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Surgery versus no surgery in stage IV gallbladder carcinoma: A propensity score-matched analysis

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ABSTRACT

Objective: Patients with stage IV gallbladder cancer (GBC) have a dismal prognosis. Mostly, they are not amenable to surgical treatment. However, in some of them, a potentially curative surgical resection is possible. There is paucity of the literature comparing survival of patients with surgically resectable stage IV GBC to the patients with unresectable stage IV GBC.

Material and Methods: This retrospective study was conducted on patients with AJCC stage IV GBC who were managed by a surgical unit at a tertiary care center from May 2009 to March 2021. Patients were grouped into either surgery group (cases) or no surgery group (control). Cases were compared to controls for demographic characteristics, clinical parameters, and survival rates. A comparison was made in both unmatched and matched (propensity score matching 1:1 with covariates age, gender, ECOG, chemotherapy, and TNM staging) groups.

Results: The total number of patients with stage IV GBS was 120, out of that, 29 were cases, and 91 were controls. After matching, each group had 28 cases (28 + 28= 56). Post-matching AJCC stage, chemotherapy, and other parameters were equally distributed between the groups (p= 1.00). However, cases had more patients with N2 metastasis (p< 0.001), and controls had more patients with distant metastasis (p< 0.001). Cases vs. controls, overall survival before matching was 22 vs. seven months (p= 0.001) and after matching was 22 vs. 11 months (p= 0.005).

Conclusion: Patients with stage IV GBC amenable to potentially curative surgical resection (R0) have significantly better survival than patients with non-surgical treatment. Therefore, it may be more appropriate to classify these group differently.

Keywords: Carcinoma gallbladder, stage IV, surgery

INTRODUCTION

Gallbladder cancer (GBC) is the most common biliary tract cancer; more than nine per 100.000 Indian women are affected by this cancer every year (1). Overall prognosis of patients with GBC is poor due to delayed presentation and aggressive nature of the disease (2). However, in less than 10% patients, the disease is limited to the gallbladder (3). These early stage gallbladder cancers are those tumours that are limited to the gallbladder without significant lymph node involvement: stage I and stage II (4). Since stage I tumours are difficult to diagnose preoperatively, most are discovered incidentally. They represent a proportion of gallbladder cancer that could be easily cured. A simple cholecystectomy is sufficient for pT1a (mucosal tumour) while a radical resection is indicated for pT1b (muscularis layer involvement) and T2 (stage II) tumours (5). Most stage IV (AJCC VII) patients are beyond surgical resection, so palliative care is offered (2,6). There are some patients who presents with a resectable GBC but classified under stage IV B GBC due to extensive lymph nodes metastasis. Kondo et al. have reported that surgical resection is unlikely to benefit the patients with extensive LN metastasis (N2 stage) (7). However, other authors have reported survival benefit of surgical resection in such patients (8,9). Recently, Chen et al. (2019) have also reported survival benefit in patients with advanced GBC provided that R0 resection has been achieved (9). In view of conflicting literature, we compared the survival outcome of patients with surgically resectable stage IV GBC to those with non-surgical treatment.

MATERIAL and METHODS

This retrospective case-control study was done from a prospectively maintained database of a single unit at a tertiary care centre. A total of 124 patients diagnosed with stage IV gallbladder cancer (as per AJCC 8th edition) were treated from May

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2009-March 2021. One hundred and twenty patients were included in the final analysis after excluding the patients with in-hospital mortality (n= 4).

The following data were collected for all patients from our prospectively maintained records: sex, age, performance status, comorbidities, clinical features, CEA and CA 19-9 levels, primary tumour characteristics (location, T category, lymph nodal status, locoregional involvement, distant metastasis and histological grade according to the 8th edition of the AJCC staging manual), details on chemotherapy, biliary drainage and surgery-associated variables (type of procedure, duration, blood loss, postoperative complications). Complications were graded based on Clavien-Dindo classification (10).

Cases (surgery group, n= 29): Patients with surgically resectable GBC who were diagnosed as stage IV GBC following histopathological examination.

