Resection of Isolated Port Site Metastasis in Gall Bladder Cancers—Careful Selection and Perioperative Systemic Therapy May Improve Outcomes

Vivek Agarwala¹ · Anant Ramaswamy¹ · Sanyo Dsouza¹ · Nikhil Pande¹ · Mahesh Goel² · Shraddha Patkar² · Vikas Ostwal¹

Received: 16 October 2017 / Accepted: 2 August 2018 / Published online: 10 August 2018

© Indian Association of Surgical Oncology 2018

Abstract

Excision of port site (PSE) for patients having undergone laparoscopic cholecystectomy (LC) is not a standard recommendation. We retrospectively evaluated a cohort of patients with isolated PSM without any prior cancer-directed therapy who were assessed for resection between March 2012 and July 2016 at Tata Memorial Hospital, Mumbai. Eleven of a total 13 patients underwent wide excision for PSM in the given time period. Upfront resection was undertaken in six patients while seven patients received neoadjuvant chemotherapy (NACT) and two received neoadjuvant chemo radiotherapy (NACTRT) prior to attempted resection. With the median follow-up of 22 months, post PSM disease-free survival (DFS) was 20 months (95% CI 15–24 months) and overall survival (OS) was 37 months (95% CI 22–51 months). Careful selection along with an aggressive management strategy may be a step forward in the treatment of patients with isolated PSM.

Keywords Gall bladder cancer (GBC) · Port site metastasis · Port site excision · Palliative chemotherapy

Introduction

India has sharp differences in geographical distribution of gallbladder cancer (GBC) occurrence, with the highest incidences registered in registries from North and Northeast regions [1]. Laparoscopic cholecystectomy (LC) is one of the commonest surgeries performed today for gall stone disease especially in endemic areas of India. However, LC also results in patients being diagnosed as incidentally detected gall bladder cancer (iGBC) where GBC gets diagnosed on histopathological evaluation presuming initially benign GB disease. Further treatment of these patients is often not undertaken due to various logistic or socioeconomic reasons. This sets the stage for the emergence of port site metastases (PSM), whose growing incidence has coincided with the increase in laparoscopic surgeries. Drouard et al. reported the first case of port site metastasis in an unsuspected gallbladder carcinoma [2] while Paulocci's literature review

concluded that 14–30% patients post LC detected iGBC developed PSM [3]. Studies have shown a higher incidence of PSM occurrence after LC (10.3%) compared to open cholecystectomies (7%) performed for iGBC [4, 5]. Excision of port site (PSE) for patients undergoing LC is not a standard recommendation [6], with some data to suggest that patients with PSM are associated with poorer outcomes [7, 8]. Not all PSM may be an indicator of systemic disease and some selected patients may have disease solely due to local seedling but it is difficult to identify these two groups separately. Therefore, a carefully selected multidisciplinary approach in which isolated PSM are treated with a combination of systemic chemotherapy and resection may alter outcomes in potentially good risk patients.

At our institution, we treated patients with the only PSM (oligo metastatic disease) as site of recurrences with a combination of resection and systemic chemotherapy. We present a case series of carefully selected patients with PSM who were treated with this approach.

Material and Methods

We retrospectively evaluated patients with isolated PSM without prior any treatment for iGBC who were assessed for

✉ Vikas Ostwal
dr.vikas.ostwal@gmail.com

¹ Department of Medical Oncology, Tata Memorial Centre (TMH), E. Borges Road, Parel, Mumbai 400012, India

² Department of Surgical Oncology, TMH, Mumbai 400012, India

PSM resection between March 2012 and July 2016 at Tata Memorial Hospital, Mumbai. None of these patients had undergone any neoadjuvant therapy or radical surgery (revision cholecystectomy) after the diagnosis of iGBC. Information regarding this patient cohort was extracted from a prospectively maintained metastatic GBC database. Demographic data and baseline clinical data were collected retrospectively from existing case records. Findings of F18 FDG PETCT performed as an institution protocol to rule out disease at other sites were noted. Treatment details captured included disease-free interval post prior index surgery, the use of chemotherapy, and response rates when chemotherapy was used prior to surgical resection.

Inclusion criteria:

1. Patient who was diagnosed to have isolated PSM based on clinical- and imaging-based evaluation
2. Had undergone simple cholecystectomy and found to have incidental gall bladder cancer

Exclusion criteria:

1. Has received any neoadjuvant therapy prior to inclusion
2. Has undergone radical surgery after the diagnosis of iGBC
3. Radiological evidence of metastatic disease beyond PSM

In patients who received neoadjuvant therapy, gemcitabine cisplatin (GC) and gemcitabine oxaliplatin (GO) regimes were used, while patients who received neoadjuvant chemoradiation, gemcitabine or capecitabine was given concurrently with radiotherapy (RT). The doses used were as follows:

GC: gemcitabine 1000 mg/m² + cisplatin 25 mg/m² D1 and D8 every 21 days.

GO: gemcitabine 1000 mg/m² D1 + oxaliplatin 100 mg/m² every 14 days.

