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Hepatocellular Carcinoma: Our 22-year Experience

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There have being reported 18 million new cancer cases worldwide for the year 2020, with 10 million deaths attributed to cancer for the same year while 33% of cancer cases are linked to tobacco smoke worldwide. Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and also comprises the fourth leading cause of death worldwide while approximately 841000 new cases are diagnosed annually. In the US, HCC is of the few cancers that increases in incidence and death in the current period. It is two to four times more common in males than in females. Chronic liver disease such as Hepatitis B and C infection, fatty liver disease and large amounts of alcohol consumption are causative factors for HCC.

Patients and Methods

A retrospective analysis was performed for the 30 patients with primary hepatic tumours that were treated by our team for the period 2000-2022. From the 30 patients there were 18 males and 12 females (M/F ratio =18/12, 60%:M, 40%:F). Hospital Records were reviewed. The patients were treated in 4 Hospitals (Athens Medical Group, European Interbalcan Medical Center, Metaxa Cancer Memorial Hospital, Mesolongi General Hospital).

Statistical Analysis

Time-to-event outcomes were estimated using Kaplan-Meier curves. The log-rank test was used to assess the effect of the predictors, respectively, on Overall Survival (OS) and Progression-Free Survival (PFS). OS defined as the time from the surgery time to death (for any reason). PFS defined as the time from the start of randomization to the progression of tumor (in any aspect) or death (for any reason).

Continuous data are reported as median and categorical data are reported as number. All p values < 0,05 were considered to be statically significant. All data were analyzed using SPSS software version 26.0 (SPSS Inc., Chicago, IL) for Windows.

Results

Of the 30 patients included in the analysis, 12 females and 18 males, the 17 (56.7%) were ≥55 years old. 19 patients (63.3%) have died whereas 11 (36.7%) were the censored cases. The median overall survival time was 30 months (95% CI: 17.4 - 42.7). The median progression-free survival time was 26 months (95% CI: 10.1 – 41.9).

Table 1: Patients' charateristics

		N	N %
Age	<55	13	43,3%
	≥55	17	56,7%
Biological sex	Female	12	40,0%
	Male	18	60,0%
Follow up	Alive	11	36,7%
	Death	19	63,3%

Overall survival by Age

For age <55 years the median overall survival time was 30 months (95% CI: 14.1 – 46). For age ≥55 years the median overall survival time was 30 months (95% CI: 16 – 44).

A log rank test was conducted to determine if there were differences in the survival distribution for the different groups of age. The survival distributions for the group of age <55 years wasn't statistically different from group of age ≥55 years, $\chi^2(1) = 0.004$ ($p = 0.948$).

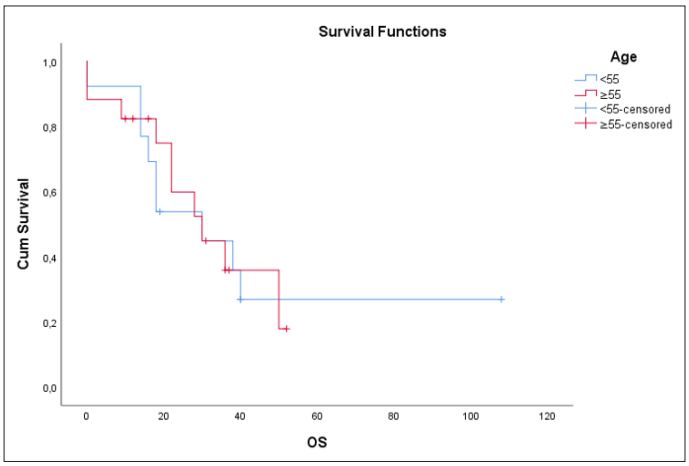

Figure 1: Overall survival by Age

Overall survival by type of treatment
For Resection the median overall survival time was 38 months (95% CI: 32 – 44). For RFA the median overall survival time was 30 months (95% CI: 19.5 – 40.1). For Chemoemb the median overall survival time was 16 months (95% CI: 12.8 – 19.2).

