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Hepatocellular carcinoma associated other primaries: common types and prognosis

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Abstract

Hepatocellular carcinoma (HCC) is the commonest malignancy in Egypt secondary to endemic hepatitis virus. Dual malignancy with HCC is infrequently reported. We herein retrospectively collected data of HCC patients with another primary tumor from a tertiary cancer center. Fifteen patients were enrolled in this case series, epidemiologic data, type of second malignancy, time interval between both tumors, treatment applied, and pattern of recurrence and survival are displayed. Third of the tumors were synchronous, while in the rest HCC was mostly the second malignancy. Breast cancer was the commonest encountered other primary. None of the second malignancies recurred after treatment except for prostate cancer which was not treated radically. The median overall survival of the patients was shorter than previously published series about 29 months. In conclusion, dual malignancy with HCC had more complicated treatment panels; however, they are not necessarily carrying a worse prognosis. HCC tumor outcome remains the main predictor of survival.

Keywords Hepatocellular carcinoma, Double malignancy, Breast cancer, Second tumor

Background

The commonest sites of cancer in Egypt according a national registry in 2014, was the liver in males, while in females liver cancer was the 3rd, counting for 18.7% and 4.6% of all body cancer, respectively [1].

A patient may have multiple primary tumors, i.e., with > 1 tumor arising in different organs and/or are with a different pathologic subtype. According to previous studies, the incidence of multiple primary malignancies (MPMs) ranges from 2 to 17% [2–4].

The cutoff duration to classify the second tumor as synchronous or metachronous is set to 6 months instead of 2 months as per the definition assigned by the International Association of Cancer Registries and the International Agency for Research on Cancer (IACR/IARC) [5].

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MPMs in a single patient were first described in 1879 by Billroth [6]. A study analyzing the SEER Program database has revealed that the incidence of multiple primaries varies from 1% if initial liver primary to 10% if the initial primary is the breast [7].

The pathophysiology behind the occurrence of MPMs has been theorized to be common carcinogen induced multiple cancers in an exposed epithelial surface, called "field-cancerization" as seen in head-neck tumors, as a late side effect of treatment used to treat the first tumor, and a genetic predisposition to neoplasia [8].

Methods

This is a retrospective study, where the authors reviewed all patients with hepatocellular carcinoma treated in a tertiary cancer center in the last 10 years, and those who had pathologically proven second malignancy were retrieved.

Patients without a clear histopathological confirmation of each malignancy, or patients for whom the second tumor was suspected to be a metastasis of the first site were excluded from the study.

The age of those patients, the type of the second malignancy, the management of both the HCC and the second tumor were analyzed. In addition, the recurrence of actively treated patients and the overall and disease-free survival of the studied cohort were recorded.

The data of these patients was analyzed using SPSS version 26 (Inc., Chicago, IL, USA). Continuous variables are presented as mean when symmetrical or median and range when asymmetrical. Categorical variables are presented as proportions. Survival was measured using Kaplan-Meier curve and significance was determined using log rank test with p value < 0.5 categorized as significant.

Results

Fifteen patients were recruited. The mean age at diagnosis of HCC was 63.3 ± 10.8 years old. The group had nearly equal sex distribution (7 males and 8 females).

The second tumor was synchronous in 5 and metachronous in 10 patients. In the 10 patients with metachronous tumors, the HCC was the initial malignancy in only 3 patients (30%). In the metachronous patients, the time interval between the 2 tumors ranged from 8.7 years earlier to 1.6 years later to HCC diagnosis (Table 1).

All HCC were on top of cirrhosis secondary to viral hepatitis. The HCC was diagnosed with classic uptake in triphasic computed tomography scan in 10 patients, while in 5 patients a guided biopsy was taken. Pathology confirmed HCC in hematoxyllin and Eosin stain in 4 patients, while 1 patient required Hep-par immunohistochemistry to confirm the diagnosis. The HCC was treated medically in 3 patients, with interventional procedures (Radiofrequency ablation, Microwave ablation, Transarterial chemoembolization, or combination of them) in 9 patients, surgery in 1 patient and expectant supportive management in 2 patients. HCC was mostly stage I (8 patients). Eleven of the patients were Child-Pugh A and 4 were child B. 53.3% of the patients had 1 focus of HCC and 13.3% had 2 foci. Finally, the HCC recurred in 6 patients (Table 2).