Controls (no surgery group, n= 91): Patients either had inoperable GBC at initial presentation or were no amenable to surgical resection following staging laparoscopy or laparotomy.

These two groups were compared for their baseline demographic characteristics, clinical parameters, and survival rates. Propensity score matching was done between these groups, one to one nearest neighbor match with covariates: age, sex, ECOG, chemotherapy, and TNM staging. The comparisons were made between both unmatched and matched groups (Figure 1).

Patient Management Protocol

All patients with suspected or diagnosed GBC were evaluated clinically which was followed by CBC, LFT, RFT, INR, tumour markers, ultrasonography (USG) of the abdomen and contrast enhanced computed tomography (CECT) of the chest and abdomen. Endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) were utilized selectively. Patients with suspicion of M1 disease underwent guided biopsy and cases with confirmed metastatic GBC were considered for chemotherapy and palliative care. Patients with possible involvement of the bile duct were confirmed with MRCP, and after confirmation, all such patients were referred for preoperative/palliative biliary drainage. Patients with deemed resectable disease would undergo staging laparoscopy. Any suspicious metastatic deposits were sent for frozen histopathological examination (HPE). On negative HPE, curative resection was performed. On positive HPE, palliative procedures such as gastrojejunostomy, colo-colic bypass, or segment 3 bypass were performed depending on the symptoms.

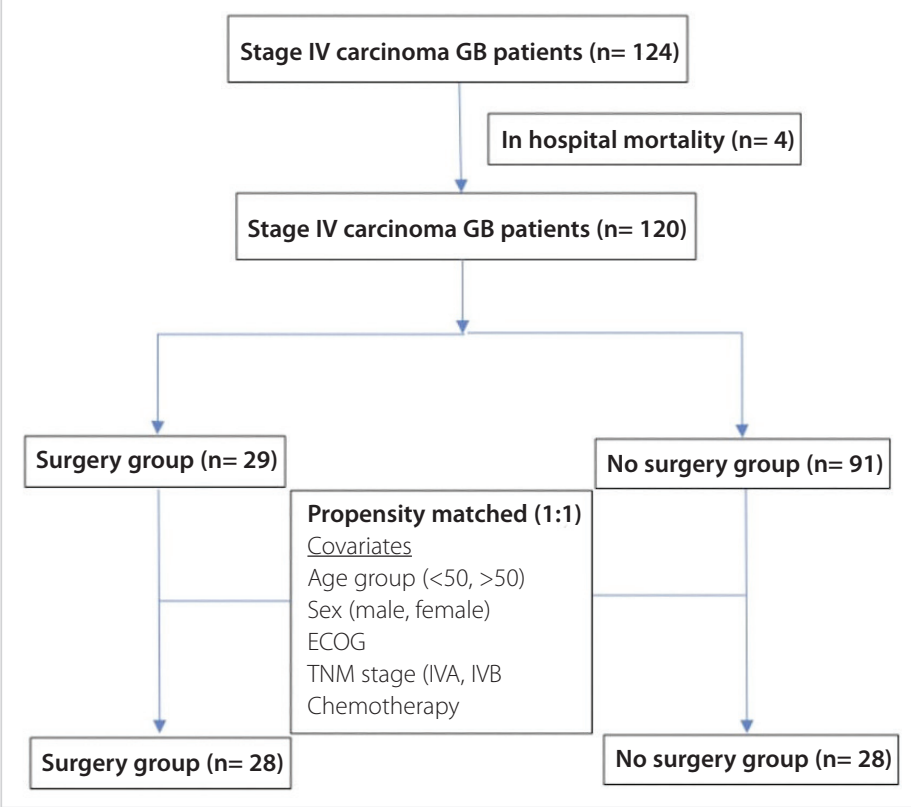

Figure 1. Flow diagram of patient selection.

