Chapter 16
Liver Cancer

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Introduction

Primary malignancies of the liver typically include hepatocellular carcinoma (HCC) and biliary carcinoma (cholangiocarcinoma, CC). Although there are other primary cancers of the liver, such as hepatoblastoma, their rarity makes description and analysis of them difficult. An estimated 30,000 people in the USA developed liver cancer in 2008, and the incidence is increasing [1]. Nearly 20,000 people die of primary liver cancer each year [1]. Despite improved treatments for HCC, the overall 5-year survival rate in the USA for patients with this disease remains less than 10% [2]. Furthermore, in the USA, the most rapid increase in cancer-related deaths among men has been seen in those with HCC [3]. The standard of care remains multimodality therapy, but very few patients are candidates for curative resection or liver transplantation [4]. Intra-arterial chemoembolization is one component of multidisciplinary therapy, but it does not usually offer a cure. Even sorafenib, the most recently approved systemic (oral) drug for treatment of HCC, increased median survival length by less than 3 months compared with controls, to a total of 10.7 months [5].

The major risk factors for HCC include viral infections (hepatitis B and hepatitis C) and cirrhosis from any cause [6]. Other rare etiologies include inherited disorders, such as hemochromatosis and Wilson's disease. Of note, there is a growing, albeit poorly defined, association between nonalcoholic fatty liver disease, metabolic syndrome, diabetes, and HCC [6]. Even if this association increases the risk of HCC only slightly, the sheer number of people in the USA who are at risk

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for developing nonalcoholic steatosis or steatohepatitis may greatly increase the number of patients with HCC.

Unfortunately, despite some evidence that hepatitis C virus may be associated with CC, there are no definitive predisposing risk factors for CC [6], which makes effective and efficient screening for CC nearly impossible. Patients often present with nonspecific findings such as fever, weight loss, and a dull upper abdominal or flank pain. Jaundice may be present, especially in advanced disease.

Screening of patients for HCC, typically cirrhotic patients, is highly recommended [based on National Comprehensive Cancer Network (NCCN) 2009 guidelines; see guidelines for the complete algorithm] [6]. Usually, patients have known risk factors such as chronic hepatitis C virus infection. It has been demonstrated that screening based on high-risk patients' serum alpha-fetoprotein (AFP) and transabdominal hepatic ultrasonography decreased HCC mortality by more than 37% [7]. Ideally, screening begins early in the disease course to evaluate changes in AFP or new findings on hepatic ultrasonography. Since both of these screening studies are relatively inexpensive and nearly risk-free, the clinical benefit is potentially significant.

Prognosis is associated with tumor characteristics, patient characteristics, and the treatment received. Tumor characteristics include stage/location, aggressiveness, vascular invasion, and growth rate. Larger, more aggressive, and faster-growing tumors are all associated with worse outcomes. Patient characteristics include overall health and liver function, as measured by one of the clinically validated scoring systems [i.e., Child-Pugh or Model End Stage Liver Disease (MELD) score] [6]. As expected, healthier people with normal liver function tend to have better outcomes with improved survival and decreased morbidity. The type of treatment that can be offered is based on the stage of disease and liver function (resection, thermal ablation, other local therapy, or systemic) and is directly related to survival. Tumors that can be completely resected are associated with a greater chance of long-term survival, whereas ablative therapies typically do not result in cure rates as high.

The diagnosis of HCC is typically made in a cirrhotic patient who either is symptomatic (dull/vague upper abdominal pain, anorexia/weight loss, or even occasionally a palpable mass) or has undergone screening as described. The most important imaging study is triphasic computed tomography (CT) to evaluate for the presence of lesions with significant arterial enhancement followed by contrast washout on the venous phase [6]. If a patient cannot undergo contrast CT, magnetic resonance imaging (MRI) may be a reasonable alternative. CC, however, is often best visualized on delayed phase CT or MRI, but there are no pathognomonic radiologic findings.