A log rank test was conducted to determine if there were differences in the survival distribution for the different groups of type of surgery. The survival distributions for the type of surgery group were statistically significantly different, $\chi^2(2) = 9.832$ ($p = 0.007$). Pairwise analysis showed that:

- survival distribution of Chemoemb was statistically different from Resection distribution, $\chi^2(1) = 1.223$ ($p = 0.005$).
- survival distribution of Chemoemb was statistically different from RFA distribution, $\chi^2(1) = 4.109$ ($p = 0.043$).

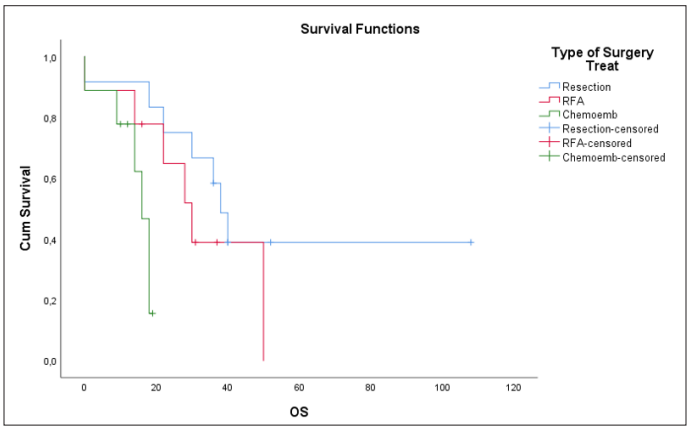

Figure 2: Overall survival by type of treatment

Progression-Free survival by type of treatment
For Resection the median progression-free survival time was 32 months (95% CI: 26.5 – 37.5). For RFA the median progression-free survival time was 22 months (95% CI: 14 – 29.9). For Chemoemb the median progression-free survival time was 10 months (95% CI: 7 – 13).

A log rank test was conducted to determine if there were differences in the survival distribution for the different groups of type of treatment. The survival distributions for the type of surgery group were statistically significantly different, $\chi^2(2) = 9.459$ ($p = 0.009$).

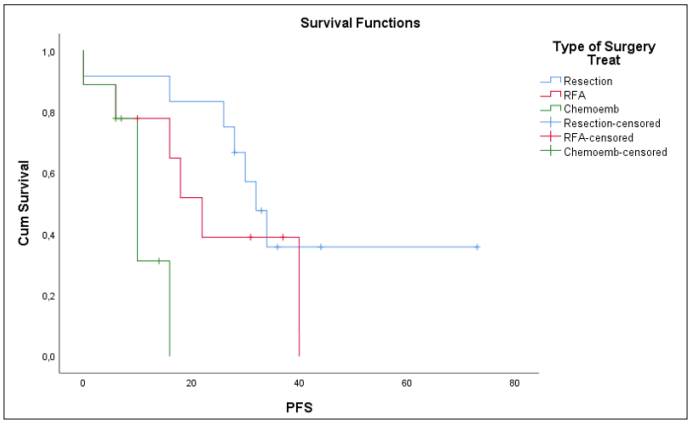

Figure 3: Progression free survival by type of treatment

Pairwise analysis showed that: survival distribution of Chemoemb was statistically different from Resection distribution, $\chi^2(1) = 9.305$ ($p = 0.002$).

Discussion
Analysing our data we see that our M/F ratio of 3/2 much differs from the stated otherwhere ratio of 4/1 [1].

Various treatment modalities exist for the treatment of hepatocellular carcinoma based on disease stage, liver function and performance status. Potentially curative options should be offered to the appropriate patients in the form of liver resection, ablation, chemoembolization, RFA and orthotopic liver transplantation.

The commonest causative factors for hepatocellular carcinoma are hepatitis B and C carrier status, alcohol and steatohepatitis, all being chronic liver disease situations.

For the judgement of remaining functional liver tissue and the feasibility of safe resection various validating systems are used, like Childs criteria [2], and ALBI [3].

Conflicting results exist regarding the use of RFA in comparison to liver resection with various factors playing their role. Our RFA results for OS coincide with those of Huang et al [4] and the progression free survival was 22 months.