Surgical Procedure

Standard procedure was a segment 4b, 5 resection (anatomic bi-segmentectomy or extended wedge resection), en-bloc cholecystectomy, and LN dissection along with stations 8, 12 and 13 (11). Frozen section for cystic duct margin was sent and if positive CBD excision was done. CBD excision was also routinely done in all cases if there was visible evidence of infiltration. Those with vascular or extensive liver infiltration were treated with extended right hepatectomy/major liver resections. Also, patients with obvious infiltration of adjacent organs underwent multi-visceral resections like duodenal sleeve/duodenectomy, colonic sleeve/segmental colonic resections, partial pancreatic head resection, and distal gastrectomy.

Follow-up

Patients received palliative or adjuvant chemotherapy after medical oncologists, surgeons and patients' informed consent. They were followed up every three months with physical examination, CEA and CA 19-9, and abdominal ultrasonography during the first year, followed by every six months after that. CECT abdomen was done yearly. Recurrences were identified either clinically or using radiological imaging. If patients could not turn up to the OPD, their status was traced telephonically.

Statistical Analysis

Data analysis was done using the SPSS version 28.0 (IBM Corp., Somers, NY, USA). Parametric numerical data were represented as mean (± standard deviation). Non-parametric numerical data are expressed as median (interquartile range). Categorical and ordinal data were represented as percentages. Parametric numerical data were compared with Student's t-test. Non-parametric numerical data were compared with Mann-Whitney U test. Chi-square test and Fisher's exact test compared categorical and ordinal data. Survival analysis was done using the Kaplan-Meier method and compared with a log-rank test. MedCalc version 20.011 (MedCalc Software Ltd. Ostend, Belgium; https://www.medcalc.org;2021) was used to obtain survival analysis graphs. A p value of ≤0.05 (two-sided) was considered statistically significant.

RESULTS

A total of 124 patients (cases= 33; controls= 91) with stage IV GBC patients were treated during the 12-year period. There were four postoperative deaths in the surgery group. Hence, 120 patients (cases= 29, controls= 91) were included for survival analysis in the unmatched population. After propensity score matching, 28 patients in each group were included for the analysis. Baseline clinical and demographic profiles were similar in both unmatched and matched populations, except poor performance status patients were statistically significantly higher in the control group. Baseline CEA and Ca 19.9 levels were significantly higher in the control group of unmatched and matched populations (Table 1). The control group has significantly more patients with an advanced T stage and M1 disease than cases of unmatched and matched population. Cases have significantly more N2 stages than controls. However, TNM staging was similar between the groups. The most common site of M1 disease was the liver, followed by the peritoneum and supraclavicular lymph node. There was a significant overall survival benefit in cases over the control groups (unmatched: 22 months vs. seven months, $p< 0.0001$; matched: 22 months vs. 11 months, $p= 0.005$) (Figure 2). Overall survival of the patients with stage IV B disease was significant in the cases than the control group (unmatched 14 vs. six months, $p< 0.0001$; matched 14 vs. three months, $p= 0.015$) (Figure 3). In the surgical group, median recurrence-free survival was nine months. The type of procedures performed in the surgery group is listed in Table 2. There were two (6.8%) R1 resections in the surgery group. Both had wedge resection, and the liver margin was positive. A patient in the surgical group had peritoneal nodule; frozen histological examination showed no malignancy and final examination showed malignancy. In the control group, 39 patients were explored; eight patients underwent palliative gastrojejunostomy; segment 3-bypass, colonic resection and anastomosis, and palliative ileo-transverse anastomosis were done in one patient each. Adjuvant chemotherapy, palliative chemotherapy was received in 69% of cases and 51.6% of controls of unmatched group respectively. After matching, 67.9% cases and controls received chemotherapy.

DISCUSSION

The treatment of advanced GBC is still not yet clearly defined. Most GBC patients are diagnosed at an advanced stage despite improved diagnostic modalities. Many of the patients in clinical practice present to us in an advanced stage (12). The prognosis of these patients is poor even after radical resection (13-15). Even studies have suggested that patients with stage IV are unlikely to benefit from surgical resection (16,17). But in recent years, many studies have supported the more aggressive surgical treatment of patients with advanced GBC (18,19).