Historical Perspective

Most of the currently available surgical options/techniques or therapies for advanced disease, such as sorafenib, were developed in recent years. Historically, regional disease was nearly as fatal as distant metastatic disease. Although conformal radiotherapy is now an option in selected cases, the use of nontargeted ionizing radiation

often results in devastating hepatic complications without major oncologic benefit. Likewise, modern techniques for hemostasis during liver resection have reduced the major perioperative morbidity and mortality combined rate from historically greater than 50% to currently less than 10% with experienced surgeons at high-volume centers. Cytotoxic chemotherapeutics used in patients with HCC or CC are neither targeted nor very effective, and as such, they do not typically offer significant benefits as first-line agents.

The MD Anderson Cancer Center Experience

Survival rates improved for non-metastatic primary liver cancer based on Kaplan–Meier analyses of the MD Anderson Cancer Center patient population over a 50-year study period (Table 16.1; Fig. 16.1). Because of the very small number of liver cancer patients who presented to MD Anderson during the first decade of its existence, this analysis focused on the period from 1955 to 2004. Improvements in surgical techniques, critical care, and earlier diagnosis all contributed to the increased survival seen in the latter two decades.

By 2004, patients with liver cancer limited to the liver had a 5-year survival rate of nearly 40%, whereas 50 years earlier, that rate was less than 20%. Moreover, the rate of 10-year survival in patients who presented with local [Surveillance, Epidemiology, and End Results (SEER) stage] disease nearly doubled over this 50-year study period (Table 16.1). In fact, some patients have even been cured of their disease, as seen in the small but significant 10-year survival rate ($P<0.0001$) (Fig. 16.2).

Just 20 years before the end of the study period, patients with regional spread (regional lymph nodes) and those with distant spread of liver cancer had the same survival rates of 0%. However, recent advancements in surgical technique and modest improvements in chemotherapeutic and multidisciplinary treatment options improved the 5-year and 10-year survival rates significantly (Fig. 16.3; $P=0.008$).

Table 16.1 Survival rate improvement for early-stage liver cancer based on Kaplan–Meier analyses of the MD Anderson Cancer Center patient population over a 50-year period[a]

	Percent survival by disease stage					
	Local		Regional		Distant	
Decade	5 years	10 years	5 years	10 years	5 years	10 years
1944–1954	–	–	–	–	–	–
1955–1964	18.2	18.2	0	0	0	0
1965–1974	16.1	12.9	0	0	4.2	4.2
1975–1984	15.6	10.4	0	0	0	0
1985–1994	27.8	19.5	8.3	4.1	6.1	4.9
1995–2004	38.6	25.9	10.1	3.4	2.4	2.4

[a]Because so few patients with hepatocellular carcinoma or cholangiocarcinoma presented to MD Anderson from 1944 to 1954 with clear diagnostic information, this analysis focused on the period from 1955 to 2004.

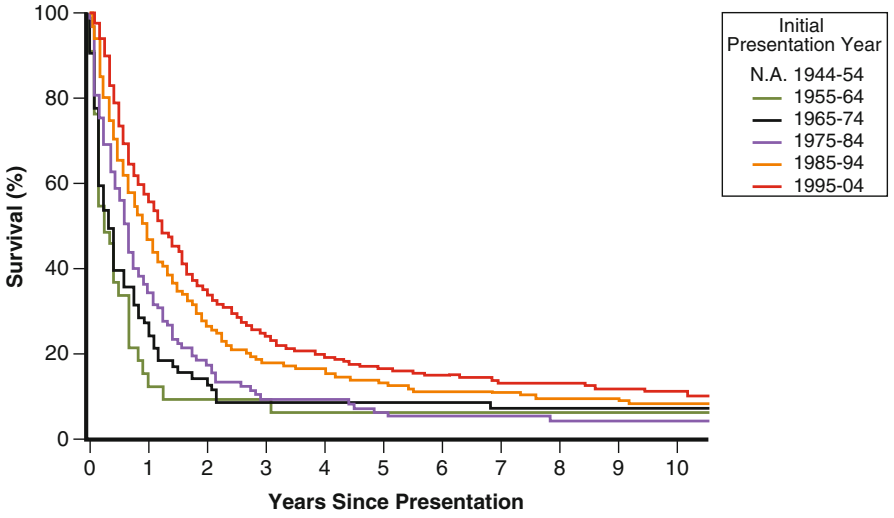

Fig. 16.1 Overall survival rates for patients who presented with liver cancer from 1955 to 2004 ($P<0.0001$, log-rank test for trend). Because of the very small number of individuals with liver cancer who were seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

