Surgical approach to hepatocellular carcinoma: a review

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Abstract

Hepatocellular carcinoma (HCC) is a primary liver cancer that arises in the setting of chronic liver inflammation and/or cirrhosis. Despite advancements in screening and treatment, the incidence and mortality of HCC continue to increase. Treatment for HCC is guided by a patient's liver function, performance status, and extent of tumor burden. Patients with early-stage HCC are often treated with surgery, liver transplantation, or liver-directed therapy. Unfortunately, many patients have limited surgical options due to advanced-stage disease, recurrent disease after resection, or pre-existing moderate to severe liver dysfunction. These patients are subsequently treated with a combination of atezolizumab and bevacizumab, or durvalumab and tremelimumab. Operative management of HCC requires experienced surgeons and a multidisciplinary team of medical oncologists, radiation oncologists, and hepatologists for appropriate patient selection. Due to the complex management required for these patients, it is critical that the surgical management is informed by updated guidelines and data. We herein review the surgical management and treatment considerations for patients with HCC.

Keywords: Surgery, hepatocellular carcinoma, resection

INTRODUCTION

Hepatocellular carcinoma (HCC) is a primary liver cancer that commonly arises in the setting of chronic

liver inflammation and/or cirrhosis. Risk factors include chronic hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, alcohol use, non-alcoholic steatohepatitis secondary to metabolic syndrome or diabetes mellitus, or other causes of liver inflammation[1]. Chronic inflammation and cirrhosis alter the microenvironment of the liver through tissue remodeling and changes to immune cell function[2]. Despite advancements in screening and treatment, the incidence and mortality of HCC have continued to increase[1].

The Barcelona Clinic Liver Cancer (BCLC) classification stages and guides treatment for HCC based on liver function, performance status, and extent of the tumor [Figure 1][3]. Patients with early-stage HCC are most effectively treated with surgery, liver transplantation, or liver-directed therapy[3]. Unfortunately, many patients present with advanced-stage HCC, develop recurrent disease after resection, or have pre-existing moderate to severe liver dysfunction, thereby limiting their surgical options. In these cases, patients are treated with a combination of atezolizumab and bevacizumab, or durvalumab and tremelimumab[4,5].

Operative management of HCC requires experienced surgeons and a multidisciplinary team of medical oncologists, radiation oncologists, and hepatologists for appropriate patient selection. The oncologic decisions regarding anatomic *vs.* non-anatomic resection, margin status, and lymphadenectomy must be balanced with the risks of postoperative hepatic insufficiency in patients with cirrhosis. Furthermore, more patients are receiving operations in a minimally invasive fashion to improve recovery time; these procedures should be performed at high-volume centers that have the requisite expertise and can handle conversion to open surgery. In addition, there are ongoing clinical trials evaluating the use of systemic therapy in combination with surgery for patients with resectable disease to improve disease-free survival and decrease recurrence. Due to the complex care required for these patients, it is critical that surgical management is informed by updated BCLC, NCCN, and international guidelines and data[3,6]. We herein review surgical management and considerations for patients with HCC.

PATIENT SELECTION

The most recent BCLC guidelines published in 2022 provide recommendations for staging, treatment, and prognosis of HCC based on disease burden, patient co-morbidities, and underlying liver function[3]. The BCLC defines five stages (very early, early, intermediate, advanced, and terminal stage). The number and size of the tumors are a critical part of this staging system, but patients can be upstaged due to poor liver function. Traditionally, liver function is defined by a combination of the MELD score and the Child-Pugh score. The updated BCLC guidelines also incorporate the albumin-bilirubin score, degree of compensation, and clinical characteristics (e.g., jaundice, ascites, encephalopathy). Patients with end-stage liver function are all included in the "terminal stage". Decisions for resection, liver-directed therapies, transplant, systemic treatment, and best supportive care are based on the BCLC stage and expected survival can be predicted based on stage and treatment choice.

The BCLC and National Comprehensive Cancer Network (NCCN) guidelines recommend resection for patients with preserved liver function (Child-Pugh A or B), no portal hypertension, and adequate future liver remnant (FLR)[3,6]. Patients with solitary tumors and no major vascular invasion are ideal candidates. Extra-hepatic metastatic disease is an absolute contraindication to surgery[6].

