

# Strategies for the delay of surgery in the management of resectable hepatobiliary malignancies during the COVID-19 pandemic

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## ABSTRACT

**Objective** We aimed to review data about delaying strategies for the management of hepatobiliary cancers requiring surgery during the COVID-19 pandemic.

**Background** Given the COVID-19 pandemic, many jurisdictions, to spare resources, have limited access to operating rooms for elective surgical activity, including cancer, thus forcing deferral or cancellation of cancer surgeries. Surgery for hepatobiliary cancer is high-risk and particularly resource-intensive. Surgeons must critically appraise which patients will benefit most from surgery and which ones have other therapeutic options to delay surgery. Little guidance is currently available about potential delaying strategies for hepatobiliary cancers when surgery is not possible.

**Methods** An international multidisciplinary panel reviewed the available literature to summarize data relating to standard-of-care surgical management and possible mitigating strategies to be used as a bridge to surgery for colorectal liver metastases, hepatocellular carcinoma, gallbladder cancer, intrahepatic cholangiocarcinoma, and hilar cholangiocarcinoma.

**Results** Outcomes of surgery during the COVID-19 pandemic are reviewed. Resource requirements are summarized, including logistics and adverse effects profiles for hepatectomy and delaying strategies using systemic, percutaneous and radiation ablative, and liver embolic therapies. For each cancer type, the long-term oncologic outcomes of hepatectomy and the clinical tools that can be used to prognosticate for individual patients are detailed.

**Conclusions** There are a variety of delaying strategies to consider if availability of operating rooms decreases. This review summarizes available data to provide guidance about possible delaying strategies depending on patient, resource, institution, and systems factors. Multidisciplinary team discussions should be leveraged to consider patient- and tumour-specific information for each individual case.

**Key Words** COVID-19, coronavirus, hepatobiliary cancer, HCC, metastases, cholangiocarcinoma, gallbladder carcinoma

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## INTRODUCTION

The evolving COVID-19 pandemic is placing unprecedented pressures on health systems. Many jurisdictions have cancelled or delayed elective surgical activity to spare precious hospital, critical care, and personal protective equipment resources; to increase system capacity; and to limit nosocomial spread of COVID-19<sup>1–4</sup>. This sudden scale-back in operative resources has led to re-triaging and

prioritization of elective surgeries, including cancer cases. As COVID-19 pressures on local resources mount, operative case categorization changes, and criteria become more stringent, resulting in a higher number of cancer surgeries potentially being deferred<sup>5</sup>.

Delays in cancer surgery could risk losing a window for resection, compromising curative-intent surgery, or delaying palliation, with impacts that can vary depending on the timing of the delay in the cancer care continuum.

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Furthermore, as hospital resources—including critical-care and specialized staff—become less available, perioperative outcomes could worsen. The ability to progress patients through the usual postoperative care pathways and to rescue potential complications could be compromised. In the mode of “safety first,” that compromised ability shifts the risk–benefit balance of surgery for individual patients and diseases, making changes to the usual decision-making and triaging for surgical cancer care inevitable and necessary.

Governing bodies and surgical societies have released statements about the need to delay and prioritize elective surgeries, including those for cancer<sup>5,6</sup>. However, those high-level statements lack either detailed disease- and patient-specific guidance or the data and resource information to support decision-making (Table 1)<sup>7–9</sup>.

The logistics of care and operating room availability can shift quickly as the pandemic evolves, and surgical decisions have to rapidly adapt. Multiple factors to consider for each case include not just the usual disease and patient factors (chance for cure or further spread of the cancer, risk for complications), but also, particularly in the pandemic, hospital resource use [for example, the need for an intensive care unit (ICU) stay], the likelihood of prolonged hospitalization, and risk of exposure to and outcomes of COVID-19. Weighing all those considerations requires an understanding of expectations with standard-of-care surgery, available mitigating or delaying strategies and their outcomes, and the risks posed by COVID-19 infection.

The aim of the present review was to provide detailed information to support decision-making for the surgical management of hepatobiliary cancers that can be adapted to rapidly evolving situations and surgical resource availability. Rather than developing guidelines or recommendations that could quickly become obsolete, we aimed to summarize within a single review the data to support difficult discussions and decisions. We focus on surgically treatable intrahepatic malignancies and endorse the logistics of operating room workflow and protocols during the pandemic that have previously been outlined<sup>3,10,11</sup>.

## METHODS

A non-systematic search was conducted of the literature (as of 10 April 2020), surgical and oncology society guidelines, and expert statements about the management of the most common hepatobiliary malignancies in surgical oncology practice:

- Colorectal liver metastases (CRLMs)
- Hepatocellular carcinoma (HCC)
- Gallbladder carcinoma (GBC)
- Intrahepatic cholangiocarcinoma (ICC)
- Hilar cholangiocarcinoma

Relevant data about standard-of-care surgical management and possible mitigating strategies to be used as a bridge to surgery were extracted and summarized. The components of care summarized for each treatment strategy were: short-term outcomes (morbidity and mortality), long-term oncologic outcomes (survival), factors

influencing and tools predicting outcomes, and resource requirements for therapy delivery. When available, we also abstracted data about patient outcomes with delays in surgery.