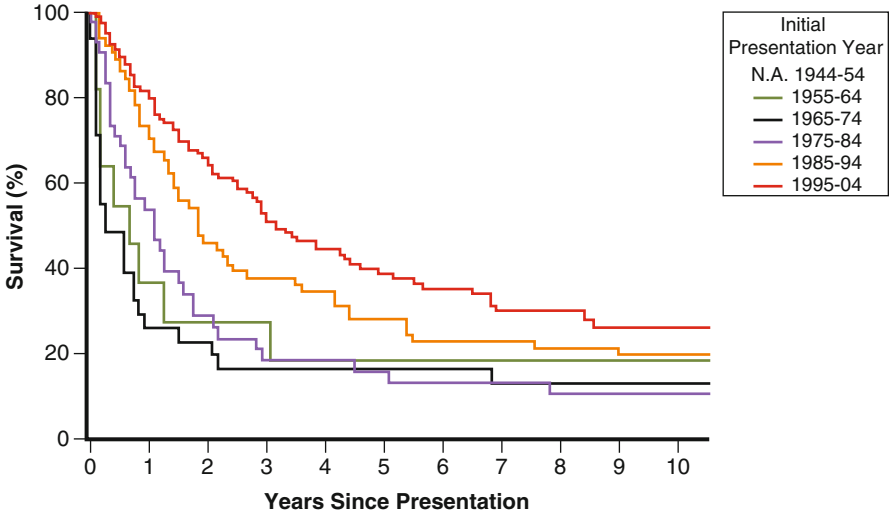

Fig. 16.2 Survival rates for patients who presented with liver cancer confined to the liver (local SEER stage) from 1955 to 2004 ($P<0.0001$, log-rank test for trend). Because of the very small number of individuals with liver cancer confined to the liver who were seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

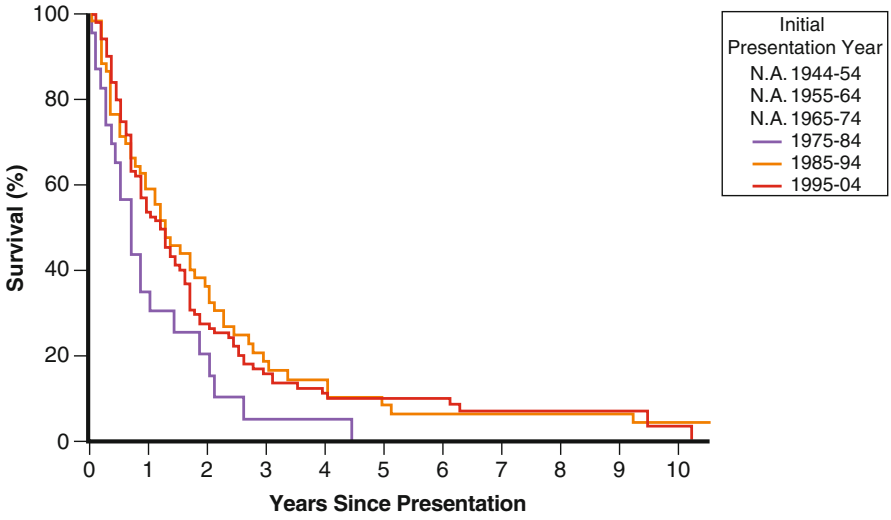

Fig. 16.3 Survival rates for patients with liver cancer who presented with regional (lymph node) disease (regional SEER stage) from 1955 to 2004 ($P = 0.008$, log-rank test for trend). Because of the very small number of individuals with regional (lymph node) disease who were seen from 1944 to 1954, from 1955 to 1964, and from 1965 to 1974, data from these periods were excluded. *N.A.* not applicable.

