

Hepatocellular cancer and colorectal liver metastasis treatment in the older population

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More than 60% of patients with primary and secondary liver tumors are older than 65 years. Thanks to improvements in radiological staging, anesthesia, surgical technique, and perioperative care it is possible to offer complex liver surgery to older patients. However, chronological age or functional status alone should not be a contraindication for multimodal radical treatment in older patients. Fit patients, according to the Comprehensive Geriatric Assessment, should be qualified for the same treatment as younger patients to ensure the same outcomes. Prefrail patients should undergo prehabilitation, and be reevaluated. Frail patients should be discussed in an oncogeriatric meeting. All patients with liver malignant tumors must be operated on in high-volume hospitals by an experienced surgeon. The introduction of parenchymal sparing surgery (instead of a major resection) in combination with other treatment tools, minimal invasive techniques, and enhanced postoperative recovery demonstrated being beneficial for older patients. In particular, frail, older patients can benefit from the wide variety of treatment options.

Key words: hepatocellular cancer, colorectal liver metastasis, older population, liver resection

The key components of successful oncologic liver surgery are: the ability to achieve an R0 resection, to maintain an appropriate vasculature and biliary system and to leave a sufficient functional liver parenchyma [1]. Thanks to improvements in radiological staging, anesthesia, surgical technique (understanding of segmental liver anatomy, parenchymal preserving surgery, bleeding control), and perioperative care it was possible to offer complex liver surgery to older patients. This is particularly important because, more than 60% of patients with primary and secondary liver tumors are older than 65 years at the moment of diagnosis [2].

At present, there are no treatment guidelines dedicated to older patients. The main reason for this situation is still the underrepresentation of older patients in trials regarding liver resection. In the majority of the published studies, only 15–20% of patients were older than 70 years [2]. Therefore, the

extrapolation of such results on the geriatric population can lead to inappropriate treatment decisions.

Normal aging of the liver

Several age-related changes can be observed in liver physiology. The most important are: a decrease in liver weight and volume (up to 25%), decrease in the hepatic blood flow (up to 40%), an increase in the hepatic dense body compartment, shifts in the expression of a variety of proteins, and a decrease in bile flow and bile acid secretion [3–8]. These changes influence the liver's metabolic function, regeneration capacity, and immunity [3–8], which, in turn, may result in an increased risk of postoperative liver failure, drug-induced liver damage, and sepsis [3–10]. 25–30% of a total healthy liver volume needs to be preserved after the resection. However, in the case of patients with liver cirrhosis, steatosis or fibrosis, a larger remnant of the organ

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needs to be intact. Despite preoperative evaluations, liver failure occurs in up to 5% patients in the postoperative period, particularly often in older patients [11]. Tzend et al. did not observe a significant difference in the preoperative LiMAx liver function between young and older patients. However, liver regeneration is significantly different in older population in the early period. Age was inversely correlated with liver regeneration potential during the first postoperative week, without any difference between young and older patients after one month [12]. None of the studies analyzed the biologic age.

Preoperative assessment and treatment decisions

As was mentioned in our previous publications, the population of older patients is very heterogeneous in terms of co-morbidity, physical reserve, cognitive function, and social support. Chronological age alone is a poor predictor of cancer treatment outcomes and toxicities [13]. Current routine pre-operative assessments cannot adequately identify patients at risk. Many older adults have unidentified, uncommunicated, and therefore unaddressed aging-related conditions that are associated with poorer outcomes. As a result, the Comprehensive Geriatric Assessment (CGA) was introduced to help determine the primary status of the older patient, to diagnose frailty syndrome, and to identify how to optimize the patient's condition before the start of treatment [14–16]. Therefore, more and more organisations, including the International Society of Geriatric Oncology, the National Comprehensive Network, the European Organisation for the Research and Treatment of Cancer, the American College of Surgeons National Surgical Quality Improvement Program, and the American Geriatric Society have called for the routine use of the Geriatric Assessment.

Rostoft et al. analyzed the literature regarding the role of the CGA in predicting the outcome in hepatobiliary and pancreatic surgery among older patients with cancer. It was concluded that although there are not many studies, frailty and elements from the CGA are significantly associated with negative short- and long-term treatment outcomes in older patients with hepatobiliary and pancreatic cancers [17].