Regarding the second tumor, breast cancer was the commonest encountered malignancy (5 patients, 33.3%) followed by skin basal cell carcinoma (3 patients, 20%) (Fig. 1).

In the patients with breast cancer, 2 were synchronous and 3 were metachronous, one of them was a male patient. The pathology of breast cancer was infiltrating duct carcinoma in 4 patients and ductal carcinoma in situ in 1 patient. The breast cancer was treated surgically in 4 patients (3 modified radical mastectomy and one simple mastectomy) and with hormonal therapy (aromatase inhibitor) only in 1 patient with supraclavicular spread; however; this patient progressed on therapy. Clinically, 3 of the patients who had invasive breast cancer were stage II and one was stage III. All were luminal B. On the final pathology one of the stage II patients was upgraded to stage III. Only in one patient the tumor was multifocal. Two received adjuvant chemotherapy and the one with stage III disease received in addition adjuvant radiotherapy and all received adjuvant hormonal therapy. None of the surgically treated patients encountered a recurrence of the breast cancer (Table 3).

Otherwise, the commonest non-breast concomitant cancer was basal cell carcinoma (BCC) in 3 patients. In addition, there was 1 patient with each of the following pathologies: palatal squamous cell carcinoma, non-Hodgkin lymphoma, papillary thyroid carcinoma, paraganglioma, retroperitoneal liposarcoma, prostate cancer, and ovarian mucinous cystadenoma with appendiceal mucocele. No evidence of recurrence of any of these tumors in median 22 months of follow-up, apart from prostate cancer which was treated by subcapsular orchidectomy.

Table 1 Epidemiologic criteria of the studied group and the survival of the patients

Variable	Value
Age at HCC diagnosis (mean ± SD)	63.3 ± 10.8 kg/m^2
Sex	
Male	7 (46.7%)
Female	8 (53.3%)
Timing of second malignancy	
Synchronous	5 (33.3%)
Metachronous	10 (66.7%)
First malignancy in the metachronous patients	
HCC first	3 (30%)[a]
Other mg first	7 (70%)[a]
Type of the second primary with HCC	
Breast cancer	5 (33.3%)
Basal cell carcinoma	3 (20%)
Squamous cell carcinoma	1 (6.7%)
Non-Hodgkin lymphoma	1 (6.7%)
Papillary thyroid cancer	1 (6.7%)
Liposarcoma	1 (6.7%)
Prostate cancer	1 (6.7%)
Paraganglioma	1 (6.7%)
Mucinous neoplasm (ovary + appendix)	1 (6.7%)
Time interval between HCC and the other metachronous tumor median (range)	− 12 (− 102–19) months
Estimated overall survival	
Mean (95%CI)	43.5 (23.9–63.2) months
Median (95%CI)	29 (12–46) months
Estimated disease-free survival mean (95%CI)	7.2 (2.2–12.2) months

[a] Valid percentage

Table 2 Data about the HCC, its treatment, and recurrence

Variable	Value
Child-Pugh score	
A	11 (73.3%)
B	4 (26.7%)
HCC treatment	
Medical	3 (20%)
Interventional	9 (60%)
Surgical	1 (6.7%)
Supportive	2 (13.3%)
HCC stage group	
I	8 (53.3%)
II	1 (6.7%)
III	2 (13.3%)
IV	1 (6.7%)
Number of HCC foci	
1	8 (53.3%)
2	2 (13.3%)
3	1 (6.7%)
Multiple	1 (6.7%)
HCC recurrence in cured patients	
No	4 (40%)[a]
Yes	6 (60%)[a]

[a] Valid percentage

The estimated mean overall survival (OAS) measured from diagnosis of HCC was 43.5 months with 95% CI (23.9–63.2 months). Being synchronous or metachronous (Fig. 2), presentation of HCC initially or as a second malignancy does not affect OAS (p value = .96 and .25, respectively). While the estimated mean disease-free survival (DFS) calculated from diagnosis of HCC was 7.2 months with 95% CI (2.2–12.2 months). Also, being synchronous or metachronous (Fig. 3), presentation of HCC initially or as a second malignancy does not affect DFS (p value = .73 and .72, respectively).