The reported survival of stage IV GBC patients is 3-4% (13,14). The AJCC TNM staging defines stage IV GBC as the presence of either T4 stage, N2 stage, or M1 disease. However, the N2 stage of AJCC 8th edition differs from the 7th edition by having lymph node positivity rather than lymph node station. This change was brought based on population-based studies (20). The designation of N2 stage beside metastatic disease (M1) in stage IVB implies prognosis N2 stage and M1 are similar (21). The latter precludes surgical resection and the former deserves a resection if the tumour is resectable. This study was attempted to evaluate the survival difference in the two groups.

Table 1. Clinical, demographic, pathological and follow-up profile of the two groups

	Before matching			After matching		
Variables	**Surgery (n= 29)**	**No surgery (n= 91)**	**p**	**Surgery (n= 28)**	**No surgery (n= 28)**	**p**
Age (years)*	50 (45-60)	50 (45-60)	0.629	50 (45-60)	50 (44-63)	0.680
Female**	18 (62.1)	58 (63.7)	0.871	18 (64.3)	14 (56.0)	0.846
ECOG 1/2/3**	3/23/3	5/40/46	0.000#	2/23/3	3/21/4	0.805
Comorbidities**	5 (17.2)	9 (9.9)	0.283	4 (14.3)	1 (3.6)	0.160
Clinical features**						
Pain	24 (82.8)	69 (75.8)	0.436	23 (82.1)	21 (75.0)	0.515
Jaundice	5 (17.2)	23 (25.3)	0.373	5 (17.9)	7 (25.0)	0.515
Abdominal lump	6 (20.7)	27 (29.7)	0.346	6 (21.4)	6 (21.4)	1.000
Stent/PTBD	9 (31.0)	33 (36.3)	0.607	9 (32.1)	8 (28.6)	0.771
IGBC	7 (24.1)	11 (12.1)	0.114	7 (25.0)	2 (7.1)	0.069
GOO	3 (10.3)	10 (11.0)	0.923	3 (10.7)	3 (10.7)	1.000
Biochemical parameters*						
Hemoglobin, gm/dL	10.5 (10.0-11.9)	10.2 (9.6-10.6)	0.022#	10.7 (10.1-11.9)	10.2 (9.7-11.4)	0.243
TLC, cells/m^3	9.0 (7.2-11.6)	7.8 (6.4-9.7)	0.017#	8.7 (7.2-11.9)	7.1 (5.8-8.9)	0.015#
Platelets, cells/	2.30 (1.96-2.40)	2.30 (1.60-3.08)	0.663	2.26 (1.94-2.40)	2.15 (1.75-3.06)	0.718
Creatinine, mg/dL	0.8 (0.6-0.9)	0.9 (0.7-1.0)	0.138	0.8 (0.6-0.9)	0.8 (0.7-0.9)	0.624
Bilirubin, mg/dL	0.9 (0.5-1.4)	1.1 (0.7-7.0)	0.013#	0.8 (0.5-1.6)	0.9 (0.7-6.7)	0.194
Albumin, gm/dL	3.4 (3.1-3.8)	3.4 (3.1-3.8)	0.725	3.4 (3.1-3.8)	3.4 (3.1-3.8)	0.818
CA 19.9, IU/mL	34.0 (18.4-62.0)	87.0 (55.2-208.0)	0.000#	37.0 (18.5-62.0)	107.0 (62.0-437.0)	0.002#
CEA	2.3 (1.2-6.0)	4.3 (2.3-7.3)	0.011#	2.4 (1.3-6.0)	4.5 (2.2-10.6)	0.028#
T stage**						
T2	9 (31.0)	4 (4.4)		09 (32.1)	02 (7.1)	
T3	18 (62.1)	48 (52.7)	<0.001#	17 (60.7)	16 (57.1)	0.007#
T4	2 (6.9)	39 (42.9)		02 (7.1)	10 (35.7)	
N stage**						
N0/Unknown	1 (3.4)	84 (92.3)		1 (6.9)	25 (89.3)	
N1	1 (3.4)	2 (2.2)	<0.001#	1 (3.6)	0 (00)	<0.001#
N2	27 (93.1)	5 (5.5)		26 (92.9)	3 (10.7)	
Metastases**	1 (03.4)	72 (79.1)	<0.001#	1 (3.6)	26 (92.9)	
TNM stage**						
Stage IV A	3 (10.3)	19 (20.9)	0.202	2 (7.1)	2 (7.1)	1.000
Stage IV B	26 (89.7)	72 (79.1)		26 (92.9)	26 (92.9)	
Site of mets						
IAC LN	0 (0)	11 (12.1)		0 (0)	4 (14.3)	
Liver	0 (0)	24 (26.4)		0 (0)	8 (28.6)	
Peritoneal nodule	1 (3.4)	14 (15.4)		1 (3.6)	6 (21.4)	
Omental	0 (0)	4 (4.4)		0 (0)	2 (07.1)	

