

Real-Life Evidence From Gallbladder Cancer: A Single Center Experience

Safra Kesesi Kanserlerinde Tek Merkez Deneyimimiz

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ÖZET

Giriş ve Amaç: Safra kesesi kanserleri nadir fakat ölümcül kanserlerdendir. Literatürde genellikle safra yolu kanserleri ile birlikte sınıflandırılmıştır. Bu yazıda safra kesesi kanserli hastaların klinik özelliklerini, adjuvan ve metastatik tedavi rejimleri ile sağ kalımlarını değerlendirmeyi amaçladık.

Yöntem ve Gereçler: Ocak 2011-Ekim 2017 tarihleri arasında Sağlık Bilimleri Üniversitesi, Dr. A. Y. Ankara Onkoloji Hastanesi Tıbbi Onkoloji Kliniği'ne safra kesesi tanısı ile başvuran hastalar retrospektif olarak değerlendirildi. Hastaların demografik özellikleri, cerrahi türleri, adjuvan ve metastatik tedavi rejimleri, tedavi yanıt durumları, genel sağkalım (OS) oranı ve hastalıksız sağ kalımları (DFS) değerlendirildi.

Bulgular: Çalışmaya dahil edilen 58 hastanın 34'ü (%58.6) lokalize veya lokal ileri evredeydi. Metastatik olmayan hastaların 13'ü (% 38.2) herhangi bir adjuvan tedavi almamıştı. Kemoradyoterapi en çok tercih edilen adjuvan tedavi seçeneğiydi (rezeke edilen hastaların% 35.2'si). Adjuvan tedavi alan hastalarda median DFS ve OS, sırasıyla 24.8 (% 95 CI: 1.5-48.1) ve 28 (% 95 CI: 20.6-35.4) ay iken adjuvan tedavi almayan hastalarda median DFS ve OS'ye ulaşılmadı.

Tartışma ve Sonuç: Rezeke edilen safra kesesi kanserlerinde adjuvan tedavinin etkinliğini göstermek ve en uygun tedavi modalitesinin seçimi için prospektif, randomize kontrollü çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: safra kesesi kanseri, safra yolu kanserleri, adjuvan tedavi

ABSTRACT

Introduction: Gallbladder cancer (GBC) is an uncommon and highly fatal carcinoma. It is usually classified with biliary tract cancers in the literature. In this report we have planned to evaluate the clinical characteristics, adjuvant and metastatic treatment options and the survival of GBC patients.

Methods: A retrospective analysis of GBC patients treated in University of Health Sciences, Dr. A. Y. Ankara Oncology Hospital, Department of Medical Oncology between January 2011 and October 2017 was performed. The files of 58 patients with GBC were screened retrospectively. Treatment regimens, response rates, overall survival (OS) rate and disease-free survival (DFS) of the patients were evaluated.

Results: A total of 58 patients of whom 34 (58.6%) were presented as non-metastatic stage. Thirteen (38.2%) of non-metastatic patients did not receive any adjuvant treatment. Chemoradiotherapy was the most preferred adjuvant treatment option (35.2% of resected patients). Median DFS and OS were 24.8 (95% CI: 1.5- 48.1) and 28 (%95 CI: 20.6-35.4) months respectively in patients who received adjuvant treatment however both were not reached in patients who did not receive any adjuvant treatment.

Discussion and Conclusion: In resected GBC, it is needed to prospective, randomized controlled trials for adjuvant treatment efficacy and choice of treatment modalities.

Keywords: gallbladder cancer, biliary tract cancers, adjuvant treatment

INTRODUCTION

Gallbladder cancer (GBC) is a rare and fatal tumor (1).The incidence of GBC in Turkey is 1.7 / 100,000 and it is quite similar to USA (2). It ranks sixth among all gastrointestinal system cancers, but it is the most frequent tumour of

all the biliary tract (3,4). Most of the patients are diagnosed incidentally (5). The majority of patients have poor prognosis as they are in advanced stage at the time of diagnosis (4).The only curative treatment option of early stage GBC treatment is surgery. Despite R0 resection, the majority of patients develop metastases. The efficacy of adjuvant



chemotherapy and radiotherapy remains uncertain (6).

The GBC is usually grouped with biliary tract cancers, and therefore the clinical characteristics of the disease are not widely reported in the literature. In addition, the benefit of adjuvant treatment for resected GBC is not clear. Observation, adjuvant chemotherapy or chemoradiotherapy are the options reported in the guidelines because of insufficient number of randomized trials.

In this report, we have planned to evaluate the clinical characteristics, adjuvant and metastatic treatment options and the survival of GBC patients from a single research oncology center.