Gem RT: gemcitabine 300 mg/m² weekly from D1 to last day of concurrent RT

Cape RT: capecitabine 1650 mg/m² daily from D1 to last day of concurrent RT

Radiotherapy: 50 Gy divided over 25 fractions, given concurrently with either gemcitabine or capecitabine

The time from development of PSM excision to the time of recurrence was considered as disease-free survival (DFS). The time from development of PSM to the last follow-up or death was considered as overall survival (OS). Data was entered in SPSS software version 21 and used for analysis. Descriptive statistics including median, frequency, and percentage for categorical variables was used to describe age, gender distribution, and other such variables. Median DFS and OS were estimated by the Kaplan Meier method. Responses were

calculated by RECIST 1.1 [9] criteria, with responses reported as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), where feasible. If RECIST was not calculable, then the response was quantified based on collusion between treating physician and the gastrointestinal radiologist as follows: CR—disappearance of all baseline lesions; PR—significant regression of lesions at baseline; SD—no significant regression of baseline lesions and no new lesions; and PD—appearance of new lesions or significant increase in baseline lesions. All survivals were calculated and described as a median value.

Results

Baseline Staging and Neoadjuvant Therapy

Three hundred ninety-six patients with metastatic GBC were evaluable of whom 13 patients satisfied our inclusion and exclusion criteria for isolated PSM. Of the 13 patients with isolated PSM, 11 underwent surgery, either upfront or post neoadjuvant therapy. Ten patients (77%) were females and the median age was 57 years (range 35 to 69). Histopathology was adenocarcinoma in all patients. All patients had undergone laparoscopic cholecystectomy and were detected to have iGBC. None of the patients received any cancer-directed therapy like revision cholecystectomy, chemotherapy, or radiation prior to diagnosis with PSM. PET-CECT scan was done in 12 patients on diagnosis with PSM, while one patient underwent MRI. All patients had PSM as the solitary site of recurrence. Six patients underwent upfront surgery with a wide excision for PSM while seven patients received neoadjuvant therapy. Of these seven patients, five patients received chemotherapy alone while two patients received additional neoadjuvant chemoradiation (median number of chemotherapy cycles—4). The two patients receiving neoadjuvant chemo radiation (NACTRT) after NACT received the same in view of poor response to chemotherapy. Of the seven patients who received neoadjuvant therapy, four patients received GC while another three received GO, respectively. Of the two patients who received additional neoadjuvant intent concurrent chemoradiation, one patient received gemcitabine while the other patient received capecitabine concurrently.

Responses and Surgical Details

Of the seven patients receiving NACT, four patients had PR, two had SD, and one patient developed PD only at local site. Eleven patients (out of the total cohort of 13) underwent PSE, with wide excision and meshplasty with polypropylene mesh, while 2 patients did not undergo surgery in view of progressive disease. Of the 11 patients who underwent surgery, nine patients received adjuvant chemotherapy. All patients

underwent average blood loss which was 50 ml (minimal—200 ml). With a median hospital stay for 5 days (2–10 days), two patients required re-exploration for hematoma and bowel evisceration. Two patients had positive resection margins on final histopathology. The details of treatment and outcomes are summarized in Table 1.

Survival Rates

With the median follow-up of 22 months (7–45 months), OS was 37 months (95% CI 22–51 months) (Fig. 1) and DFS was 20 months (95% CI 15–24 months) (Fig. 2).

Discussion

Port site metastasis can occur at the extraction site during LC, possibly due to seeding at the time of surgery. However, studies have also suggested additional mechanisms such as intra-operative tumor perforation, trocar injuries, tumor handling, specimen extraction without using the bag, CO₂ insufflation leading to increased intra-peritoneal pressure, decrease in cellular immunity, and hematogenous dissemination indicating aggressive disease biology [4, 10, 11].

Port site excision, as a routine procedure along with radical revision surgery, has not shown any survival benefit and is not considered as a standard recommendation [6, 12, 13]. However, PSM radical excision in the absence of other metastatic disease has shown survival benefit [10, 14]. Selecting patients for such an approach may hold the key to improving outcomes, considering that patients with disease sites besides PSM may have poorer outcomes [7, 8, 11]. Addition of chemotherapy in this selected group of patients may have a role in taking care of micro metastasis, which might add to improved survival.

18F-fluorodeoxyglucose (18F-FDG) has been considered a useful staging investigation for PSM after laparoscopic surgery [15]. All except one patient in our study cohort had underwent F18-FDG PETCT to rule out disease at other sites.

Whether PSM are due to “local” or “systemic” factors, it is still debatable and combining systemic chemotherapy with PSE may entail combating both aspects of the biology of PSM. Besides, the use of neoadjuvant chemotherapy, as used in 7 out of 13 our patients, is an in vivo indicator of disease biology and may help select patients for or against PSE. Five of seven patients underwent PSM resection after NACT.