The search and data abstraction were performed by 2 authors (SB, JH), with subsequent review by a multidisciplinary (surgical, medical, and radiation oncology), international (North America, Australasia, and Europe) group of oncologists to ensure applicability within various health systems and in countries at different phases of the current pandemic. No formal consensus criteria were applied to the review.

## RESULTS

### Risk of COVID-19 for the Surgical Oncology Patient

Data about outcomes of COVID-19–infected cancer patients are limited, particularly with respect to surgical oncology. Repeated visits to the hospital, risk from social and nosocomial contacts, and the immunosuppressive effects of surgical stress could contribute to a higher risk of developing COVID-19 for patients with cancer<sup>12,13</sup>. However, that risk is highly confounded by the prevalence of asymptomatic COVID-19 in the community and the lag between infection and symptoms. Information about vulnerability to COVID-19 can guide decision-making for surgical cancer patients. Comorbidities associated with higher risk from COVID-19 (for example, hypertension, diabetes, pulmonary disease, cardiovascular disease) and age could be used to arrive at the most optimal risk–benefit balance<sup>14</sup>.

Two major epidemiologic studies from China drew data from 18 and 10 cancer patients infected with COVID-19 and suggested a higher rate of ICU admission, need for ventilation, and death (39%) in that patient population compared with the general population (8%)<sup>12,13</sup>. The case fatality rate for all cancer patients with COVID-19 infection is reported to be higher than the overall case fatality rate (5.6% vs. 2.3%), although no details are available about that subpopulation<sup>15</sup>. However, most Chinese patients with cancer and COVID-19 in those series were 4 years or more from their initial cancer diagnosis, and only 1 had undergone surgery and 3 had received chemotherapy within a month of COVID-19 infection<sup>12</sup>. A Chinese series of hospitalized patients with COVID-19 that included 105 patients with and 233 without cancer observed that patients with cancer experienced higher rates of severe events of ICU admission, mechanical ventilation, and death<sup>16</sup>. After adjusting for age, sex, and comorbidities, cancer was not independently associated with increased odds of ICU admission (odds ratio: 1.5; 95% confidence interval: 0.70 to 3.1) or death (odds ratio: 2.2; 95% confidence interval: 0.46 to 5.2). Overall, those data cannot definitively support the idea that delaying therapy would protect from COVID-19 infection. However, COVID-19 infection manifesting during the postoperative period is associated with poor outcomes. An early publication described 34 patients who were operated on while incubating COVID-19 that manifested clinically after surgery; all developed pneumonia, 44% required ICU admission, and 20% died<sup>17</sup>. A large multicentre cohort study at 235 hospitals in 24 countries included 1128 patients who underwent any operation and were diagnosed with COVID-19 within a

**TABLE I** Summary of statements from major surgical and oncology societies about cancer surgery and hepatobiliary malignancy during the COVID-19 pandemic

