and lymphovascular invasion, elevated CA 19-9, portal vein encasement, and size of residual tumor on explant are predictors.[47,48]

As previously mentioned, high CA19-9 levels and residual explant tumors were also found to be predictors of tumor recurrence according to a study of the Irish National Liver Transplant Program, in line with results from the Mayo Clinic.[37]

These predictive factors assist in identifying patients at elevated risk for disease recurrence and, hence, can guide post-transplant management of such patients (i.e. additional therapy in the form of adjuvant therapy etc.).[49]

PSC-associated pCCA versus De Novo pCCA

Outcomes also differ between pCCA occurring de novo and pCCA developing in the context of PSC. An intention-to-treat analysis from the Mayo Clinic reported survival rates for patients with PSC-associated pCCA at 1, 5, and 10 years to be 78%, 60%, and 52% versus 83%, 39%, and 32% in patients with de novo pCCA.50 A statistically significant difference in survival after LT at 1, 5, and 10 years was also noted (92%, 76%, and 70% versus 90%, 58%, and 49%).[49]

LT in Intrahepatic Cholangiocarcinoma

LT for iCCA historically produced poor outcomes and, as a result, has largely been a contraindication in this patient population.[50,51] A large 2016 multicenter cohort study aimed to further evaluate whether LT could result in acceptable outcomes in patients with "very-early" iCCA.[19] The study included patients who underwent LT for HCC or decompensated cirrhosis and were diagnosed with iCCA based on the explant pathology. Two study groups were then established: one with "very-early" iCCA (defined as single tumor ≤2 cm; n = 15) and the other with "advanced" iCCA (defined as single tumor >2 cm or multifocal disease; n = 33). In the very-early iCCA group, the actuarial survival rates at 1, 3, and 5 years were 93%, 84%, and 65%, respectively, while in the advanced iCCA group, these rates were 79%, 50%, and 45%. The very early iCCA group also demonstrated a statistically significant lower risk of recurrence.[19] However, it remains unclear how clinically significant these results

could be given that iCCA is frequently asymptomatic until advanced disease and the challenges associated with diagnosing iCCA at such an early stage (i.e, single tumor <2 cm, etc). A 2023 propensity score-matched study compared LT for iCCA with resection and noted better prognosis in patients who underwent LT versus those who underwent resection in both unmatched (HR 0.65, p=0.002) and matched cohorts (HR 0.62, p=0.009).[53] Their results also indicated an improved 5-year overall survival rate (61.7%) in patients who received neoadjuvant chemotherapy with LT. This suggests that neoadjuvant chemotherapy before LT may improve outcomes in patients with iCCA, much like in pCCA.

Standard MELD Exception and Living-Donor LT

In 2009, a standard MELD score exception was introduced for pCCA in patients listed for LT.[18] Currently, the standard MELD exception score for pCCA patients aged 18 and older is calculated as the Median MELD at Transplant (MMaT) minus 3 points.[18] There is an extensive set of criteria to qualify for the MELD exception for pCCA. A detailed patient care protocol must be submitted to the Liver and Intestinal Organ Transplantation Committee for review and approval. This protocol should include patient selection criteria, administration of neoadjuvant therapy prior to LT, and operative staging aimed at excluding patients with regional hepatic lymph node metastases, intrahepatic metastases, or extrahepatic disease, along with any additional information requested by the committee. The patient must meet the diagnostic criteria for pCCA, which includes a malignant-appearing stricture on cholangiography along with at least one of the following: (i) biopsy or cytology confirming malignancy, (ii) CA19-9 level >100 U/ml without evidence of cholangitis, (iii) presence of aneuploidy, or (iv) a hilar mass <3 cm in radial diameter. Moreover, the tumor must be considered unresectable either due to technical considerations or poor hepatic reserve secondary to underlying liver pathology. Cross-sectional imaging must demonstrate a single tumor <3 cm in radial (perpendicular to duct) diameter, with no consideration for the longitudinal extension of the stricture along the bile duct in terms of measurement. Cross-sectional imaging of the chest and abdomen must also exclude intrahepatic or extrahepatic metastases. Operative staging must also be performed after completing neoadjuvant therapy to evaluate regional hepatic lymph node involvement and detect peritoneal metastases. Importantly, transperitoneal biopsy or aspiration of the primary tumor is contraindicated due to the high risk of tumor seeding regardless of the percutaneous, endoscopic, or surgical approaches.[18,53]

Despite a MELD score exception for pCCA, the waiting time for patients is still considerably long secondary to critical organ shortage. This could lead to increased morbidity and mortality for those awaiting transplantation.[54] In addition, patients experiencing prolonged wait times before transplantation are at higher risk of developing radiation-induced fibrosis, which complicates staging and presents technical challenges during transplantation.[49] Living-donor LT allows for more timely access to LT, which may reduce waitlist-associated morbidity and mortality.[29,54] Outcomes with living-donor LT and deceased-donor LT for pCCA developing in the setting of PSC are comparable.[49] However, living-donor LT for de novo pCCA may be related to increased tumor recurrence and slightly inferior survival rates compared to deceased-donor LT.[49] Hence, it may be useful to monitor select patients for disease progression post-neoadjuvant therapy to potentially exclude at-risk patients from undergoing LT to avoid eventual recurrence after transplantation.

Living-donor LT may also increase the risk of late vascular complications (i.e., of hepatic artery and portal vein), but these complications have not been shown to affect long-term survival.[55]

Directions for Future Research

There remains a need for larger, high-quality studies to provide more information to guide the use of LT in patients with pCCA, particularly regarding the use of living-donor organs. A similar need for robust studies is required for iCCA, as current data is limited, although promising, for LT use in early-stage, small iCCA. If new studies provide results similar to early data, a shift in management towards LT for early-stage iCCA may be warranted.[19] Challenges persist for RCTs and other prospective trials, as demonstrated by the premature termination of trials secondary to issues like low accrual and recruitment.[44,56]

Avances in neoadjuvant and adjuvant therapy also present potential to further improve outcomes in patients who undergo LT for CCA. Newer neoadjuvant techniques like stereotactic radiation have demonstrated efficacy with reduced toxicity compared to conventional external beam radiotherapy and might offer advantages for patients undergoing LT.[57] Further research is needed to evaluate the role of newer advanced neoadjuvant therapies for LT.

Furthermore, continued refinement of patient selection criteria will be helpful to improve outcomes in patients who undergo LT and exclude those who are at high risk of falling out prior to LT. Analysis of future large studies will be helpful to aid further refinement of patient selection criteria.

Conclusion

In summary, LT following neoadjuvant chemoradiation is a viable and effective treatment alternative for patients with pCCA who meet strict selection criteria, with outcomes comparable or superior to surgical resection. LT for pCCA has also achieved outcome results comparable to other indications for LT, justifying MELD score exception and the potential use of living-donor organs. The evidence for LT use in iCCA remains limited, but some studies have shown promise in patients with early-stage iCCA, comparable or superior to resection. Advances in neoadjuvant therapy also represent potential to further improve outcomes in patients undergoing LT. Larger, multicenter studies are needed for each CCA subtype, particularly to provide further elucidation on whether LT is an acceptable treatment for early-stage iCCA.

Disclosures

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