Discussion

In patients with synchronous multiple primaries, several questions need to be addressed in the multidisciplinary meeting before a treatment plan is established including: which tumor is more aggressive/carry poorer prognosis? Is there a chance for cure or the situation is palliative? Can one of the synchronous tumors be treated radically and then the second sequentially? Can an antitumor regimen be chosen that is active for both tumours? Can the tumors be profiled (gene sequencing) to assess a common genetic background or common mutation, which can be targeted [9].

In the only study of multiple primary malignancies from Arab world, the most frequently observed histopathology in the synchronous and metachronous malignancies was adenocarcinoma. Breast–colorectal,

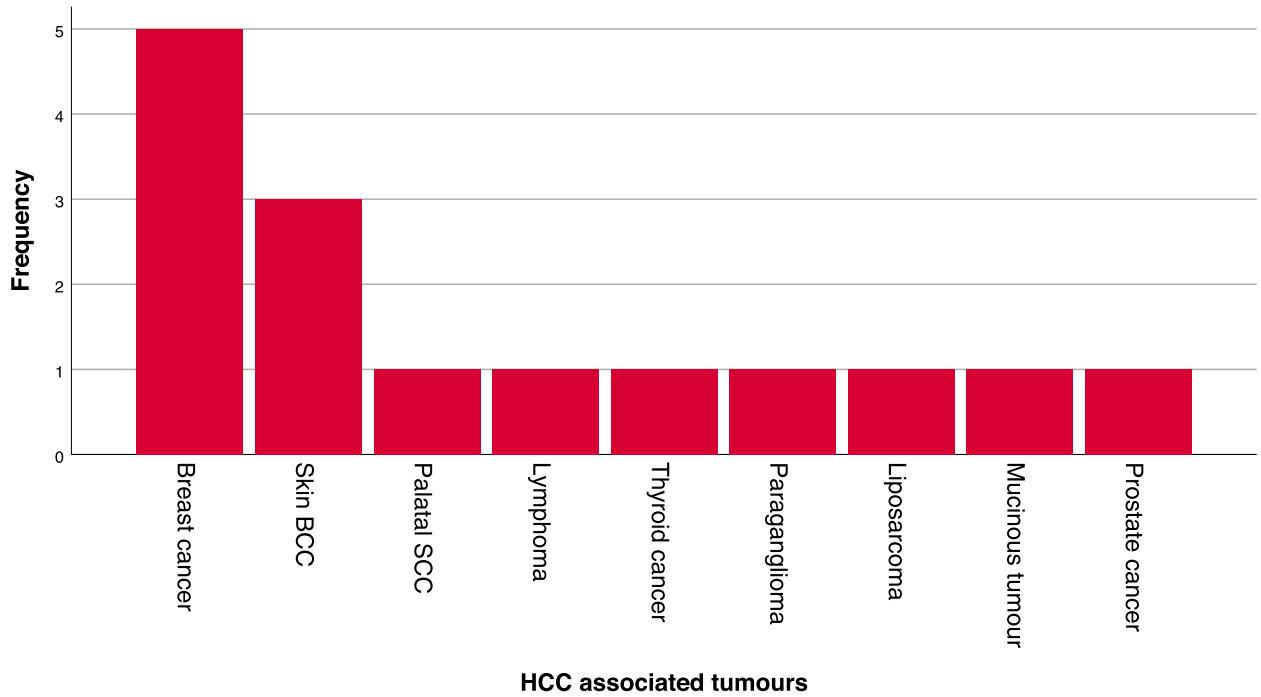

Fig. 1 A bar chart showing the frequency of tumor associated with HCC

Table 3 Data about the breast cancer, its treatment, and recurrence

Variable	Value
Timing of appearance of breast cancer	
Synchronous with HCC	2 (40%)
Metachronous with HCC	3 (60%)
➢Breast cancer first	2
➢HCC first	1
Breast pathology	
IDC	4 (80%)
DCIS	1 (20%)
Breast tumor focality	
Unifocal	4 (80%)
Multifocal	1 (20%)
Breast neoadjuvant therapy	
No	4 (80%)
Yes	1 (20%)
Breast surgery	
None	1 (20%)
Modified radical mastectomy	3 (60%)
Simple mastectomy	1 (20%)
Estrogen receptor status	
Negative	0
Positive	4 (80%)
Progesterone receptor status	
Negative	1 (20%)
Positive	3 (60%)
HER2neu status	
Negative	2 (40%)
Positive	1 (20%)
Molecular type	
Luminal B	4 (80%)
Pathologic stage	
Is	1 (20%)
II	3 (60%)
III	1 (20%)
Chest wall recurrence post mastectomy	0

breast–thyroid, and kidney–colorectal were the most frequently observed malignancy combinations. In addition liver cancer was found as one of the primaries in 46 patients, nearly equally synchronous and metachronous (22/24 cases) [10].

The occurrence of second primary malignancy (SPM) in HCC was first reported in 1979 [11]. Later, three population-based studies were published to describe the development of SPM in HCC [12–14]