It is unclear whether multifocal disease represents metastatic disease within the liver or multiple primary tumors in the setting of a global field defect (e.g., cirrhosis). Given the unclear cause of multifocal disease, resection of these patients, as well as individuals with major vascular invasion, remains somewhat controversial[6-9]. As such, while the combination of resection and ablation for HCC can be employed,
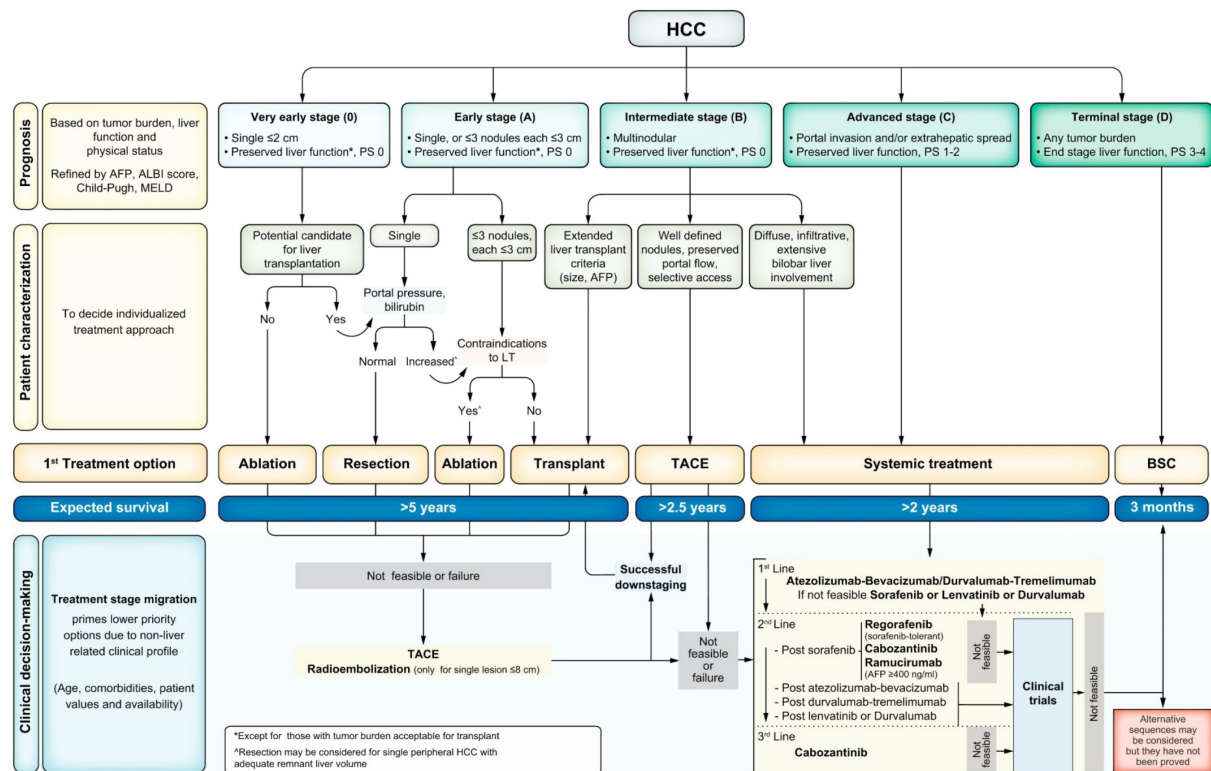
Figure 1. The BCLC system establishes a prognosis in accordance with the 5 stages that are linked to first-line treatment recommendation. The expected outcome is expressed as the median survival of each tumor stage according to the available scientific evidence. Individualized clinical decision making, according to the available data on November 15, 2021, is defined by teams responsible for integrating all available data with the individual patient's medical profile. Note that liver function should be evaluated beyond the conventional Child-Pugh staging. This figure has been reprinted with copyright permission from Reig *et al.*[3]. AFP: Alpha-fetoprotein; ALBI: albumin-bilirubin; BCLC: barcelona clinic liver cancer; BSC: best supportive care; ECOG-PS: eastern cooperative oncology group-performance status; LT: liver transplantation; MELD: model of end-stage liver disease; TACE: transarterial chemoembolization.

whether this approach is curative in nature is debated and a point of controversy in the BCLC staging. For the most part, patients with multifocal disease should be treated with systemic therapy. These patients should be considered for transplantation if the person meets traditional or extended criteria. Of note, the Japan Society of Hepatology Clinical Practice Guidelines (JSH-HCC) does recommend resection/ablation of multifocal disease for patients with preserved liver function and up to three nodules[10]. In contrast, the BCLC guidelines recommend ablation or transplantation rather than resection for multifocal disease[3].