Society	Statement						
<i>American Society of Clinical Oncology</i>	<ul style="list-style-type: none"> <li>Individual determinations about the need for cancer surgery based on potential harms of delaying surgery, including consideration of the need for postoperative ICU care.</li> <li>Reasonable to consider neoadjuvant therapy or delay in surgery in situations in which neoadjuvant therapy is available, but not routinely considered: <ul style="list-style-type: none"> <li>Weigh risks of delay in surgery against burden on hospital resources and patient risk of exposure to COVID-19, and consider risks of exposure to COVID-19 and of immunosuppression with chemotherapy.</li> </ul> </li> <li>No evidence that immunosuppressive therapy should be delayed or held. Individual risk assessment required.</li> </ul> <p><i>Hepatobiliary cancers specifically:</i> links to statement from Society of Surgical Oncology</p> <p>For details: <a href="https://www.asco.org/asco-coronavirus-information">https://www.asco.org/asco-coronavirus-information</a></p>						
<i>National Comprehensive Cancer Network</i>	<ul style="list-style-type: none"> <li>Cancer surgery is not considered elective, but requires prioritization.</li> <li>Shared decision-making optimized with surgeon-to-patient discussions (telephone calls).</li> </ul> <p><i>Hepatobiliary cancers specifically:</i> no statement</p> <p>For details: <a href="https://www.nccn.org/covid-19/">https://www.nccn.org/covid-19/</a></p>						
<i>American College of Surgeons</i>	<ul style="list-style-type: none"> <li>Patients should receive appropriate and timely surgical care, including operative management, based on sound surgical judgment and availability of resources.</li> <li>Virtual multidisciplinary discussions for triage of cases based on local resources, COVID-19 prevalence, and alternative nonsurgical therapies.</li> </ul> <p><b>Three phases</b> guide decision-making relative to level of the pandemic:</p> <ul style="list-style-type: none"> <li>Semi-urgent setting – preparation phase</li> <li>Urgent setting</li> <li>Local resource scarcity</li> </ul> <p><i>Hepatobiliary cancers specifically:</i> For oligometastatic colorectal cancer, use effective systemic therapy, if available. No statement for hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and gallbladder cancer.</p> <p>For details: <a href="https://www.facs.org/covid-19/clinical-guidance/elective-case">https://www.facs.org/covid-19/clinical-guidance/elective-case</a></p>						
<i>Society of Surgical Oncology</i>	<p>Follows the American College of Surgeons phases of the pandemic.</p> <p><i>Hepatobiliary cancers specifically:</i></p> <table border="1"> <thead> <tr> <th>Phase 1 – Semi-urgent setting</th> <th>Phase 2 – Urgent setting</th> <th>Phase 3 – Local resource scarcity</th> </tr> </thead> <tbody> <tr> <td>           Procedures to be done: <ul style="list-style-type: none"> <li>Intrahepatic cholangiocarcinoma (symptoms or not)</li> <li>Colorectal liver metastases finishing neoadjuvant therapy in which further chemotherapy would be detrimental to liver function</li> </ul>           Consider alternative therapies: <ul style="list-style-type: none"> <li>Large intrahepatic cholangiocarcinoma requiring major hepatectomy – chemotherapy</li> <li>Hepatocellular carcinoma – ablation or liver-directed therapies</li> <li>Incidental gallbladder cancer requiring staging or re-resection – delay</li> </ul> </td> <td>           Procedures to be done: <ul style="list-style-type: none"> <li>Advanced tumour at risk of becoming unresectable with delay</li> <li>Management of complications if interventional approach not feasible</li> <li>Bleeding tumours that cannot be managed with interventional radiology, radiation, or endoscopy</li> </ul>           Consider alternative strategies: <ul style="list-style-type: none"> <li>Chemotherapy upfront for tumours in which it is not routine, if can be done safely</li> <li>Radiation therapy upfront for tumours in which it is not routine, if can be done safely</li> <li>SBRT for liver metastasis</li> <li>Liver-directed therapy as bridge to surgery</li> </ul> </td> <td>           Procedures to be done: <ul style="list-style-type: none"> <li>Management of complications if interventional approach not feasible</li> <li>Bleeding tumours that cannot be managed with interventional radiology, radiation, or endoscopy</li> </ul>           Alternative strategies: <ul style="list-style-type: none"> <li>Same as Phase 2</li> </ul> </td> </tr> </tbody> </table> <p>For details: <a href="https://www.surgonc.org/resources/covid-19-resources/">https://www.surgonc.org/resources/covid-19-resources/</a></p>	Phase 1 – Semi-urgent setting	Phase 2 – Urgent setting	Phase 3 – Local resource scarcity	Procedures to be done: <ul style="list-style-type: none"> <li>Intrahepatic cholangiocarcinoma (symptoms or not)</li> <li>Colorectal liver metastases finishing neoadjuvant therapy in which further chemotherapy would be detrimental to liver function</li> </ul> Consider alternative therapies: <ul style="list-style-type: none"> <li>Large intrahepatic cholangiocarcinoma requiring major hepatectomy – chemotherapy</li> <li>Hepatocellular carcinoma – ablation or liver-directed therapies</li> <li>Incidental gallbladder cancer requiring staging or re-resection – delay</li> </ul>	Procedures to be done: <ul style="list-style-type: none"> <li>Advanced tumour at risk of becoming unresectable with delay</li> <li>Management of complications if interventional approach not feasible</li> <li>Bleeding tumours that cannot be managed with interventional radiology, radiation, or endoscopy</li> </ul> Consider alternative strategies: <ul style="list-style-type: none"> <li>Chemotherapy upfront for tumours in which it is not routine, if can be done safely</li> <li>Radiation therapy upfront for tumours in which it is not routine, if can be done safely</li> <li>SBRT for liver metastasis</li> <li>Liver-directed therapy as bridge to surgery</li> </ul>	Procedures to be done: <ul style="list-style-type: none"> <li>Management of complications if interventional approach not feasible</li> <li>Bleeding tumours that cannot be managed with interventional radiology, radiation, or endoscopy</li> </ul> Alternative strategies: <ul style="list-style-type: none"> <li>Same as Phase 2</li> </ul>
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<i>European Society of Surgical Oncology</i>	<p>Liaise with colleagues regarding feasibility and practicality of chemotherapy, radiation therapy, and targeted treatment to reduce impact on hospital beds for surgery, and decision on case-by-case basis.</p> <p><i>Hepatobiliary cancers specifically:</i> no statement</p> <p>For details: <a href="https://www.essoweb.org/news/esso-statement-covid-19/">https://www.essoweb.org/news/esso-statement-covid-19/</a></p>						

