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Clinical research of hepatocellular carcinoma in the 21st Century

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One century has gone by since the scientific basis was established. Much has been done and much remains to be done in the field of clinical research of hepatocellular carcinoma (HCC). In the first half of the 20th Century, no remarkable progress was made in the clinical aspect of HCC research; the average survival of patients with HCC was around 2-5 mo. In 1950s-1960s, based on the understanding of intrahepatic anatomy as well as the biochemical changes that occur after surgery, major resection was the only hope for a curative outcome of large HCC. In 1960s-1970s, with progress in immunology, liver transplantation became an option. In 1970s-1980s, due to alpha fetoprotein (AFP) serosurveys and ultrasonography monitoring in the high-risk population, small HCC resection opened a new era in the clinical research of HCC, resulting in a marked improvement in the survival rate. In 1980s-1990s, rapid progress in medical imaging and regional cancer therapies enabled substantial advances the in diagnosis and treatment of both small and large HCC, Along with multimodality combination treatment, cytoreduction and sequential resection for initially unresectable HCC has been a significant advance.

An analysis of three decades of materials in the Liver Cancer Institute of Shanghai Medical University indicated that HCC has been converted from "incurable" into "partly curable". During the period of 1960-1989, 212 HCC patients with ≥ 5-year survival were treated in the author's institute, whereas in 1905-1970, only 45 HCC patients with ≥ 5-year survival were reported in the worldwide literature (Curutchet, *et al*. 1971). The analysis of these 212 HCC patients with ≥ 5-year survival revealed that surgery remained the principal approach to long-term survival. The treatment modalities of the 212 patients were small HCC resection, 51.4%; large HCC resection, 34.9%; cytoreduction and sequential resection for unresectable HCC, 8.0%; and palliative surgery other than resection, 5.7%.

Resection remains the best option for a curative outcome, and resection for small HCC is more effective. In the author's institute, a comparison between small HCC (≤ 5 cm) resection (n = 549) and large HCC resection (n = 831) revealed that in the small HCC group, the resectability rate was higher (93.2% *vs* 49.9%), the curative resection rate was higher (95.1% *vs* 76.7%), the operative mortality rate was lower (1.3% *vs* 4.0%), and the 5-year survival rate was higher (62.9% *vs* 34.6%). By the end of 1994, 109 HCC patients survived more than 5 years in the small HCC resection group, whereas only 75 patients did so in the large HCC resection group. In the author's series, 86.1% of the HCC cases coexisted with cirrhosis. With the increasing proportion of limited resection (from 53.9% to 72.3%), the resectability of small HCC increased from 78.8% in the 1970s to 95.2% in the 1980s.

Re-resection for subclinical recurrence is important for further improving survival after the initial resection. In the author's institute, the 5-year recurrence rate was 61.5% in the entire series, and 43.5% in the small HCC resection group. Therefore, it is important to monitor with both AFP and ultrasonography every 2-3 mo for 5-10 year after the initial resection for an early detection of recurrence. Re-resection was the treatment of choice for subclinical recurrence in the liver or for solitary lung metastases. In author's institute, of the 97 patients with re-resection, the 5-year survival rate was 51.2% from the first resection and 38.7% from the re-resection.

Cytoreduction with sequential resection is a new approach to the treatment of localized unresectable HCC. With the progress of regional cancer therapies and multimodality treatment, some of the localized unresectable HCC cases could be converted into resectable ones. In the author's institute, 72 of the 663 cases with surgically verified unresectable HCC have been converted into resectable ones. Successful cytoreduction with a median diameter reduction from 10 cm to 5 cm was mainly due to triple or double combination treatment with hepatic artery ligation (HAL), hepatic artery cannulation with infusion (HAI), radioimmunotherapy and fractionated regional radiotherapy. The operative mortality rate was 1.4% for sequential resection and the 5-year survival rate was 61.2%. The analysis revealed that a single nodule, well-encapsulated, situated in the right lobe or hepatic hilum, associated with micronodular cirrhosis, had a higher sequential resection rate when treated with triple or double combination modalities. Patients with a solitary tumor confined to one lobe, without a tumor embolus or residual cancer in the specimen of sequential resection, had a longer survival rate. For cytoreduction, double or triple combination treatment was more effective than single treatment. Since 1985, clinical trials of targeting therapies has added weight to the combination of HAL and HAI. Regional fractionated radiotherapy was an alternative to radioimmunotherapy. The sequential resection rates were 14.3%-34.0% for triple combination treatment (HAL, HAI and radioimmunotherapy/radiotherapy), 10.1% for double combination treatment (HAL and HAI), and only 1.1% for single treatment. The

recent advance of transcatheter hepatic arterial chemoembolization (TACE) has provided a nonsurgical approach to cytoreduction of unresectable HCC, and sequential resection after TACE has also been reported in the author's institute.

Intraoperative regional cancer therapy is a recent trend for the treatment of unresectable HCC, namely: HAL, HAI, cryosurgery, and intralesional ethanol injection. In the author's institute, the 5-year survival rate for 107 patients treated by cryosurgery was 22.0%.

In short, the approaches that substantially improved survival were the early resection of small HCC, re-resection for subclinical recurrence, and cytoreduction and sequential resection for initially unresectable HCC. Progress in tumor markers, medical imaging, regional cancer therapies, and the concept of multimodality combination treatment have all contributed to the realization of these approaches.

In China, HCC was the second-most lethal cancer in rural areas and ranked third in cities. Approximately 110000 people were killed annually, which accounted for 40% of the HCC-related deaths worldwide. As the mortality rate of HCC was very close to that of gastric cancer in 1990, and because it is predicted that gastric cancer in China will gradually decrease, as it did in Japan, HCC will probably surpass gastric cancer as China's most lethal cancer in the 21st Century. Clinically, the major obstacle for further prolonging survival of HCC patients was recurrence and metastasis after resection. The recurrence rate of HCC after resection was as high as 80%-90%, and was 60%-70% after curative resection and 40%-50% after small HCC resection. Re-resection was an effective approach to prolonging further survival; however, it was limited by the multicentric origin of HCC. The current available modalities, such as TACE and percutaneous intralesional ethanol injection (PEI), might be useful for preventing and treating recurrence. Biotherapy might add weight to surgical therapy. Recently, several biological prognostic factors have been noted. In the author's institute, HCC invasiveness-related oncogenes and growth factors included p53, H-ras, c-erbB-2, TGF-α, and the epidermal growth factor (EGF) receptor; however, these factors did not correlate well to tumor size. Therefore, biological approaches, including gene therapy and tumor vaccines, will probably become important in the forthcoming years for further improving the prognosis after surgery. The establishment of an HCC metastatic model in nude mice is needed for research on HCC recurrence and metastasis, as well as for seeking new treatment modalities for metastasis. However, because gene therapy and other biotherapies are complex, the study of better combining old modalities will still be an useful approach. With progress on a humanized or bioengineered human-mouse chimeric antibody, immunotargeting therapy will probably be a routine treatment for HCC. Studies on multicentric origins was also important, particularly on the prevention of new lesion development. Liver transplantation will be significant in this particular aspect. However, the difficulty in getting donor organs, as well as the expenses, will make this study difficult, particularly in developing countries. The effective approach for noncompensated liver cirrhosis (Child C) was another challenge. In short, slow but substantial progress in the field of clinical research of HCC will be achieved in the forthcoming 21st Century.

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