Table 1. Clinical, demographic, pathological and follow-up profile of the two groups (continue)

Variables	Before matching			After matching		
	Surgery (n= 29)	No surgery (n= 91)	p	Surgery (n= 28)	No surgery (n= 28)	p
SCLN	0 (0)	6 (6.6)	0.897	0 (0)	02 (07.1)	0.813
Malignant ascites	0 (0)	3 (3.3)		-	-	
Krukenberg	0 (0)	2 (2.2)		-	-	
Port site	0 (0)	1 (1.1)		0 (0)	01 (03.6)	
Pulmonary	0 (0)	1 (1.1)		-	-	
Unknown	0 (0)	6 (6.6)		0 (0)	03 (10.7)	
CBD involvement	10 (34.5)	42 (46.5)	0.269	10 (35.7)	12 (42.9)	0.584
PV/HA involvement	3 (10.3)	25 (27.5)	0.040#	3 (10.7)	4 (14.3)	0.565
Pancreas involvement	1 (3.4)	3 (3.3)	0.968	1 (3.6)	2 (7.1)	0.553
Duodenal involvement	6 (20.7)	31 (34.1)	0.174	6 (21.4)	8 (28.6)	0.537
Stomach involvement	1 (3.4)	8 (8.8)	0.341	1 (3.6)	1 (3.6)	1.000
Colon involvement	1 (3.4)	13 (14.3)	0.113	1 (3.6)	2 (7.1)	0.553
Adjuvant/Palliative chemo-therapy	20 (69.0)	47 (51.6)	0.102	19 (67.9)	19 (67.9)	1.000
Partial chemotherapy	8 (27.6)	11 (12.1)	0.046#	8 (28.6)	4 (14.30)	0.193
Overall survival in months, Median (95% CI)	22 (16-24)	7 (6-10)	<0.0001#	22 (16-24)	11 (7-15)	0.005#
Recurrence free survival in months, median (95% CI)	9 (7-15)			9 (7-15)		

BMI: Body mass index, ASA: American Society of Anesthesiologists, TLC: Total leukocyte count, CEA: Carcinoma embryonic antigen, IAC LN: Inter aortocaval lymph node, SCLN: Supraclavicular lymph node, CBD: Common bile duct, PV: Portal vein, HA: Hepatic artery.
*Values expressed in median (inter quartile range).
**Expressed in n (%).
#p value significant.