Clinical characteristics of older HCC patients

Hepatocellular carcinoma (HCC) is the primary tumor of the liver with the greatest incidence worldwide. It is the fifth most common neoplasm and the third highest cause of cancer-related mortality [18]. The risk of developing HCC increases with age, reaching the highest incidence in the geriatric population during the seventh decade of life. Moreover, improvements in the treatment of chronic liver disease have caused an increase in the number of potential patients who may develop HCC [19]. In Europe, HCC older patients are more likely to be women and to be infected with HCV, less common with HBV. Moreover, in older patients, HCC develops more commonly in healthy livers [19]

Liver surgery in older patients with HCC

The Barcelona Clinic Liver Cancer (BCLC) stage system is the most used tool for treatment planning in patients with HCC. Based on the characteristics of the tumor, the degree of liver failure and physical condition, patients are stratified into five categories:

- very early (BCLC 0),
- early (BCLC A),
- intermediate (BCLC B),
- advanced (BCLC C),
- terminal (BCLC D).

For the two first stages (BCLC stage 0 and A), there is a wide range of treatment options including liver resection, liver transplantation, and local ablation. In the BCLC B stage, transarterial chemoembolization is usually proposed. In turn, in the BCLC C stage patients are qualified for treatment with Sorafenib. In the terminal stage (BCLC D), the best supportive treatment seems the optimal option [20]. There are also other staging systems. However, none of them is using the comprehensive geriatric assessment caps earlier or any other geriatric scale that allows determining frailty.

Concluding recently published studies on older populations undergoing various liver resections due to HCC, the morbidity and mortality rates ranged from 9% to 51% and from 0% to 7.5%, respectively. In high volume hospitals, there was no difference between younger and older patients in short-term morbidity, mortality, and length of hospital stay [21–23]. The 5-year overall survival rate ranged between 26% and even 75.9% in well-selected older patients. However, surgical treatment was only possible in up to 14% of older patients, compared with the younger group (12–28%) [24–27].

The introduction of parenchymal sparing surgery resulted in a decrease in mortality in older patients compared with older patients undergoing major hepatectomy [28]. In experienced hands, laparoscopic and robotic techniques further reduce surgical stress and improve the outcomes. Reported morbidity ranges were 10–15% and mortality was around 1%, respectively [29]. However, when analyzing the outcomes, various selection bias must be considered. A systematic review and meta-analysis, published in 2019, showed no significant difference in terms of blood loss, transfusions, liver failure, Clavien-Dindo III/IV complications, postoperative mortality, hospital stay, R0 resection, and operative time between younger and older patients undergoing laparoscopic hepatectomy [29]. Moreover, the minimal invasive approach in HCC cirrhotic patients has also the potential to reduce risk of post-operative liver decompensation and morbidities [30, 31]. However, most of the studied patients were evaluated based on chronological age, comorbidities, and physical function – not on the comprehensive geriatric assessment.

Liver transplant in older patients

Data from the United Network for Organ Sharing and the European Liver Transplant Registry show a significant increase

in the number of patients over 70 years with end-stage liver disease who qualified for a liver transplant in the last decade; it was also one of the fastest-growing patient populations [32]. In the 2019 systematic review and meta-analysis, Gavara et al. did observe acceptable short- and long-term results. They also did not find any difference in the risk of complications between young and older patients [33]. Although long-term liver transplant results are very good, older patients are rarely qualified because of their low priority on the list of available organs [32, 33].

Radiofrequency ablation for older HCC patients

The European Association for the Study of the Liver (EASL) guidelines recommends RFA as a standard of care for patients with BCLC stage 0–A, in the case of tumors not suitable for surgical resection [34, 35]. However, in the case of older patients, the results of published studies are inconsistent. Some of them report comparable outcomes between young and older population [36–38]. In turn, others reveal higher complication rates due to patients' comorbidities, use of antiplatelet or anticoagulant drugs, and preoperative low functional levels. The overall survival rates in the older group were significantly lower than those in the younger population and the recurrence-free survival rates were comparable [39].