In fact, a very small cohort of patients with advanced disease (2.4%) achieved significant long-term survival during the last decade of the analysis, as seen in the similar rates of 5-year and 10-year survivors (Figs. 16.2 and 16.3).

Although significant improvements have been made in the survival rates of patients with liver cancer limited to the liver and lymph nodes (regional), the same cannot be said about those with distant spread (stage 4 disease) at the time of presentation (Fig. 16.4). There is no clinical or statistical difference in 5-year or 10-year survival rates in patients with metastatic liver cancer. However, short-term (less than 3 years) survival has significantly increased over the past 50 years ($P < 0.0001$). The clinical and personal (patient) significance of this added survival time to patients should not be ignored.

Current Management Approach

Screening

The most important step in the management of HCC is active screening to detect early-stage disease. Fortunately, development of the two major etiologies of HCC—cirrhosis and inherited disorders—can often be predicted well before the development of HCC. Specifically, we recommend that all high-risk cirrhotic patients (and

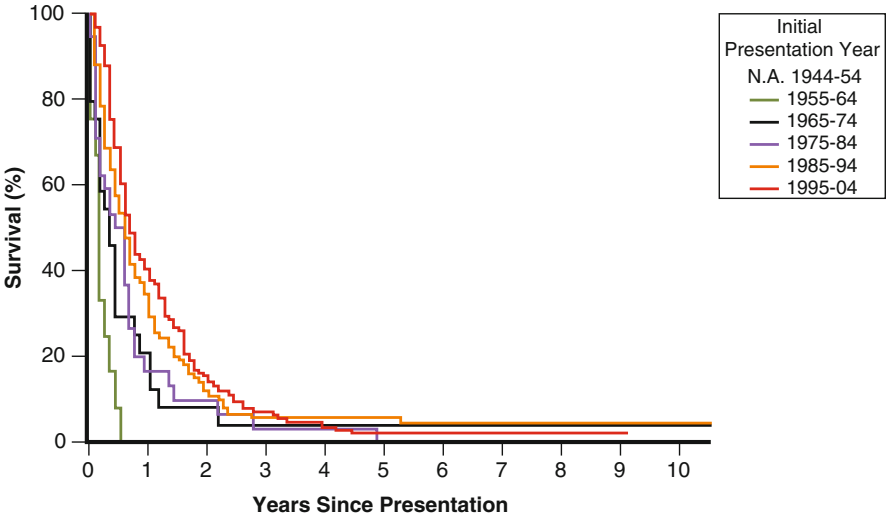

Fig. 16.4 Survival rates for patients with metastatic liver cancer (distant SEER stage) from 1955 to 2004 ($P < 0.0001$, log-rank test for trend). Because of the very small number of individuals with metastatic liver cancer who were seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

patients with known inherited disorders involving liver metabolism) undergo screening every 6 months with transabdominal ultrasound and testing for serum AFP levels. In addition, contrast-enhanced ultrasonography should be used if available. Unfortunately, since there are no confirmed predisposing risk factors for CC, the precise population to screen remains unknown.

Diagnosis

As mentioned, the imaging modality of choice to suggest a diagnosis of HCC (and CC) is noninvasive, triphasic CT imaging. However, if the classic CT pattern is not seen, other imaging modalities may be used. Because of its high resolution, MRI is an excellent confirmatory tool. Ultrasound, if not already performed, is an option if it can be performed with intravenous microbubble contrast enhancement.

If noninvasive imaging does not confirm HCC, another option is diagnostic biopsy, typically performed as percutaneous fine-needle biopsy. Finally, surgical biopsy, preferably performed laparoscopically, is an option of last resort to confirm the histological diagnosis. Often, a nondiagnostic fine-needle or core biopsy is repeated before a surgical procedure is performed.

Serum biomarkers also play an important diagnostic role in HCC, but less so in CC [6, 7]. AFP, already mentioned as a screening tool, is used more importantly as a

diagnostic tool. Any significant increase in serum AFP level should be considered evidence of HCC unless proven otherwise in high-risk patients undergoing screening. Furthermore, any serum AFP level above 200 ng/mL needs to be addressed as probable HCC, especially in conjunction with any finding on liver imaging studies.