The top 5 most common SPMs after initial diagnosis of HCC were bronchogenic carcinoma, prostate cancer, non-Hodgkin lymphoma, colon cancer, and breast cancer in a SEER database study. In addition, they found that paradoxically poorer tumor characteristics such as larger tumor size, vascular invasion, high AFP level, higher tumor grade, and distant spread were associated with a decreased risk of developing SPM; furthermore, patients who received curative treatments for their HCC such as local tumor destruction, hepatectomy, and transplantation were related to a higher risk of developing SPM. They explained that patients with poorer tumor-related characteristics without treatment might die before the development of SPM [14]. In the current study, the commonest SPM with HCC was breast cancer; however, the sequence of cancer development was in favor of non-HCC tumor appearing initially in 70% of metachronous cases.

In Shah et al.'s population-based study, the risk of stomach and thyroid cancer were significantly increased among older patients, while the risk of lung cancer and another type of hepatobiliary cancer were significantly higher in younger patients with HCC compared to the general population after two years of latency [13]. In our study, none of the patients were younger than 40 years old, and the patient who suffered papillary thyroid cancer was 53 years old.

Most HCC patients have accompanying portal hypertension or cirrhosis mainly due to HCV infection which is the main risk factor for HCC in Egypt [1, 15]. Cirrhosis is considered to play a role in the carcinogenesis of several cancers through change in metabolism or hormones, lipids, and other chemicals. Sorensen and colleagues reported increased risks of tobacco-related cancers (i.e., urinary bladder, kidney cancer, lung, pancreas and stomach) and alcohol-related cancer (i.e., buccal cavity and pharynx, esophagus and larynx) in patients with cirrhosis [16]. However, of forementioned cancers, we encountered only one case of palatal SCC as SPM in our HCC series, questioning whether the second primary tumor was ever related to cirrhosis

In a large Taiwanese study, although the HCC patients were predominately male, sex was not an independent risk factor for predicting SPM after HCC diagnosis. In their study, other than age, chronic kidney disease was the most important independent factor associated with SPM [12]. In coincidence with that, our studied cohort did not show any sex predilection, but of notice that the number of males to females was nearly equal. In addition none of our patients were suffering renal disease.