TABLE I Continued

Society	Statement
<i>Americas Hepato-Pancreato-Biliary Association</i>	
Follows the American College of Surgeons phases of the pandemic.	
<i>Hepatobiliary cancers specifically:</i>	
<ul style="list-style-type: none"> <li>• Consider patient comorbidities and age to assess relative risks and benefits with potential exposure to COVID-19 compared with alternative treatment options.</li> <li>• Consider changes in resources available at various stages of the pandemic.</li> <li>• For patients facing a potentially prolonged hospital stay or at higher risk for complications requiring ICU management, surgery should be timed to available resources.</li> </ul>	
<p><b>Phase 1 – Semi-urgent setting</b></p> <ul style="list-style-type: none"> <li>• Hepatocellular carcinoma – hepatectomy, transplant, ablation</li> <li>• Colorectal liver metastases – hepatectomy for intermediate-acuity surgery and healthy patient, chemotherapy for intermediate-acuity surgery and unhealthy patient</li> <li>• Intrahepatic cholangiocarcinoma – hepatectomy for intermediate-acuity surgery and healthy patient, chemotherapy for intermediate-acuity surgery and unhealthy patient</li> <li>• Hilar cholangiocarcinoma – resection or transplantation as indicated</li> </ul>	<p><b>Phase 2 – Urgent setting   Phase 3 – Local resources scarcity</b></p> <ul style="list-style-type: none"> <li>• Hepatocellular carcinoma – delay definitive therapy; TACE ablation or observation</li> <li>• Colorectal liver metastases – chemotherapy</li> <li>• Intrahepatic cholangiocarcinoma – chemotherapy or embolic therapy</li> <li>• Hilar cholangiocarcinoma – chemotherapy, chemoradiation, or transfer to a facility with more resources</li> </ul>
For details: <a href="https://www.sages.org/sages-ahpba-recommendations-surgical-management-of-hpb-cancer-covid-19/">https://www.sages.org/sages-ahpba-recommendations-surgical-management-of-hpb-cancer-covid-19/</a>	

ICU = intensive care unit; SBRT = stereotactic body radiation therapy; TACE = transarterial chemoembolization.

window of 7 days preoperatively to 30 days postoperatively<sup>18</sup>. The overall 30-day mortality rate was 23.8%, and the rate of pulmonary complications was 51.2%.

### Standard of Care and Role of the Multidisciplinary Team

Despite the limitations imposed by the COVID-19 pandemic, surgeons should strive to provide standard-of-care therapy. All treatment decisions, particularly those in which standard therapy has to be altered or delayed, must be made in a multidisciplinary team. Given that access to chemotherapy and radiation therapies might also be restricted, ongoing communication with oncology colleagues is essential. Treatment options, risks and benefits, and the perceived outcome of each intervention have to be discussed with the patient to arrive at the situational best solution and at informed consent with the patient. Notably, patients and surgeons will have different personalities, values, and expectations, all of which could affect choice of treatment. However, opting for risk-averse pathways might also be justified for the common good in a situation in which resources and access to intensive care support might be restricted.

### Therapeutic Options and Resource Use

Table II summarizes general resource use for possible treatment strategies, to be interpreted in light of specific institutional care processes and resource availability before, during, and after the pandemic.

Hepatectomies are a heterogeneous group of procedures, ranging from laparoscopic wedge resection of a single segment to trisegmentectomy with bile duct resection and reconstruction<sup>19</sup>. Patients at highest risk of morbidity and

mortality after hepatectomy are those with comorbidities, an age of 75 years or greater, or underlying cirrhosis; those undergoing major liver resection ( $\geq 4$  liver segments), synchronous colorectal and liver resection, and biliary reconstruction; and those needing blood transfusions<sup>19–21</sup>. The risk of requiring care in an ICU after surgery is higher for patients undergoing major hepatectomy and those receiving blood transfusions<sup>22</sup>. For patients with minor liver disease, a laparoscopic approach can be beneficial, with lower morbidity and a shorter hospital stay<sup>19</sup>.

The risk of morbidity and mortality can be predicted using the National Surgical Quality Improvement Program developed by the American College of Surgeons based on multi-institutional prospectively validated data<sup>23</sup>. Blood transfusion is another important marker of postoperative morbidity and higher use of resources after hepatectomy, and can be estimated using the validated transfusion risk score based on data about preoperative anemia, background liver disease, and extent of planned hepatectomy<sup>24,25</sup>. Transfusion is especially important to consider, given that the COVID-19 pandemic can lead to allogeneic blood shortages as a result of physical distancing and confinement policies<sup>26</sup>.