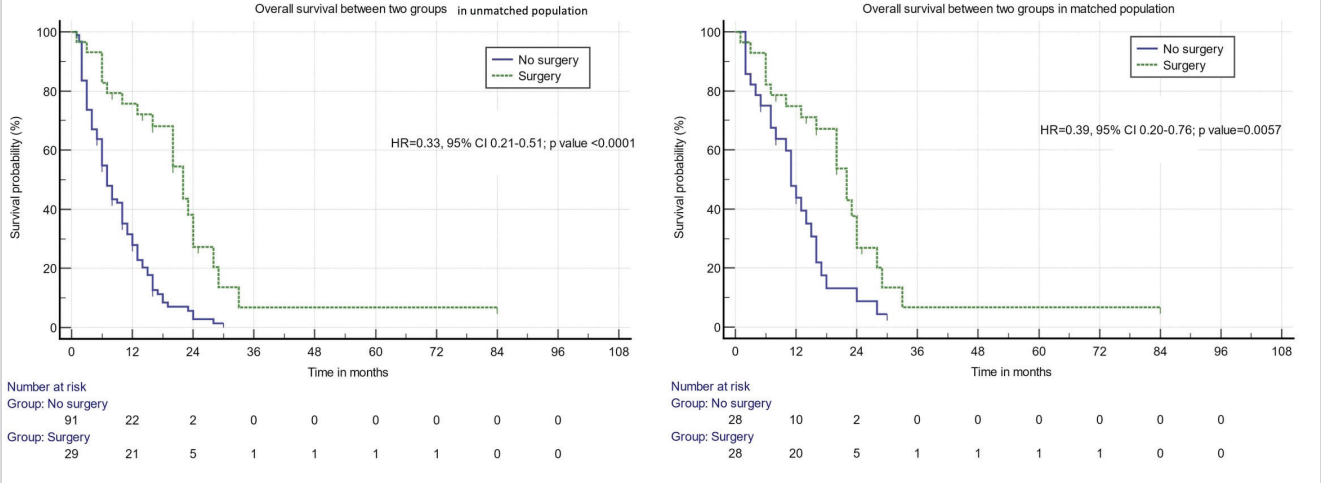

Figure 2. Overall survival between the two groups in unmatched and matched population.

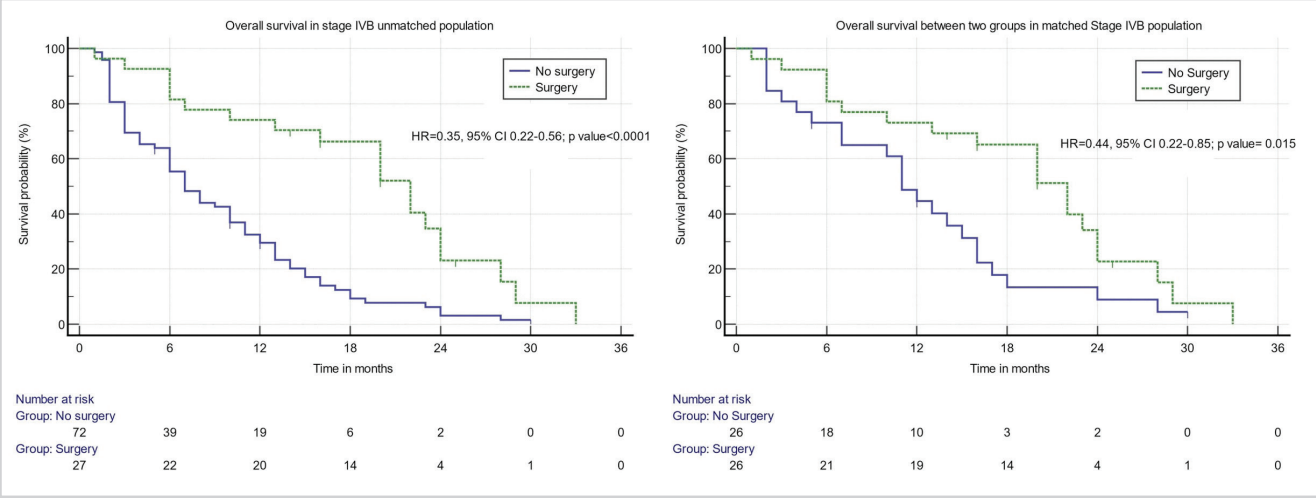

Figure 3. Overall survival between the two groups of stage IV B in unmatched and matched population.