LIVER FUNCTION AND FUTURE LIVER REMNANT

Patients should undergo an assessment of their underlying liver function and ensure an adequate FLR. For patients with HBV or HCV, postoperative anti-viral therapy can suppress and sustain a viral response, which has been demonstrated to prevent progression to cirrhosis and protect against new HCC formation[6,11]. There is some evidence, however, that new direct-acting anti-viral medications for HCV may contribute to HCC development. Whether the risk is due to the medications or the underlying cirrhosis remains unclear[6,11]. Baseline liver function should be assessed through laboratory tests and the Child-Pugh score [Table 1]. Patients should also be evaluated and followed by a hepatologist to minimize the risk of worsening liver dysfunction.

Table 1. Components of the child-pugh score

Variable	1 point	2 points	3 points
Ascites	None	Slight	Moderate
Encephalopathy	None	Grade 1-2	Grade 3-4
Total bilirubin (mg/dL)	< 2	2-3	> 3
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
INR	< 1.7	1.7-2.3	> 2.3
Child-Pugh A	5-6 points		
Child-Pugh B	7-9 points		
Child-Pugh C	10-15 points		

Hepatectomy is a complex operation and patients with co-morbidities and poor physiologic reserve may not recover well or cope with complications. If a patient is deemed an appropriate surgical candidate, the FLR should be evaluated relative to the extent of resection to prevent postoperative hepatic insufficiency. The FLR can be calculated using volumetric analysis on computed tomography (CT) or magnetic resonance imaging (MRI). Technetium-99m mebrofenin hepatobiliary scintigraphy can be used to assess FLR function if there is concern for a discrepancy between FLR volume and FLR functional capacity[12]. Furthermore, an indocyanine green (ICG) clearance test can also predict hepatic functional reserve. Retention of contrast at 15 minutes is associated with the risk of post-hepatectomy liver failure[13]. Typically, 20% FLR is adequate for patients with a healthy liver; however, among patients with steatosis, fibrosis, or cirrhosis, an FLR of at least 30%-40% is generally recommended[14-19].

Patients who have inadequate FLR may benefit from procedures to preoperatively induce hypertrophy of the FLR or treatment strategies that combine liver-directed therapies with resection[12]. The traditional approach to augmenting the FLR is portal vein embolization (PVE) of the tumor-bearing side of the liver. In cirrhotic livers, there generally is approximately a 5%-10% increase in volume within the first 2-3 weeks[20]. Hypertrophy after PVE is often less common among patients with cirrhosis than in individuals with a healthy liver, who can have an increase in FLR volume of 40%-60%[21]. Patients typically experience the most growth in the initial 3-4 weeks, but liver volume can increase for up to 8 weeks after the procedure. Another potential procedure to increase FLR is the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure. This is a two-stage operation that first involves *in-situ* portal vein ligation on the tumor bearing side of the liver and combined parenchymal transection. The hepatic artery and bile duct are not divided at this time. In the second stage, the hepatic artery and bile duct are divided and the hepatectomy is completed[21]. ALPPS may induce significant hypertrophy up to 80% of the FLR in a few days, probably because the intrahepatic portal vein collaterals are also ligated during the first stage of the procedure. Additionally, there is an increase in growth factor release after the first stage of an ALPPS, which may induce rapid FLR hypertrophy[22]. The use of ALPPS *vs.* PVE remains controversial. In a study comparing ALPPS to PVE among patients with chronic hepatitis or cirrhosis-related HCC, Chan *et al.* reported that ALPPS was associated with a higher chance of resection with comparable short- and long-term oncologic outcomes[23]. In a single-center, prospective randomized comparative study of patients with hepatitis B HCC were assigned to either receive ALPPS or TACE with PVE[24]. ALPPS resulted in a better three-year OS rate (65.8%) *vs.* TACE/PVE cohort (42.1%); however, there was a much higher incidence of perioperative morbidity. In turn, ALPPS should be used sparingly in patients with HCC who have compromised liver function.