MATERIALS and METHODS

Between January 2011 and October 2017, a retrospective analysis of patients with GBC treated in University of Health Sciences, Dr. A. Y. Ankara Oncology Hospital, Department of Medical Oncology, was performed. The demographic characteristics of the patients (sex, age), smoking history, presence of cholelithiasis, date, and stage of diagnosis (localized, locally advanced, metastatic), type

of surgery (cholecystectomy, extended liver resection), details of adjuvant and palliative therapy, date of last control and exitus status were evaluated from the hospital registry system, retrospectively.

The 7th edition of the AJCC TNM staging for GBC was used. Stage I/II was defined as localized, stage III as locally advanced and stage IV as metastatic disease.

SPSS version 24 was used for statistical analysis. DFS was defined as the time from diagnosis until the date of recurrence (local, regional or distant metastasis) or death. PFS was defined as the time from onset of chemotherapy to progression or death. OS was defined as the time from diagnosis to death. The Kaplan-Meier method was used to construct survival curves. Survival curves compared by log-rank test. The value of $p < 0.005$ was statistically significant.

RESULTS

Of the 58 GBC patients with a median age of 61 years (range:36-85), 45 (77.6%) were female. The characteristics of patients are shown in table 1.

Table 1: Patient Characteristics

	<i>n</i> :58	%
Age -years (Median)	61 (Range:36-85)	
Sex		
Female	45	77.6
Male	13	22.4
Smoking Status		
Smoker	15	25.8
Non-smoker	43	74.1
Gallstones		
Yes	42	72.4
No	16	27.6
Histology		
Adenocarcinoma	55	94.8
Adenosquamous carcinoma	2	3.4
Ring cell carcinoma	1	1.7
Stage		
Localized (Stage I/II)	18	31
Locally advanced (Stage III)	16	27.6
Metastatic (Stage IV)	24	41.4

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Surgery		
Cholecystectomy	10/34	29.4
Extended hepatic resection	24/34	70.5
Adjuvant treatment		
Chemoradiotherapy	12/34	35.2
Chemotherapy	5/34	14.7
Radiotherapy	4/34	11.7
No treatment	13/34	38.2
Stage I/II	9/18	50.0
Stage III	12/16	75.0

The majority of early-stage patients were diagnosed incidentally (82.3%). All localized stage patients (n:18) were completely resected (R0) and only two in 16 locally advanced stage patients were R1 resected (12%). Extended hepatic resection was performed in 70.4% of non-metastatic patients.

All of non-metastatic patients had ECOG performance score 1 and half of metastatic patients had ECOG performance score 2. Half of the patients had at least one comorbid disease.

Thirteen of non-metastatic patients did not receive any postoperative treatment. Nine (69%) of the patients who did not receive postoperative treatment had early stage disease. For the 21 patients who received postoperative treatment, 12 of them had stage III disease and 10 of them were lymph node positive. Chemoradiotherapy was the most preferred adjuvant treatment option (35.2% of resected patients). All of the patients in the chemoradiotherapy group were administered 5-fluorouracil based chemotherapy and radiation target volume was 45 Gy at 1.8 Gy/fraction. Cholecystectomy was performed 29.4% of adjuvant treatment group and extended hepatic surgery was performed 38.2% of non-adjuvant treatment group.

The duration of median follow-up of nonmetastatic patients was 23.7 months. Median DFS was 24.8 months (95% CI: 1.5-48.1) in patients who received postoperative treatment and was not reached in patients who did not receive any postoperative treatment (Fig.1; p=0.103). Two-year DFS was 42.2% for patients who received postoperative treatment, and 57.1% for patients who did not receive postoperative treatment.

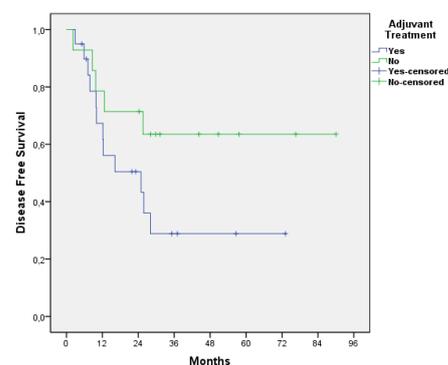


Fig.1: Disease Free Survival For Adjuvant Treatment in Resected Patients (n=34)

In the metastatic stage, 80% of the patients received at least one line of chemotherapy however 25% of patients underwent second-line treatment. Cisplatin/gemcitabine combination was the most preferred regimen in the first-line treatment of choice. Median PFS was 4.3 months (1-12.2) for the first-line chemotherapy.