Eleven of the 13 patients underwent PSE with acceptable morbidities and such an approach leads to improved survival

Table 1 Clinical characteristics and outcome of individual patients

Serial no.	Neoadjuvant therapy	Upfront PSE	Underwent PSE	Adjuvant therapy	Recurrence/progression	Current status	Comments
1	N	Y	Y	Y	Y	D	
2	N	Y	Y	Y	Y	A	
3	N	Y	Y	Y	Y	A	
4	N	Y	Y	Y	N	A	
5	N	Y	Y	Y	N	A	
6	Y	N	Y	Y	Y	A	
7	Y	N	Y	Y	N	A	
8	Y	N	Y	Y	Y	D	Received chemoradiation post chemotherapy in view of poor response to NACT
9	Y	N	Y	Y	N	A	Received chemoradiation post chemotherapy in view of poor response to NACT
10	Y	N	Y	N	Y	A	
11	N	Y	Y	N	Y	D	
12	Y	N	N	N	Y	D	Patient had progressive metastatic disease on NACT intent chemotherapy; did not undergo PSE
13	Y	N	N	N	Y	D	Patient had progressive metastatic disease on NACT intent chemotherapy; did not undergo PSE

N, no; Y, yes; PSE, port site excision; NACT, neoadjuvant chemotherapy; D, dead; A, alive

Fig. 1 Overall survival in months after port site metastatectomy

Fig. 2 Disease-free survival in months after port site metastatectomy

along with perioperative chemotherapy in carefully selected patients as opposed to considering only palliative intent chemotherapy without resection.

Within the confines of a small cohort of patients as in our series, our strategy of combining chemotherapy and PSE in a selected group of oligometastatic patients has yielded favorable survival outcomes as compared to previously published data [10, 13, 14, 16]. A median survival of 37 months in this cohort is also a reflection of careful patient selection as well as the potential benefits of combining PSE and chemotherapy.

PSM is one of the rarer forms of gall bladder cancer metastatic disease and treatment strategies may have to be based on data from large registries or case series. Our series is one such addition to the growing literature and emphasizes a method to improve outcomes in this group of patients.

Conclusion

Careful selection of patients with isolated PSM along with an aggressive management strategy of combining PSM excision and perioperative chemotherapy may be a step forward in the treatment of this rare group of patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

- Mhatre SS, Nagrani RT, Budukh A, Chiplunkar S, Badwe R, Patil P, Laversanne M, Rajaraman P, Bray F, Dikshit R (2016) Place of birth and risk of gallbladder cancer in India. *Indian J Cancer* 53: 304–308
- Drouard F, Delamarre J, Capron JP (1991) Cutaneous seeding of gallbladder cancer after laparoscopic cholecystectomy. *N Engl J Med* 325:1316
- Paolucci V (2001) Port site recurrences after laparoscopic cholecystectomy. *J Hepatobiliary Pancreat Surg* 8:535–543
- Berger-Richardson D, Tyler RC, Marina E et al (2017) Trends in port-site metastasis after laparoscopic resection of incidental gallbladder cancer: a systematic review. *Surgery* 161(3):618–627
- Lundberg O (2000) Port site metastasis after laparoscopic cholecystectomy. *Eur J Surg Suppl* 11:27–30
- Aloia TA, Jarufe N, Javle M et al (2015) Gallbladder cancer: expert consensus statement. *HPB (oxford)* 17:681–690
- Shoup M, Fong Y (2002) Surgical indications and extent of resection in gallbladder cancer. *Surg Onco J Clin N Am* 11:985–994
- Povoski SP, Quellette JR, Chang WW et al (2004) Axillary lymph node metastasis following resection of abdominal wall laparoscopic port site recurrence of gall bladder cancer. *J Hepatobiliary Pancreat Surg* 11:197–202
- Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 45:228–247
- Lundberg O, Kristoffersson A (1999) Port site metastasis from gallbladder cancer after laparoscopic cholecystectomy. Results of a Swedish survey and review of published reports. *Eur J Surg* 165: 215–222
- Z'Graggen K, Birrer S, Maurer CA et al (1998) Incidence of port site recurrence after laparoscopic cholecystectomy for preoperatively unsuspected gallbladder carcinoma. *Surgery* 124:831–838
- Fuks D, Regimbeau JM, Pessaux P et al (2013) Is port site resection necessary in the surgical management of gallbladder cancer? *J Visc Surg* 150:277–284
- Maker AV, Butte JM, Oxenberg J et al (2012) Is port site resection necessary in the surgical management of gall bladder cancer? *Ann Surg Oncol* 19:409–417
- Ciulla A, Romeo G, Genova G, Tomasello G, Agnello G, Cstronovo G (2006) Gallbladder carcinoma late metastasis and incisional hernia at umbilical port site after laparoscopic cholecystectomy. *G Chir* 27:214–216
- Hu JB, Sun XN, Xu J, He C (2008) Port site and distant metastases of gallbladder cancer after laparoscopic cholecystectomy diagnosed by positron emission tomography. *World J Gastroenterol* 14:6428–6431
- Hamila F, Letaief R, Khnissi M, Derbel F, Mazhoud J, Ben Ali A, Dahmene Y, Ben Hadj Hamida R (2006) Port site recurrence after laparoscopic cholecystectomy. *Tunis Med* 84(11):697–700