Chemotherapy is delivered in an outpatient setting. It involves repeated visits to cancer clinics, with associated risks related to social exposure because of travel, waiting room crowding, and sequential use of a chemotherapy chair that could increase the risk of exposure to COVID-19 infection. Moreover, chemotherapy means exposure to agents that might compromise the quality of the liver remnant and create a risk of immunosuppression<sup>27</sup>.

Percutaneous ablation, such as radiofrequency ablation (RFA), can be delivered as outpatient care in radiology

**TABLE II** Safety profile and resource use for treatment strategies

Strategy	Safety profile (adverse effects)	Clinical setting	Length of stay	Unplanned ICU admission <sup>a</sup>	Typical PPE <sup>b</sup>	Immuno-suppression
Hepatectomy	Major morbidity: 20% Mortality: 2%	Inpatient	3–6 Days	5%–10%	Yes	Relative: postoperative SIRS
Systemic therapy	Depends on regimen. Consider neutropenia and lymphopenia.	Outpatient	Recurrent visits (every 1–3 weeks)	Rare	Yes	Yes
Percutaneous ablation	4% Grade 3 events	Outpatient	1 Day	Rare	Yes	No
		Inpatient (possible OR)	1–2 Days			
Ablative radiation therapy (SBRT)	6%–7% Grade 3 gastrointestinal events (if proximity to duodenum or stomach)	Outpatient	3–5 Daily visits	Rare	No	No
Intra-arterial liver embolization	15%–30% Pain, fatigue, vomiting	Outpatient	1 Day (might require repeats, 4–6 weeks apart)	Rare	Yes	No
		Inpatient (possible OR)	1–2 Days			

<sup>a</sup> Excludes routine planned postoperative admissions for monitoring.

<sup>b</sup> That is, mask, gown, gloves—PPE requirements for usual care (could vary during COVID-19 pandemic, depending on institutional protocols). ICU = intensive care unit; PPE = personal protective equipment; SIRS = systemic inflammatory response syndrome; OR = operating room; SBRT = stereotactic body radiation therapy.

suites or in the operating room, depending on the institution. Grade 3 adverse events in percutaneous ablation occur in 4%–5% of patients<sup>28</sup>. Ablative radiation therapy [stereotactic body radiation therapy (SBRT)] is an outpatient procedure in radiation therapy facilities. The adverse effects profile of SBRT is minimal, with a 6%–7% risk of grade 3 gastrointestinal toxicity<sup>29,30</sup>.

Finally, liver embolization is typically performed in the radiology suite or in the operating room, as an outpatient or inpatient procedure, depending on the institution. Post-embolization syndrome—with fever, abdominal pain, and elevated transaminases—is the most frequent complication<sup>31</sup>. For transarterial chemoembolization (TACE, using drug-eluting beads containing irinotecan) in patients with CRLMs, 15%–30% experience either pain, vomiting, fatigue, or fever, with most adverse events being grade 2<sup>32,33</sup>. For TACE in patients with HCC, most adverse effects are also grade 2. Across studies, 20%–30% of patients experience either pain, fever, nausea, or fatigue, and 5%–30% can develop ascites depending on liver function<sup>31</sup>.

## Colorectal Liver Metastases

### Hepatectomy and Oncologic Outcomes

The 5-year overall survival (OS) for patients with resectable CRLMs (liver only) can reach 60%, with a median OS of 74 months after curative-intent surgery<sup>34,35</sup>. In a retrospective series of patients with fewer than 4 metachronous metastases treated between 2000 and 2010, longer time from diagnosis to CRLM resection was associated with worse OS<sup>36</sup>. Median OS was 76 months in patients who underwent surgery within 3 months of diagnosis, compared with 58 months for those whose surgery occurred later, adjusted for preoperative receipt of chemotherapy.

### Systemic Therapy

Median survival with systemic therapy alone for unresectable CRLMs has been reported to be 22 months for patients who do not achieve conversion to resectability<sup>37</sup>; other series have reported durations up to 40 months<sup>38</sup>. The availability of effective systemic therapies has led to an increased use of neoadjuvant chemotherapy. In patients with resectable liver metastases (low disease burden), upfront surgery is often favoured. However, for patients with larger lesions or borderline resectable disease, neoadjuvant chemotherapy is the preferred approach. In the neoadjuvant setting, chemotherapy can be used to assess disease biology and patient selection, with potential benefit in recurrence-free survival, but no proven gain in OS<sup>39,40</sup>.

Recent guidance from the American College of Surgeons (24 March 2020) recommends that surgery be delayed for patients with oligometastatic colorectal cancer for which effective systemic therapy is available<sup>41</sup>. If case prioritization requires a delay in resection of CRLMs, administration of chemotherapy before resection would be reasonable. For patients who are finishing pre-hepatectomy chemotherapy initiated before an operating room resource restriction, consideration can be given to continuing with further cycles depending on patient tolerance and the balance between risk of hepatotoxicity from chemotherapy (given the expected future liver remnant) and the risk for disappearing metastases that will complicate future curative-intent resection.