RESECTION CONSIDERATIONS

The goal of surgery is a margin-negative resection. However, most of the data come from retrospective studies and are subject to selection bias. As such, there is no consensus on the optimal margin width. A randomized trial compared 1- and 2-cm margins among patients with solitary HCC in the setting of preserved liver function[25]. Patients with a 2-cm margin had better survival and a lower incidence of recurrence *vs.* patients with a 1-cm margin width. HCC has a propensity to spread along the pedicle tracts, which is why a wider margin may provide long-term benefits. The extent of resection needs to be weighed against the underlying pre-existing liver dysfunction and size of the FLR.

Because HCC spreads along the pedicle tracts, anatomic resection to remove the tumor-bearing portal branches has been advocated. The European Association for the Study of the Liver (EASL) guidelines recommend anatomic resection when feasible, especially for tumors ≥ 2 cm[11]. In a large nationwide Japanese analysis, patients with solitary tumors who underwent anatomic *vs.* non-anatomic resection were stratified by tumor size (< 2 cm, 2-5 cm, and > 5 cm)[26]. There was no difference in overall survival among the groups. In a separate meta-analysis of 43 studies, anatomic *vs.* non-anatomic resection was compared for the surgical treatment of HCC[27]. Despite heterogeneity among the studies, there was comparable perioperative morbidity and mortality among patients who underwent an anatomic and non-anatomic resection. Notably, anatomic resection was associated with better disease-free and overall survival, especially among patients without cirrhosis. In addition, local intra-hepatic recurrence within 2 years of the initial operation was more common among patients who had undergone a non-anatomic resection. These data collectively suggest that resection of the tumor-bearing portal branches and liver parenchyma with an anatomic resection may be more effective at eliminating micrometastatic disease and confer a survival benefit. A subsequent randomized controlled trial compared anatomic *vs.* non-anatomic resection for solitary HCC in 105 patients with Child-Pugh A cirrhosis[28]. Anatomic resection was associated with a lower incidence of local recurrence and a longer time to recurrence. In turn, anatomic resection of HCC should generally be recommended; however, this decision needs to be balanced against the preservation of liver parenchyma and mitigation of the risk of liver insufficiency among patients with underlying liver dysfunction. As such, patients should be evaluated by experienced hepatobiliary surgeons and parenchymal-sparing strategies can be employed in select cases.

LYMPHADENECTOMY

While lymph node metastasis generally indicates stage III disease for most cancers, nodal disease in patients with HCC represents stage IV disease. Generally, a lymph node dissection is not routinely performed as part of the surgical management of HCC. Preoperatively, it can be difficult to assess whether any lymphadenopathy is secondary to hepatitis or other underlying liver disorders. In one systematic review and meta-analysis of patients with HCC, lymphadenectomy was performed in 51.6% of patients[29]. Among patients who underwent a lymphadenectomy, 44.5% had lymph node metastases. In a separate SEER database study, Yang *et al.* reported a lower utilization of lymphadenectomy of 14.3% among patients who underwent resection for HCC[30]. In this study, the incidence of nodal metastasis was much lower at 8.4%. Furthermore, regional lymphadenectomy was not associated with improved prognosis. A study based on the National Cancer Database reported that 17.8% of patients with HCC underwent a lymphadenectomy and 5.9% had lymph node metastases[31]. In aggregate, given the relatively low incidence of nodal disease and some potential morbidity, routine lymphadenectomy is not recommended unless preoperative imaging suggests metastatic nodal disease (e.g., enlarged lymph nodes)[6]. Even enlarged nodes may be due to hepatitis and inflammation rather than metastatic disease. In addition, lymph node metastasis represents stage IV disease, and these patients may not benefit from a surgical resection and should be considered for systemic therapy.