Table 2. Clinical data of the surgical group (n= 29)

Type of procedure	**n (%)**
Extended cholecystectomy-wedge resection (ECW)	13 (44.8)
Alone	7 (24.1)
Plus, duodenal sleeve resection	1 (0.03)
Plus, segmental colon resection plus distal gastrectomy	1 (0.03)
Plus, CBD excision	1 (0.03)
Plus, colonic resection	1 (0.03)
Plus, resection of IVC wall	1 (0.03)
Plus, pancreatico duodenectomy	1 (0.03)
Extended cholecystectomy-S4b + S5 resection	11 (37.9)
Alone	6 (20.0)
Plus, CBD excision	4 (13.7)
Plus, segmental colonic resection of sleeve resection of duodenum	1 (0.03)
Completion cholecystectomy	2 (06.8)
Extended right hepatectomy	1 (03.4)
Extended cholecystectomy-S4, S5, S6 resection plus distal gastrectomy plus CBD excision	1 (03.4)
Extended cholecystectomy-S4, S5, S6 resection plus CBD excision	1 (03.4)
Surgery duration in minutes, median (IQR)	300 (240-410)
Blood loss in mL, median (IQR)	200 (190-300)
Complications	
Bile leak	4 (13.7)
Duodenal leak	1 (0.03)
SSI	6 (20.0)
Paralytic ileus	2 (0.06)

The role of surgery in N2 stage patients were studied with conflicting results. A review by Fong Y et al. in 2001 did not support surgery in N2 stage patients (22). Wakabayshi et al. in 2004 and Chijiiwa et al. in 2007 had shown no benefit for N2 stage patients (15,23). A study by Birnbaum et al. showed that surgery can be offered to N2 stage patients (24). A review by Koerkampet al. in 2014 states that the presence of distant metastases, nodal metastases beyond hepatoduodenal

ligament, and T4 tumours are unlikely to benefit from surgical resection (17). However, Chen et al. have shown that R0 resection has significant superior survival in stage IVA GBC and stage IVB GBC without distant metastases (9). A similar result was seen in the present study.

As per the recent AJCC 8th edition, N2 stage can be confirmed by the presence of more than three lymph nodes metastases, which can usually be detected by postoperative histopathological examination. There were a few N2 patients of the control group in the present study. The diagnosis of the N2 stage was made based on the malignant features of nodes, i.e., loss of hilar structure, matting, circular shape, size >10 mm, and heterogenous internal architecture based on imaging. However, these patients, too, had distant metastases. Interestingly, a study from Japan has suggested confirming N2 disease (>4 regional nodes) by intraoperative frozen section before performing major resections (21).

Chen et al. and Kang et al. could obtain R0 resection in 17% and 15% of stage IV GBC patients, respectively (9,19). In our study, 32/124 (25%) had R0 resection. To achieve such R0 resection, we had less threshold for multi-visceral resection. Surgeons refrain from multi-visceral resection because of significant morbidity and mortality. There were four (12%) postoperative deaths in the present study, and one patient each had Clavien-Dindo grade 3 and grade 4 complications among 33 patients in the surgery group. Stage IV GBC patients in the surgery group were majorly due to the N2 stage. There was a survival benefit in patients who had curative resection in the present study. This suggests that the presence of the N2 stage did not preclude curative resection and had better survival than the patient's distant metastases, which precluded curative resection. However, Kang et al. have shown that the removal site of metastases along with primary in limited metastases to liver and peritoneum had better survival than palliative surgery alone (19).

The AJCC system has some stages with heterogenous groups with different long-term outcomes, especially in advanced stages of GBC (25). Median survival was 22 months in patients who underwent surgery with curative intent for stage IV GBC vs. 11 months in patients not treated by curative surgical intervention. Stage IVB includes patients with N2 stage or M1 disease; the former is a potentially resectable group and the latter does not deserve resection. A similar result has been shown by a study that some patients with N2 disease were able to undergo R0 resection, in which regional lymph nodes are routinely removed during radical GBC resection and had longer survival times than patients with M1 disease (20). The study results may prompt us to say that patients with stage IV amenable to R0 resection may be placed differently in the AJCC classification system. However, this needs to be validated with larger sample studies.