The median follow-up was 15.3 months for the whole cohort (follow-up for metastatic disease 10.7 months versus non-metastatic disease 26.9 months) Median OS was 38.9 months (95% CI: 9.8-68) for localized stage, 30.6 months (95% CI: 18.7- 42.5) for locally advanced stage and 9.5 months (95% CI: 5-13.9) for metastatic patients. There was no difference between localized and locally advance stages in terms of OS (p:0.68). Overall survival of the metastatic patients was worse than the other two groups (Fig 2; p<0.001)

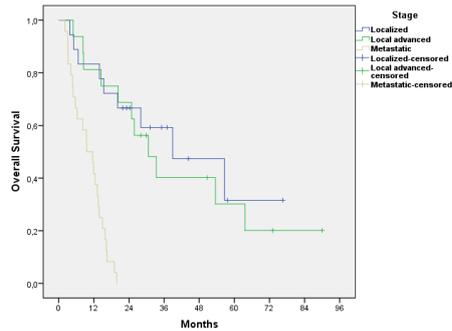


Fig. 2: Overall Survival For Localized, Locally Advanced and Metastatic Stage

Median OS was 28 months (%95 CI: 20.6-35.4) in patients who received postoperative treatment and was not reached in patients who did not receive postoperative treatment. Two year OS was 54% (SE: 11.4%) for patients who received postoperative treatment and 66.7% (SE: %12.2) for patients who did not receive postoperative treatment (Fig 3; p:0.097)

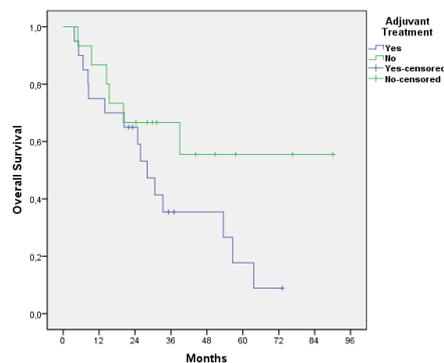


Fig.3 Comparison of overall survival according to adjuvan treatment

DISCUSSION

GBC is a rare and highly fatal carcinoma with different clinical features compared to other biliary tract cancers. In previous studies, GBC was generally assessed with biliary tract cancers. In addition, the benefit of adjuvant treatment in the resected GBC patients is not clear. There is no consensus on the use of adjuvant treatment for completely resected GBC. In this study, we have aimed to evaluate the single center experience with GBC retrospectively.

Similar to previous studies, the median age of 58 patients, of whom 77% were women, was 61 (6,7).The rates of smoking (76.9% for men,

11.1% for women) and cholelithiasis (72.4%) for GBC patients were found to be similar to the other studies which were conducted in different geographic areas (8,9).

In this study, 29.4% of non-metastatic patients underwent cholecystectomy. These patients were not considered as candidates for re-exploration by the surgeon. Due to different reasons (physician preference, co-morbidities), 38.2% of the completely resected patients did not receive adjuvant treatment (50% (n: 9/18) of stage I-II patients and 25% (4/16) of stage III).

Median DFS was 24.8 months in patients who received postoperative treatment and was not reached in patients who did not receive postoperative treatment (p=0.103). Two-year OS was %66.7 for adjuvant treatment group and was %54 for patients who did not receive postoperative treatment. Similarly, Duffy and colleagues found that poorer survival was obtained when adjuvant therapy was added to curative surgery (6).In another study adjuvant chemoradiation had a modest early survival advantage in locally advanced tumors; however, in the long term it was seen that this OS benefit did not continue (10).On the other hand, in the study of Park at al., adjuvant chemotherapy alone group showed a statistically significant improvement in OS compared to no adjuvant treatment or chemoradiotherapy groups (11).In a recent study of patients with gallbladder and biliary tract cancer, it was reported that adjuvant therapy improved DFS of about 3.2 months, but this result was not statistically significant. It was also reported that adjuvant treatment did not result in an OS benefit in this study (12).

In our study, for the non-adjuvant treatment population, despite reaching better DFS and OS outcomes numerically, it was not statistically significant. This may be explained by the low number of patients. Patients were stratified into adjuvant chemoradiotherapy, chemotherapy and radiotherapy arms, but none subgroup analysis were performed due to small number of patients. However, patients who received adjuvant treatment had higher relapse risk than patients who did not receive adjuvant treatment. Additionally, extended hepatic resection ratio was not similar in adjuvant treatment and non-adjuvant treatment group.



In the metastatic group median PFS was 4.3 months and OS was 9.5 months. These results were similar to previous studies (13,14).

The limitations of this study include retrospective study nature and the small number of patients for the evaluation of adjuvant treatment efficacy for the adjuvant treatment group who has a higher risk of relapse. However, it represents real world data. In conclusion, it is needed to prospective, randomized controlled trials for adjuvant treatment efficacy and choice of treatment modalities, in resected GBC.

Conflict of interest: None

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