MINIMALLY INVASIVE *VS.* OPEN SURGERY

Minimally invasive surgery (MIS) has been associated with quicker recovery and better pain control for some patients. Furthermore, compared with laparoscopy, robotic surgery provides a 3-dimensional view and the use of instruments with articulation that mimic and extend wrist movement. Advancements in MIS surgery have resulted in improved operative dexterity, making dissection around critical structures (e.g., hepatic hilum) and access to difficult anatomic areas (e.g., superior posterior tumors in segment 7) easier and a lower risk for conversion to open[32-35]. Robotic surgery also improves operative ergonomics and decreases physical/mental fatigue among surgeons performing long, complex operations[36]. In turn, there has been increasing interest in the use of a MIS approach for HCC. One large, multi-center retrospective study evaluated the use of MIS *vs.* open surgery for patients with HCC[37]. Among 1,974 patients, 33% underwent MIS. Following propensity score matching to match the open and MIS surgery cohorts, there was a higher incidence of complications and longer length-of-stay among patients who underwent an open procedure. A sub-analysis that included patients with portal vein hypertension demonstrated similar results, with open surgery being associated with a longer length of stay and higher morbidity. In addition, there was no difference in long-term oncologic outcomes among patients who underwent an open *vs.* MIS approach to HCC. More recently, there has been a proliferation of data to demonstrate the safety and efficacy of MIS for HCC, which has resulted in several guidelines incorporating MIS into their recommendations[3,6,11,38]. As such, patients with a disease that is anatomically amenable to a minimally invasive approach and who are treated at high-volume centers with experience in laparoscopic/robotic surgery will benefit from MIS.

ADJUVANT THERAPY FOR RESECTABLE HCC

To date, routine adjuvant therapy following curative-intent resection for HCC is not recommended as no data have demonstrated an oncologic benefit. The STORM trial evaluated adjuvant sorafenib after resection or ablation for patients with HCC, but failed to demonstrate any long-term benefit[39]. The success of combined atezolizumab and bevacizumab for unresectable HCC has led to its investigation in the adjuvant setting. The IMbrave050 trial is currently evaluating the efficacy of atezolizumab and bevacizumab compared with active surveillance in the adjuvant setting after resection or ablation of high-risk HCC[40]. High-risk features for patients who underwent resection included individuals with ≤ 3 tumors (largest having a size > 5 cm), ≥ 4 tumors (largest having a size ≤ 5 cm), or ≤ 3 tumors (largest having size ≤ 5 cm with vascular invasion and/or poor tumor differentiation). Among patients who underwent ablation, high-risk features included a tumor between 2-5 cm or ≤ 4 tumors all sized ≤ 5 cm. On interim analysis, a combination of atezolizumab and bevacizumab demonstrated increased recurrence-free survival over a median follow-up period of 17.4 months. There was no difference, however, in overall survival between atezolizumab/bevacizumab and active surveillance. The lack of survival benefit may be attributable to the high cross-over in the trial or be related to the overall survival data being immature at the time of preliminary analysis (the event rate was only 7%).

There are several ongoing phase III trials evaluating the use of adjuvant immunotherapy for HCC after ablation or curative intent resection. The Keynote-937 trial evaluated adjuvant pembrolizumab *vs.* placebo after resection or ablation (NCT03867084), whereas the Checkmate 9DX trial evaluating adjuvant nivolumab in high-risk patients after curative resection or ablation (NCT03383458). In addition, the EMERALD-2 trial compared adjuvant durvalumab with or without bevacizumab after curative treatment in high-risk patients (NCT03847428), and the JUPITER 04 trial compared adjuvant toripalimab *vs.* placebo after resection of HCC (NCT03859128). Over the next few years, preliminary data from these trials should be published and hopefully guide therapy for patients undergoing curative resection or ablation for HCC. In turn, data from these trials have the potential to change how patients with HCC are treated.

NEOADJUVANT THERAPY FOR HCC

Neoadjuvant therapy for patients with resectable HCC has the potential to treat micrometastatic disease and delay or prevent postoperative recurrence. This is especially true for individuals treated with immunotherapy/immune checkpoint inhibitors. The intact primary tumor provides more neoantigens to prime the T cells and enhance the effects of immunotherapy. Pathology assessment of the resected tumor can demonstrate treatment response and guide future treatment decisions in the setting of recurrent or metastatic disease.