In Kong et al. paper, the HCC patients with SPM had a median overall survival (OAS) of 55 months which is better than those in the one primary malignancy (OPM) group from the initial diagnosis of HCC; however, these patients had a comparable prognosis with those in the OPM group after the second diagnosis [14]. Herein, we

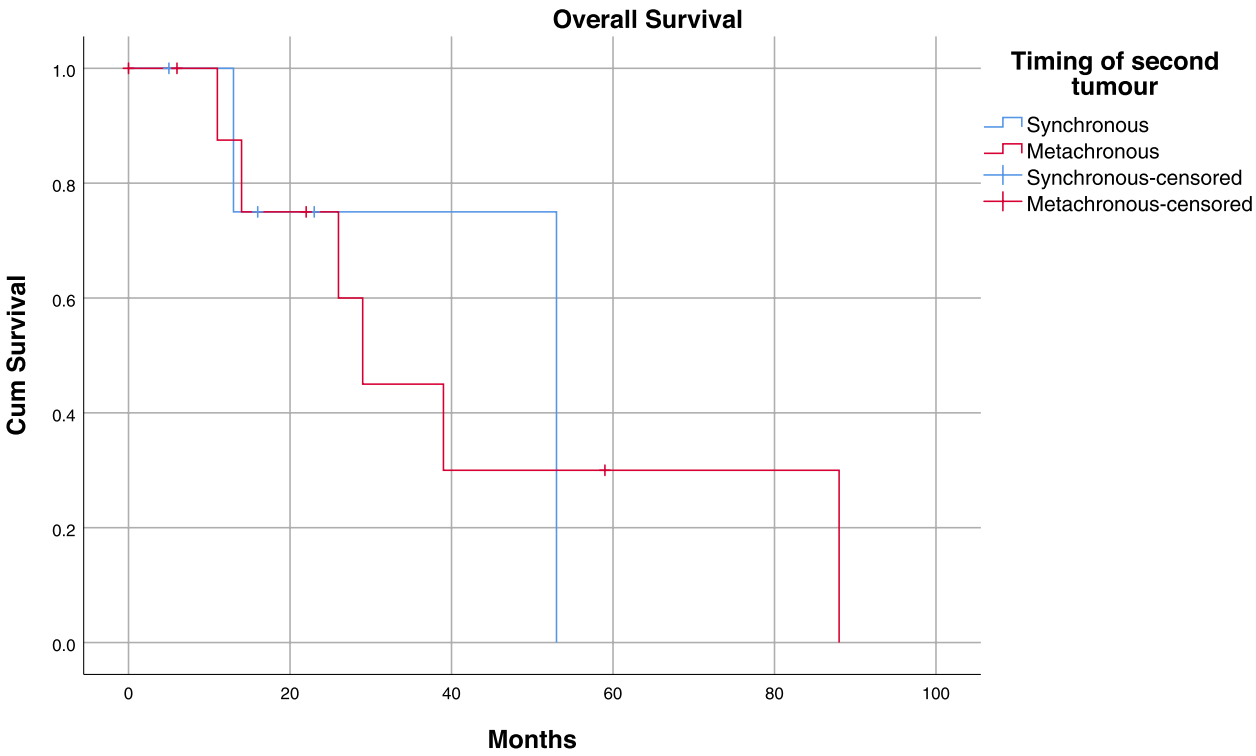

Fig. 2 Kaplan-Meier curve showing overall survival in synchronous vs. metachronous tumors