### Ablation

Data about the outcomes of percutaneous ablation come from cohorts of patients with unresectable CRLMs. In a phase II randomized trial involving 119 patients with

unresectable, liver-only CRLMs, better median OS was observed for RFA combined with systemic therapy (45.6 months) than for systemic therapy alone (40.5 months)<sup>38</sup>. In retrospective studies of resectable disease, risk of local recurrence is higher and OS is lower with ablative techniques than with resection<sup>42–44</sup>. Local recurrence and 5-year OS after ablation are reported at 37% and 27% respectively for isolated CRLMs<sup>42</sup>. As evidenced by an ongoing randomized noninferiority trial comparing hepatectomy with ablation for resectable liver metastases, percutaneous ablation is considered by some to be a potential curative option for CRLMs<sup>45</sup>.

Retrospective series of patients with unresectable liver metastases treated with SBRT have shown promising disease control. Local control rates at 2 years range from 57% to 100% in patients with poor prognosis and unresectable disease<sup>46</sup>. In a phase II trial comparing SBRT plus chemotherapy with chemotherapy alone for oligometastases (13% liver), median OS was prolonged at 41 months for the SBRT regimen compared with 28 months for chemotherapy alone. Compared with percutaneous ablation, SBRT can treat larger lesions, but might be limited for CRLMs localized near the stomach or duodenum<sup>29,30</sup>. Treatment intent with SBRT is not curative; if used as a mitigating strategy, liver resection would subsequently be required. Surgery after SBRT is feasible, although not well described<sup>47</sup>.

If there is no access to the operating room or if pursuing chemotherapy is not possible (or both), ablation could be a delaying strategy to ensure local control while awaiting surgery. Curative-intent treatment requires subsequent resection of the ablated lesion when operating resources are available. The choice for ablation also depends on its technical limitations (tumour size, number, and localization) and required resources depending on institutional protocols (inpatient vs. outpatient care; operating room).

### TACE

Another approach for patients with unresectable or medically inoperable disease is TACE, with a goal of local control and improved OS. No prospective comparison of TACE with resection has been conducted. In the unresectable setting, TACE using drug-eluting beads containing irinotecan has an overall radiologic response rate between 60% and 80%, and a median OS ranging from 14 to 25 months<sup>33,48</sup>.

### Clinical Risk Tools

Multiple patient and disease factors influence oncologic outcomes after hepatectomy for CRLMs; clinical risk tools can assist in estimating outcomes if necessary for decision-making<sup>49</sup>. The most common tool is the Clinical Risk Score<sup>50,51</sup>. Rated from 0 to 5, the Clinical Risk Score assigns 1 point for each of these factors: node-positive primary tumour, liver metastases larger than 5 cm, more than 1 lesion, serum carcinoembryonic antigen greater than 200 ng/mL, and a disease-free interval less than 12 months. A score of 0 corresponds to a 5-year OS of 60%, and a score of 5, to a 5-year OS of 14%. The Genetic and Morphological Evaluation score is a more recent tool that incorporates molecular information and has better discrimination than the Clinical Risk Score<sup>52</sup>. Six preoperative factors produce a total score in the range 0–7: *KRAS* mutation (1 point), serum carcinoembryonic antigen greater than 20 ng/mL (1 point),

node-positive primary tumour (1 point), tumour burden score in the 3–8 range (1 point) or 9 and higher (2 points), and extrahepatic disease (2 points). The 5-year OS estimate is 73.4% for patients at low risk (score: 0–1), 50.6% for those at medium risk (score: 2–3), and 11% for those at high risk (score: ≥4).

## Hepatocellular Carcinoma

### Hepatectomy and Oncologic Outcomes

Patients with Barcelona Clinic Liver Cancer (BCLC) stage 0 or A HCC are considered for hepatectomy, with some surgeons considering resection for those with BCLC B disease<sup>53,54</sup>. With hepatectomy, these are the estimates for 5-year OS<sup>55</sup>:

- for BCLC 0: 86%.
- for BCLC A with 1 lesion of 2–5 cm or 2–3 lesions less than 3 cm: 69%.
- for BCLC A with 1 lesion of 5 cm or larger: 57%.
- for BCLC B with 2–3 lesions of 3 cm or larger, or with 4 or more lesions: 50%.

In the present review, we focus on patients who are candidates for resection and who might be delayed or re-prioritized during the pandemic. Liver transplantation also plays a crucial role in the management of HCC. Transplantation presents unique considerations related to operating room resource availability, changes in the donor pool, risk for living donors, and risk of infection and transmission of COVID-19, which are beyond the scope of the present review and have been summarized elsewhere<sup>56–58</sup>. Any consideration of strategies meant to mitigate operating room delays for resection of HCC should include the understanding that access to transplantation might still be compromised after the pandemic, such that delaying strategies should not rely on availability of salvage transplantation.