Transarterial chemoembolization for older HCC patients

The transarterial chemoembolisation (TACE) is a procedure combining the transcatheter delivery of an anticancer drug into the hepatic artery followed by vascular obstruction with embolic agents [40]. Current guidelines recommend TACE as the standard of care for patients with multinodular, asymptomatic tumors without vascular invasion or extrahepatic spread (BCLC stage B tumors). Recent studies showed that the TACE is a safe and effective treatment in older HCC patients. The morbidity rate ranged from 4.5% to 27%, without any significant difference between older and younger patients, including also contrast medium-induced renal dysfunctions [41]. The 3-year and 5-year OS ranged between 14.9–48% and 8.4–33.8%, respectively [42–44].

Immunotherapy for older HCC patients

Sorafenib has shown efficacy in two randomized trials, resulting in a significant 30% improvement in survival of HCC patients [45]. The European Association for the Study of the Liver recommends sorafenib as the preferred treatment for patients with HCC who cannot tolerate potentially more effective therapies, particularly in the case of preserved liver function (Child–Pugh grade A) and advanced tumor stages (BCLC stage C) [46]. In the case of the older population, it turned out to be equally safe among older and younger patients with similar toxicity-related discontinuation rates between these groups [47]. There was also no difference between these groups

regarding overall survival and time to treatment failure [48]. After 10 years, another multikinase inhibitor, Lenvatinib, was approved in first-line treatment [49]. Studies have proven its non-inferiority compared with sorafenib in cases of overall survival. Moreover, lenvatinib may have some potential benefits over sorafenib for patients with HBV chronic infection [49]. Atezolizumab plus bevacizumab as first-line treatment is the next treatment possibility in the treatment of advanced HCC [50]. However, we have to wait for further studies including those on the geriatric population.

Concluding, we need well-designed studies on a larger group of older patients using various advances of geriatric oncology. The Comprehensive Geriatric Assessment, evaluation of life expectancy, and analysis of patients' goals should become routine preoperative instruments allowing for better selection of older patients for a tailored treatment. They are proven to correlate much more with the short- and long-term outcomes in comparison to the currently evaluated factors. Therefore, Suda et al. proposed the percent life expectancy (%LE). It is the survival time for each patient divided by the life expectancy. This parameter may evaluate the benefits of a given treatment for older HCC patients. The authors showed that patients aged 80 years or older had the best survival benefit according to the %LE [52].

Moreover, there are currently many unintentional selections bias in most of the studies. The physicians tend to qualify older patients for surgical treatment with a good performance status and preserved liver function. This might favor similar outcomes to those of younger patients. In turn, the chronologically oldest patients are often qualified for non-curative treatment, which might favor poorer prognosis compared with younger patients [51].

Colorectal liver metastasis in older patients

Recent studies have shown that patients aged 70 and more who undergo liver resection for colorectal liver metastases have the possibility to achieve a 5-year survival of 21–44%, with postoperative morbidity and mortality rates of approximately 20–40% and 0–7%, respectively. This is despite patients undergoing more complex treatment for more extensive disease [53–62]. The main reason for the outcome improvement is the introduction of parenchymal sparing liver surgery. It has been shown to be associated with less surgical stress, fewer postoperative complications, non-inferior cancer-related outcomes, and higher feasibility of future resections [63]. There is also a higher rate of R1 resection. However, it is not associated with poorer disease free survival [64, 65]. Therefore, major resection should be limited only to patients where it is the only curative option.

More and more older patients are getting neoadjuvant chemotherapy with intend to downstage the disease and to converse the disease into resectable. It has been proven that chemotherapy in combination with surgical techniques was

not associated with poorer postoperative outcomes in older patients in comparison to younger groups [66]. So, excellent perioperative outcomes can be achieved with morbidity and mortality of 38.2% and 0.3%, respectively, using parenchymal sparing liver surgery, chemotherapy, and ablation. That combination should be used to avoid unnecessary major liver resection [67–71]. Implementation of the ERAS program in the postoperative period may further improve outcomes. A 2015 meta-analysis of randomized controlled trials on the efficacy of the ERAS program in liver surgery showed that this approach significantly reduces post-operative morbidity, length of stay, and accelerates functional recovery [72].

For older patients with unresectable CRLM who meet the eligibility criteria for radioembolization, 90Y-radioembolisation microspheres appear to be effective and well-tolerated, regardless of age. Therefore, the selection of patients for radioembolization should not include chronological age as an exclusion factor [73].

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