Editorial

Improving actual survival after hepatectomy for intrahepatic cholangiocarcinoma—still a long way to go

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Complete resection stands as the only potentially curative treatment. Being often late diagnosed, vascular and biliary structures are frequently involved owing to centrally located and/or large lesions at the time of diagnosis. Consequently, complete resection can require complex hepatectomy often on diseased liver, associated with important risks of mortality and morbidity while benefits in terms of prolonged survival remain often uncertain. To date, only one large series investigating actual long-term survival after curative-intent hepatectomy reported an actual 5-year OS of 13% (1). Indeed, around two thirds of patients experience recurrence, mostly to the liver, and eventually die of disease recurrence (2). These observations suggest first that patient selection for resection might be inadequate. Second, surgery alone seems not able to provide sufficient disease control. For instance, recurrence is frequently observed even with early tumours classified AJCC 8th Edition stage IA disease resulting in an estimated 5-year disease specific survival nearing 60% only.

A better understanding of the tumour biology remains paramount for identifying the most adequate candidates for upfront resection. Some patients harbouring adverse tumour features associated with very poor survival might first benefit from disease control instead of upfront resection. However, current prognostic models mostly rely on tumour features assessed on final pathology. A few preoperative prognostic models have been developed but validated models are lacking. Yet, established prognostic tumour features could be assessed before initiating hepatectomy. Tumour size and number can be accurately evaluated on preoperative imaging and intraoperative ultrasonography (2,3). Notably, multifocal disease stands as one of the most adverse prognostic factors and its presence on imaging or at exploration should be systematically weighed in decision making. From a retrospective analysis among 116 patients harbouring multifocal disease, Wright *et al.* stated that surgical resection did not confer any survival advantage over liver-directed therapies (4). Baheti *et al.* recently defined accurately multifocal disease as follows: single tumor (type I), single tumor with satellite nodules in the same Couinaud liver segment (type II), and multifocal scattered tumors in different Couinaud liver segments (type III) (3). While survival is classically poorer in patients with type III disease as compared to those with type I–II disease, long-term survival remains achievable in case of type III multifocal disease (1,5). Consequently, whether resection should be precluded in case of multifocal disease remains unclear. Nevertheless, no survivors at 3 years were identified in patients combining type III multifocal disease along with portal nodes involvement (6). Similar results were found in a large multicenter cohort from the IHCC-AFC study group where patients with type II–III multifocal disease and pN1 disease had an actual 5-year OS of 2.9% and an actual 2-year RFS of 8.8% (7). Strikingly, their actual median OS was equivalent to those observed in metastatic patients receiving palliative chemotherapy (median 13 months; 95% CI, 5.8–20.1). Accordingly, portal nodes assessment stands as of determining importance for decision-making in the setting of multifocal disease. Although inaccurate on imaging, pathologic nodal status

can be reliably assessed during surgery using intraoperative frozen section. Routine portal lymphadenectomy adapted to the tumour location has been recently recommended for IHCC management. Laparoscopic portal lymphadenectomy has proved equal to open lymphadenectomy regarding feasibility, safety and extent in the management of biliary tract cancers (8). Consequently, a staging portal lymphadenectomy with frozen section analysis, whether open or laparoscopic, could be an option before initiating complex hepatectomy in patients at risk, especially with multifocal disease.

A preoperative predictive score including tumour size and multifocality on imaging and the pathologic nodal status was recently developed for predicting 5-year recurrence-free survival (7). It allowed classifying patients in 3 groups with a probability of 5-year recurrence-free survival of 4.8%, 22.1% and 46.4% respectively, and an observed median OS of 19, 31 and 57 months respectively. While this model needs external validation, such a prognostic approach would help identifying patients who might first benefit from disease control instead of upfront resection. Further, serum biomarkers reflecting immune host-tumour interaction are known as related to cancer-specific survival (9,10). Such circulating biomarkers are easily obtained preoperatively and should be considered in future prognostic models.

Although disease control is classically sought after resection, the benefit of adjuvant chemotherapy remains debated in spite of the BILCAP trial. Before resection, a neoadjuvant therapy is currently not recommended in case of resectable disease. Yet, outcomes after a neoadjuvant approach are promising as recently reported while in the setting of locally advanced or initially unresectable disease converted to resection (11). Indeed, in this single center experience, highly selected patients with locally advanced IHCC treated by surgery following neoadjuvant chemotherapy had similar survival as compared to patients with initially resectable IHCC who underwent upfront resection. Additionally, a neoadjuvant approach allows a test of time on the natural evolution of the disease. Stable or responsive disease under neoadjuvant therapy might be an incentive for aggressive resection in patients with high-risk disease. Still, the role of neoadjuvant therapy for resectable IHCC remains to be defined as only one neoadjuvant multicenter trial is currently accruing (NCT03579771).

Besides defining the timing between disease control and surgery, various options for improving disease control have to be considered. First, based on data derived from trials in the palliative setting, systemic chemotherapy alone provides limited response rates and results in marginal survival benefit. Second, given the organotropism of recurrence to the liver, there might be a rationale for liver-directed therapies in order to improve disease control before and/or after resection. Hepatic arterial infusion (HAI) chemotherapy represents a locoregional approach that administers cytotoxic drug directly into the liver and thereby allows much greater drug delivery to the tumour without increasing systemic toxicity. Aggregated results from two phase II trials conducted at MSKCC evaluating the benefit of hepatic arterial infusion of floxuridine combined with systemic therapy in 78 patients showed promising results with an overall response rate of 59% and a conversion to resection rate of 10% (12). Transarterial chemoembolization (TACE) is an alternative approach that relies on embolization, and permits the synergistic action of the occlusion of the arterial supply to the tumour and increased local levels of chemotherapeutic agents that can be potentiated using drug-eluting beads. Yttrium-90 radioembolization represents another meaningful approach in the neoadjuvant setting as it is effective in reducing tumor volume with potential increase in local tumour control while simultaneously inducing hypertrophy of the liver contralateral to the tumour. Such approaches yielded response rates ranging from 25% to 35% allowing conversion to resection in several cases (13). One can hypothesize that disease control would be thereby enhanced in the setting of resectable disease. Finally, liver transplantation represents a potential approach for preventing disease recurrence to the liver. A preliminary experience has been recently reported in patients with locally unresectable IHCC, stable under neoadjuvant therapy (14). Its role remains to be defined and is not currently recommended.

In summary, prognosis after hepatectomy for IHCC remains dismal. Increased disease control is needed to prevent recurrence after resection, especially in high risk patients. Preoperative prognostication is paramount for refining patient selection. Portal nodes assessment should weigh in decision making before initiating hepatectomy, particularly in patients at high risk with multifocal disease. Further development of preoperative biomarkers and prognostic models are warranted. Notably, molecular profiling is starting to gain importance for patient stratification in case of advanced disease (15). Its role remains to be defined in the management of resectable patients. While poorly investigated, the neoadjuvant approach is of interest to increase disease control and resectability and guide patient

selection. Given the organotropism of disease recurrence to the liver, increasing disease control might involve liver-directed therapies.

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Footnote

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