Surgical Resection

Although complete tumor resection or liver transplantation is the optimal curative treatment option currently available, only a small subset of patients with primary liver cancer are candidates for these surgical approaches. Current treatment planning focuses on determining whether a given patient can have the entire lesion(s) safely removed. Although this is a very complex decision, the subsequent treatment is rather straightforward: some combination of resection, ablation, regional treatment, or systemic therapy. If a lesion can be resected, it should be. If a lesion cannot be resected but can be ablated, the patient should be informed of the risk of recurrence and offered aggressive ablation. If neither resection nor ablation is feasible, the patient may choose to undergo regional or systemic therapy based on the stage of disease and severity of concomitant chronic liver disease. Radiotherapy benefits some patients in a few very specific circumstances [8].

When considering resection, the function of the liver needs to be addressed in the context of the planned resection. Moderately cirrhotic patients should have at least 40% of their liver remaining after resection; very mildly cirrhotic patients should have 30% remaining; and noncirrhotic patients should have at least 20% [9]. Severely cirrhotic patients typically do not tolerate major operations such as hepatic resection [10]. Finally, before performing any procedure, the patient's health should be maximized from a cardiac, pulmonary, and renal perspective whenever possible.

Radiotherapy

Controlled, specific, and localized ionizing radiotherapy can be used to treat unresectable HCC in patients who are not candidates for transplantation or other appropriate locoregional therapies [6, 8]. Both electron beam and proton conformal external beam are reasonable options for some patients, albeit for a highly selected population. Radiotherapy is not recommended for treatment of distant metastatic disease except for palliation for bone metastases. Use of radiation is recommended as part of conformal external beam therapy to prevent injury to surrounding nonmalignant liver tissue [8]. Although the exact benefit is unknown, conformal radiotherapy is associated with improved outcomes [8]. Furthermore, conformal external beam proton radiotherapy is becoming more effective, with 5-year survival rates of 25–50% in unresectable patients [8]. Late-phase clinical trials may soon demonstrate reasonable effectiveness of this therapy in selected patients if results from early-phase trials are confirmed.

Unresectable Disease

Other local therapeutic options for unresectable HCC include radiofrequency or microwave thermal ablation and transarterial chemoembolization (TACE) [6]. These procedures may occasionally offer a chance for cure, but randomized studies to assess long-term survival have not yet been completed. Adverse events from these procedures, compared with those from resection, are infrequent, but the event rate varies significantly from study to study. The best use of TACE or ablative therapies seems to be as an adjunct for smaller HCC tumors in patients awaiting transplantation or to prolong survival and control symptoms in patients with large or multifocal tumors.

Systemic therapy is given to most patients with HCC since advanced disease is often diagnosed. Most chemotherapies are ineffective. Currently, the standard of care, based on multiple randomized placebo-controlled trials, is for patients to receive sorafenib [6]. It is generally recommended that patients receiving any treatment other than sorafenib be treated in the context of a clinical trial. The authors, however, feel strongly that nearly all eligible patients should be offered a clinical trial because the small 3-month survival benefit from sorafenib is not clinically sufficient to truly describe this drug as the "gold standard" for HCC treatment.

There is even less of a role for chemotherapy in patients with CC who are unable to undergo resection or who have recurrence of disease. This is because of the minimal benefit of chemotherapy in these patients, established with randomized controlled trials. However, cisplatin- and gemcitabine-based treatment protocols are beginning to show promising results. The authors, again, highly recommend that patients be referred to clinical trials for the best chance of treatment with an active systemic agent when resection is not possible or has failed.

Future Options

The outlook for patients with cancers of the liver is not entirely bleak. The recent approval of sorafenib has opened the door to other small-molecule inhibitors that may improve survival. In addition, other systemic treatments for unresectable HCC are in early-phase clinical trials. Over our 50-year analysis period, incremental improvements have taken place, and we look forward to further improvements over the next 50 years.

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