### Ablation

Radiofrequency ablation is associated with local recurrence rates of 0.9%, 1.4%, and 25% for HCCs of less than 2 cm, less than 3 cm, and 3–5 cm respectively<sup>59,60</sup>. Although no difference in OS has been observed with liver resection or RFA for HCCs less than 5 cm in randomized controlled trials, the local recurrence rate is higher with RFA (5-year recurrence-free survival: 51.3% vs. 28.7%; hazard ratio: 0.56; 95% confidence interval: 0.40 to 0.78)<sup>61</sup>. If ablation is used without subsequent resection, and if the tumour recurs, patients can be candidates for salvage resection or salvage transplantation with outcomes similar to those with upfront transplantation<sup>62</sup>.

The SBRT modality is used for unresectable HCC, but has not been prospectively compared with resection. Prospective series have demonstrated local control rates between 80% and 100% at 1–3 years<sup>63–65</sup>. The ability to safely deliver SBRT is restricted by the underlying liver function, with a Child–Pugh score of 8 or greater being a relative contraindication<sup>66</sup>. The modality can be a bridge to liver transplantation comparable to both TACE and RFA<sup>67</sup>.

### TACE

Outcomes of TACE have been reported mostly for unresectable HCC, with the 5-year OS being 30%<sup>68</sup>. Literature

about neoadjuvant TACE for HCC reported no difference in OS between TACE followed by hepatectomy and hepatectomy alone in higher-risk HCC<sup>69</sup>. If TACE is used as a strategy to delay surgery, resection should eventually follow so as not to compromise OS. Although operating time is longer after TACE, postoperative morbidity and mortality are unchanged<sup>69,70</sup>.

### Systemic Therapy

Sorafenib and lenvatinib are used for advanced and unresectable HCC, with a median OS of 12–13 months being reported in the REFLECT trial<sup>71–73</sup>. The emergence of new data showing responses to lenvatinib as evidenced by the Response Evaluation Criteria in Solid Tumors could herald the use of systemic therapy to downstage or delay surgery until optimal conditions are achieved in patients who might not be eligible for other delaying strategies as described earlier.

### Clinical Risk Tools

A variety of scoring tools are available to assess outcomes of liver transplantation for HCC, but fewer are available for hepatectomy. A risk score developed using the Surveillance, Epidemiology, and End Results program database incorporates sex, tumour size, number of tumours, presence of bilobar disease, and major vascular invasion to predict OS, but has not been externally validated<sup>74</sup>. The predicted 5-year OS is 69% with a low-risk score, 51% with a medium-risk score, and 19% with a high-risk score.

## Gallbladder Cancer

### Hepatectomy and Oncologic Outcomes

Gallbladder cancer amenable to resection most often presents incidentally after simple cholecystectomy<sup>75,76</sup>. After a negative metastatic work-up, indications for radical re-resection include T1b or higher node-positive disease or a positive cystic duct margin<sup>77</sup>. Resected localized GBC (stages I–II) typically has a 5-year OS of 50%–60%<sup>78,79</sup>. Compared with simple cholecystectomy, radical resection with extended cholecystectomy is associated with improved OS for T2 and higher disease<sup>78</sup>. In T1b tumours, radical resection has been associated with a decrease in the risk of local recurrence without improvement in OS<sup>80</sup>. Major liver resection, including multivisceral resection, is advocated by some for OS benefit, but in the setting of the pandemic, the associated increased risks of major morbidity, prolonged ICU stay, and mortality should be carefully weighed against that benefit<sup>81,82</sup>. Finally, it should be mentioned that the extent of hepatectomy and lymph node dissection is debated and heterogeneous between studies, and that available data are biased by selection of fitter patients for extended resection<sup>83–86</sup>.

### Delaying Strategies

For incidental GBC eligible for radical re-resection, delaying strategies can include observation with short-term re-imaging or chemotherapy<sup>76</sup>. Use of chemotherapy is contingent on the availability of an effective regimen for GBC, which can be appreciated based on data from the adjuvant setting. Although the BILCAP trial's intention-to-treat

analysis was negative for its primary endpoint, the trial (which included all biliary tract cancers) indicated favourable OS with 8 cycles (24 weeks) of capecitabine as adjuvant therapy in the per-protocol population (which excluded ineligible patients and patients failing to complete at least 1 cycle of capecitabine)<sup>87</sup>. Although statistical significance was not reached in BILCAP's intention-to-treat population, a survival benefit of several months for those patients with usually dismal outcomes can be considered clinically meaningful. Therefore, when tumour control is needed while surgery is delayed, chemotherapy could be considered<sup>88</sup>. While not supported with data, preoperative chemotherapy appears ethically acceptable given that it is currently the subject of a randomized controlled trial<sup>89</sup> and has been introduced as routine in some centres<sup>90</sup>.