For tumours >2cm but < 5cm or up to 3 tumours maximum 3cm each (Milan criteria) [5] orthotopic liver resection is considered with 5year OS 78% [6]. Contradicting results between liver resection and orthotopic liver transplantation, so new studies are needed [7].

Liver resection has showed a 5year OS of 62% [8]. Even for large tumours > 10cm, liver resection has been associated with an OS between 27-53% [9]. Our liver resection group OS is in the region of 44.5 mont hs, well in the upper limits of the range, while progression free survival was 32 months.

Transarterial chemoembolization as compared to liver resection has inferior results to liver resection (5year OS 18.5% in contrast to 41.3%) [10]. Our results of 14.5% 5year OS are in the low part of the otherwhere reported, with progression free survival being 10 months.

As far as vascular invasion and portal vein tumour thrombus OS rates after liver resection vary from 10% to 41% [10].

The operative philosophy in liver surgery is to achieve R0 resections preserving the maximum possible liver parenchyma especially when cirrhosis exists and the residual liver function is marginal. On ths basis portal vein embolization (lobe with tumour) and 4 to 8 weeks consequent hypertrophy of the contralateral lobe is an option for limited residual reserve cases with the results to be similar to non-embolisation cases [11-13].

Another option that complies with this philosophy is the limiting of the extent of liver resection but with complete margin negative operative borders such as right posterior segmentectomy, central segmentectomy (IV, V, VIII, middle hepatic vein) with good reported results as with extended resections [14].

The matter of anatomical vs non-anatomical liver resections has various aspects with most surgeons preferring anatomical resections as from lower local recurrences and higher 5 year disease free survival [15]. For peripheral lesions though wedge resections can be the choice [16].

As from the screening point of view adding AFP measurement to US imaging increases diagnostic sensitivity from 92% to 99.2%. [17]. The CT/MRI findings on hepatocellular carcinoma are arterial hyperenhancement, venous washout and capsule enhancement and usually enable non-invasive diagnosis [18]. Biopsy is indicated when no history of hepatocellular carcinoma exists [19].

The classical Child-Pugh criteria for liver function are the commonest used but with 2 subjective parameters (encephalopathy and ascites) [20]. Other models are MELD score, that is more precise when cirrhosis exists and last the ALBI score that has been applied to both patients with and without cirrhosis and with its capacity been among patients with favourable prognosis [21-23].

For hepatocellular carcinoma staging the TNM system is widely used but it is based on tumour histology and location and so it does not take into consideration liver function. Another staging system with broad acceptance is the so called Barcelona Clinic Liver Cancer that incorporates tumour size and number, liver function and patient per,formance status and apply to both patients with and without cirrhosis [24,25].

From the various treatment options lets consider if we consider orthotopic liver transplantation, that seems the ideal situation since we deal with various locations of the disease intrahepatic and also with functional impairment if it exists but first the availability of an organ as well as the lifetime use of immunocompressants makes its use not widely accessible. So, liver resection remains the mainstay except when cirrhosis. However, 5year survival after liver transplant reaches 70% [26-29].

Microwave is being used, especially for very small and/or early stage hepatocellular carcinomas with results similar to resection [30]. For single tumours >2cm liver resection is the preferred modality [31,32]. For multinodular early stage tumours (up to 3 tumours of <3cm) ablation is recommended than resection [24].

Palliative therapies for hepatocellular carcinoma include transarterial ones, radiation therapy and systemic therapies. Transarterial therapies include transarterial embolization with beads (TACE), or radioembolization (TARE) or hepatic artery infusion with pump (HAI). Radiation therapy is being used cautiously due to radiosensitivity of the liver and shows similar results with RFA in local control of disease while it can improve pain control and ascites [33].

Systemic therapy with sorafenib was the main medication for a decade, but later it was substituted with the combination atezolizumab and bevacizumab that showed improved survival oversorafenib [34,35]. Other medications include tremelimubac and durvalumab combination for advanced hepatocellular carcinoma with improved results than sorafenib or durvalumab alone [36].

In conclusion, patients with hepatocellular carcinoma should receive the best available treatment by the use of a multidisciplinary approach with the collaboration of specialized surgeons, medical oncologists, radiation oncologists and interventional radiologists as new knowledge comes out all times that needs to be applied to complex cases.

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