Neoadjuvant therapy for resectable HCC

In a randomized trial of patients with resectable HCC, perioperative nivolumab and combined nivolumab and ipilimumab were compared[41]. Both cohorts tolerated the treatment with acceptable toxicity levels. The median progression-free survival was 9.4 *vs.* 18.5 months in the nivolumab *vs.* nivolumab/ipilimumab cohorts, respectively. Furthermore, three patients in each cohort had marked tumor necrosis on pathology (> 70%). There is an ongoing phase I study, the PRIME-HCC trial, evaluating the safety of nivolumab and ipilimumab in patients with early-stage HCC[42]. On interim analysis, the combination was noted to be safe in the neoadjuvant setting and did not delay liver resection. Nine patients at the time of preliminary analysis had undergone surgery and seven of them had achieved a pathologic response.

In a phase II trial, neoadjuvant cemiplimab was given to 21 patients with resectable HCC[43]. Twenty patients underwent surgery and four had > 70% tumor necrosis on final pathology. A different single-arm phase II trial studied neoadjuvant camrelizumab with apatinib in patients with resectable HCC[44]. The one-year recurrence-free survival was 54% for patients who underwent a resection (*n* = 17/18). The data related to neoadjuvant immune checkpoint inhibitors for patients with resectable HCC are limited, but this is a promising area of future research. Of note, there is often discordance between radiologic and pathologic responses following treatment with immune checkpoint inhibitors. As such, other methods - including functional imaging - are needed to measure response and should be incorporated into future trials involving immunotherapy for HCC.

Immunotherapy to downstage HCC

Data on using immunotherapy to downstage patients with unresectable HCC are limited, but promising data have been published. The *in vivo* tumor provides more neoantigens to prime the T cells and hopefully improve the efficacy of immune checkpoint inhibitors. Zhu *et al.* performed a retrospective study that evaluated 63 patients with unresectable HCC[45]. Patients were treated with a combination of tyrosine kinase inhibitors and PD-1 inhibitors (pembrolizumab or camrelizumab). Ten patients with initially unresectable disease subsequently underwent an R0 resection within three months of therapy initiation. Among these 10 patients, six had a complete response on final pathology. At a median follow-up of 11.2 months, eight had no recurrent disease. In a separate study, Zhang *et al.* reported a retrospective study of patients with HCC and major vascular invasion treated with a tyrosine kinase inhibitor and PD-1 inhibitor (pembrolizumab, toripalimab, or sintilimab)[46]. Eight out of ten patients were downstaged to resectable disease. One patient had a complete pathologic response and seven patients had partial responses. At one year, RFS was 75%.

In a single-arm phase I trial, patients with borderline resectable HCC were treated with nivolumab (PD-1 inhibitor) and cabozantinib (tyrosine kinase inhibitor)[47]. Patients included in this study had either a solitary tumor > 5 cm, multifocal unilobar disease, bilobar disease, or high-risk tumors (size > 3 cm with macrovascular invasion). Fifteen patients were enrolled and 12 underwent an R0 resection. Five patients had a major pathologic response. Individuals with a pathologic response also had an increase in T effector cells on pathologic specimens. Immunotherapy may be able to downstage patients to facilitate resection and

subsequently improve long-term outcomes. However, larger phase III trials are required to better identify which patients will best respond to immune checkpoint inhibitors and be converted to resectable disease.

CONCLUSION

HCC is a primary liver cancer that occurs in patients with chronic liver inflammation and/or cirrhosis. The standard of care treatment for early-stage HCC is curative intent resection or transplantation. Treatment decisions should be made by a multidisciplinary team of experienced hepatobiliary surgeons, medical and radiation oncologists, and hepatologists. The multidisciplinary team should design a personalized treatment plan for the patient based on the clinical status of the patient, the response to other treatments, time to recurrence or metastatic disease, and mor characteristics. For many patients, the personalized treatment approach will require a combination of multiple treatments. Given the relatively high morbidity associated with liver surgery, it is critical that patients are optimized prior to surgery and appropriately selected to prevent postoperative liver insufficiency. The risk of the operation should be balanced against the oncologic benefit of a resection. Surgeons need to be aware of the importance of margin status, anatomic *vs.* non-anatomic resection, and surgical approach. Neoadjuvant and adjuvant immunotherapy for patients with resectable disease has demonstrated promising results and will become a more integral part of the perioperative treatment of HCC in the near future. Future research is necessary to identify patients who will respond best to immunotherapy and combined treatment approaches with loco-regional therapies (e.g., surgery, ablation).

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