### Clinical Risk Tools

Clinical tools for GBC detected incidentally after cholecystectomy or diagnosed on imaging are few, were developed on small cohorts, are not well validated, and include information available only after surgery<sup>91–93</sup>. One scoring system focused on preoperative factors, but included both surgical and nonsurgical (metastatic) cases<sup>94</sup>. That system uses age, Eastern Cooperative Oncology Group performance status, serum alkaline phosphatase, tumour size, and presence of metastasis to create a score from 0 to 30 to predict OS. In surgical cases, median survival is 37 months for scores of 0–21.9, 30 months for scores of 22–25.9, 15 months for scores of 26–29.9, and 8 months for a score of 30.

## Intrahepatic Cholangiocarcinoma

### Hepatectomy

The typical curative-intent management of ICC is hepatectomy, with a 5-year OS of 30%<sup>95</sup>. Postoperative mortality of 7.6% after hepatectomy for primary liver tumours is considerably higher than the rate typically cited for all hepatectomies<sup>19</sup>.

### Systemic Therapy

Retrospective cohort studies have reported on neoadjuvant chemotherapy for initially unresectable ICC. Of 74 patients with locally advanced unresectable disease receiving various chemotherapy regimens (59% being doublet gemcitabine–oxaliplatin), 39 were converted to resectability (53%) after a median of 6 cycles<sup>96</sup>. Median OS after resection in that group was 24 months, compared with 26 months in initially resectable ICC.

### Ablation

Ablative therapies appear to be effective in ICC, although experience is limited. A meta-analysis of RFA reported local tumour progression in 21% of patients and a 5-year OS of 25%<sup>97</sup>. A small series of SBRT observed a median OS of 22 months with a 1-year local control rate of 78%<sup>98</sup>.

### TACE

Radioembolization with <sup>90</sup>Y and TACE have both been used for unresectable ICC. Median OS was similar for the combination of drug-eluting beads containing irinotecan plus chemotherapy and for chemotherapy

(gemcitabine–oxaliplatin) alone, at 12 and 11 months respectively; median OS with conventional TACE was 6 months<sup>99</sup>. In a meta-analysis, <sup>90</sup>Y radioembolization was associated with a median OS of 15 months<sup>100</sup>.

### Clinical Risk Tools

Various prognostic tools have been described for ICC, but none are universally accepted<sup>101</sup>. Few tools incorporate patient characteristics such as age and sex, and most rely on pathology variables that might not be available before surgery<sup>102–104</sup>. Recently, the LabScore combined carbohydrate antigen 19-9, neutrophil-to-lymphocyte ratio, platelets, and albumin into a published formula to predict 5-year OS after resection as 55% for a score of 0–9, 38% for a score of 10–19, and 22% for a score of 20 or more<sup>105</sup>.

## Hilar Cholangiocarcinoma

### Hepatectomy and Oncologic Outcomes

For the few resectable hilar cholangiocarcinomas that are amenable to curative-intent treatment, the 5-year OS is 8.4% in node-positive disease and 25.9% in node-negative disease<sup>106</sup>. Given the extent and complexity of hepatectomy, and the need for a biliary–enteric anastomosis, major morbidity and mortality are higher in these patients<sup>107</sup>.

### Chemoradiation

Conversion from unresectable to resectable hilar cholangiocarcinoma has been reported with chemoradiation (11 of 15 patients at a single institution)<sup>108</sup>. For resectable or borderline resectable disease, single-centre experiences with neoadjuvant chemoradiation for mixed cohorts of hilar and extrahepatic cholangiocarcinoma have reported 90%–100% R0 resection rates and 25%–33% complete pathologic responses<sup>109,110</sup>. Thus, tumour control appears achievable with preoperative chemoradiation if surgery has to be delayed. Finally, for the select few patients with technically unresectable hilar cholangiocarcinoma who might be considered for transplantation, neoadjuvant chemoradiation offers benefits in selection and prognosis<sup>111</sup>.

## SUMMARY

The COVID-19 pandemic affects many treatment decisions for patients with and without the virus. Reduced access to the operating room and lessened availability of critical care services for postoperative management could force the use of treatment strategies outside the standard of care to delay surgery. A variety of delaying strategies could be considered if operating room availability decreases. All strategies have pros and cons for patients and health systems that should be weighed. The quality and availability of data are variable. Evidence comparing typical curative-intent surgery with delaying options is rarely available. In the present review, we summarized the available data to provide some guidance with respect to possible delaying strategies depending on patient, resource, institution, and systems factors. Multidisciplinary team discussions should be leveraged to consider patient- and tumour-specific information to make the best possible decision for each individual case. Finally, it is important to emphasize that

the nonsurgical therapies discussed should be used only with the goal of maintaining tumour control while awaiting hepatectomy. Curative-intent resection remains the cornerstone of therapy and the ultimate goal.

### CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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