Thus, gallbladder cancer patients with adjacent organ involvement and significant nodal disease still benefit from radical resection. With new improvements in multimodality management like neoadjuvant and adjuvant chemotherapy protocols, the combination of surgery and CT may improve the survival rate of patients with advanced GBC.

There were a few limitations in the study. The retrospective nature of the study introduces selection bias. Although matching the groups with factors affecting the survival was attempted to reduce such bias, it cannot remove the effect of unknown confounders of survival. Tumour markers of the control group were significantly higher than those of the cases, suggesting a higher tumour burden in the control group.

CONCLUSION

Patients with surgically resectable stage IV GBC have significantly better survival than patients with unresectable stage IV GBC. Thus, in stage IV GBC without M1 disease, R0 resection should be the goal whenever possible, and N2 nodal metastasis does not preclude a curative resection.

Ethics Committee Approval: This study was approved by Maulana Azad Medical College and Associated Hospital Institutional Ethics Committee (Decision no: 427, Date: 14.11.2022).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - HN, PN, SK; Design - SK, PN; Supervision - HN; Fundings - HN; Data Collection and/or Processing - PN, SK; Analysis and/or Interpretation - PN, SK; Literature Search - PN; Writing Manuscript - PN, SK; Critical Reviews - HN.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Evre IV safra kesesi karsinomlarında cerrahi tedaviye karşın cerrahi olmayan tedavi: Skor-eşleştirilmiş eğilim analizi

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ÖZET

Giriş ve Amaç: Dördüncü evre safra kesesi kanseri (GBC) olan hastaların prognozu kötüdür. Çoğunlukla cerrahi tedaviye uygun değildirler. Ancak bazılarında potansiyel küratif cerrahi rezeksiyon mümkündür. Cerrahi olarak rezeke edilebilir evre IV GBC'li hastaların sağkalımını, rezeke edilemeyen evre IV GBC'li hastalarla karşılaştıran çok az literatür vardır.

Gereç ve Yöntem: Bu retrospektif çalışma, Mayıs 2009'dan Mart 2021'e kadar üçüncü basamak bir merkezdeki cerrahi birim tarafından tedavi edilen AJCC evre IV GBC'li hastalar üzerinde gerçekleştirildi. Hastalar, ameliyat grubu (olgular) veya ameliyatsız grubu (kontroller) olarak gruplandırıldı. Olgular, demografik özellikler, klinik parametreler ve hayatta kalma oranları açısından kontrollerle karşılaştırıldı. Hem eşleşmeyen hem de eşleştirilmiş (ortak değişkenler yaş, cinsiyet, ECOG, kemoterapi ve TNM evrelemesiyle 1:1 eşleşen eğilim skoru) gruplarında bir karşılaştırma yapıldı.

Bulgular: Evre IV GBC'li toplam hasta sayısı 120 idi, bunun 29›u vaka ve 91'i kontroldü. Eşleştirmeden sonra her grupta 28 vaka vardı (28 + 28= 56). Eşleştirme sonrası AJCC evresi, kemoterapi ve diğer parametreler gruplar arasında eşit olarak dağıldı (p= 1,00). Ancak olgularda N2 metastazı olan hasta sayısı daha fazlaydı (p< 0,001), kontrol grubunda uzak metastazı olan hasta sayısı daha fazlaydı (p< 0,001). Olgular ve kontroller, eşleştirmeden önceki genel sağkalım 22'ye karşı yedi aydı (p= 0,001) ve eşleştirmeden sonra 22'ye karşı 11 aydı (p= 0,005).

Sonuç: Potansiyel olarak küratif cerrahi rezeksiyona (R0) uygun evre IV GBC'li hastalar, cerrahi olmayan tedavi alan hastalara göre önemli ölçüde daha iyi hayatta kalma oranına sahiptir. Bu nedenle bu grupları farklı şekilde sınıflandırmak daha uygun olabilir.

Anahtar Kelimeler: Karsinom, safra kesesi, evre IV, cerrahi

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