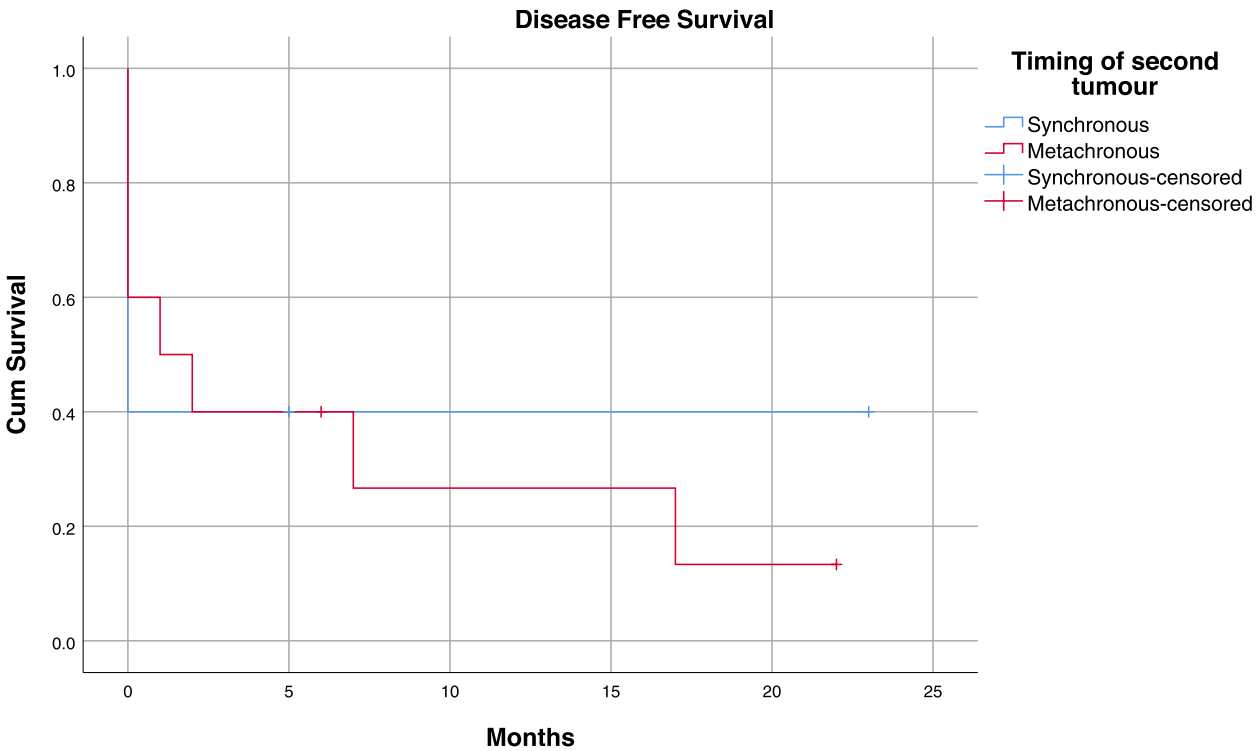

Fig. 3 Kaplan-Meier curve showing disease-free survival in synchronous vs. metachronous tumors

did not incorporate any single site cancer patients, but the median overall survival of the double malignancy patients was 29 months, quite shorter than Kong et al. series. Furthermore, the pattern of display of the dual malignancies whether synchronous or metachronous, and whether HCC presented first or later in the survivor life does not affect either overall or disease-free survival in our cohort.

Finally, this study may be the first to address the dual malignancy problem with HCC in our region; however, there are several limitations: small number of patients, retrospective nature, and heterogenous treatments received.

Conclusions

Hepatocellular carcinoma may be associated with second primary tumor. Whether the liver cirrhosis/HCC increase the risk of developing second malignancy or it is just a coincidence is not clear. The condition is more frequent in elder population with no sex predilection. Breast cancer is the commonest second malignancy followed by skin basal carcinoma. HCC especially in cirrhotic patients may limit chemotherapy options for these second malignancies. Survival and disease-free survival of the patients was dependent mainly on the hepatic carcinoma without being affected by time of presentation of the second tumor.

Take home message

No clear cause of dual malignancies with HCC known, however survival is mainly dependent on the HCC behavior and treatment.

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Authors' contributions
SE and AA drafted the data. IH wrote the manuscript and underwent literature search. All authors have read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
All procedures performed in the study involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study has been approved by Mansoura Faculty of Medicine Institutional Research Board (MFM-IRB) with approval code (R.22.09.1810).

Consent for publication
Not applicable.

Competing interests
SE, AA, and IHM declare that they have no competing interests.

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