DOI:10.1111/j.1477-2574.2010.00192.x

HPB

ORIGINAL ARTICLE

Hepatic resection for metastatic endometrioid carcinoma

Brett Knowles[1], Christopher O. C. Bellamy[2], Anca Oniscu[2] and Stephen J. Wigmore[1]

Departments of [1]Surgery and [2]Pathology, Royal Infirmary of Edinburgh, Edinburgh, UK

Abstract

Background: The role of hepatic resection for gynaecological tumours is not well defined as evidence on the subject is lacking. This article describes a tertiary hepatopancreatobiliary unit's experience with hepatic resection for liver metastases from endometrioid primaries.

Methods: Five women in whom liver metastases developed at 11 months to 10 years post-primary resection are presented. These patients subsequently underwent hepatic resection with disease-free survival of 8–66 months post-resection.

Results: Outcomes in this patient series support hepatic resection in the face of isolated liver metastasis.

Conclusions: The authors advocate that patients with hepatic deposits should be referred to specialist hepatobiliary units with a view towards hepatic resection and a subsequent good outcome.

Keywords

endometrial carcinoma, liver metastasis, liver resection

Received 19 March 2010; accepted 2 May 2010

Correspondence

Stephen J. Wigmore, Department of Surgery, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA, UK. Tel: + 44 131 242 3615. Fax: + 44 131 242 3617. E-mail: s.wigmore@ed.ac.uk

Introduction

The incidence of endometrial cancer is 18.7 cases per 100 000 people in the UK and 5646 patients are newly diagnosed each year.[1] It is estimated that up to 50% of patients who die as a result of endometrial cancer will demonstrate hepatic metastases at autopsy.[2] Liver resections for metastatic cancer have been reported for over a century, but it was not until Foster and Berman published their landmark report in 1977 that liver resections for metastatic disease began to achieve general acceptance.[3,4] In the setting of metastatic colorectal cancer, numerous studies have shown that not only is surgical resection safe, but it also offers the only potential for cure.[2,4] For symptomatic metastatic neuroendocrine tumours, hepatic resection provides longterm palliation and cure in a minority of cases.[4] Unfortunately, the role of hepatic resection for gynaecological tumours is less well defined. A plausible reason for this is that gynaecological carcinomas that metastasize to the liver tend to do so in the setting of systemic or regional dissemination, rendering hepatic resection inappropriate. Occasionally, however, isolated metastasis occurs in which hepatic resection may be beneficial. This article presents a patient series demonstrating a tertiary referral hepatopancreatobiliary unit's experience of hepatic resection for liver metastases from endometrioid primaries.

Materials and methods

A database containing details of all patients who underwent liver resection at the Royal Infirmary of Edinburgh during a 10-year period from 1 January 2000 to 31 December 2009 was examined to identify patients who had undergone liver resection for endometrioid cancer. These patients formed the basis of this study. The patients were cross-referenced by searching the pathology database to ensure that no cases of liver resection for endometrioid carcinoma had been missed. Pathological confirmation of the diagnosis was made in all patients. A selective literature review was also undertaken using the search terms 'liver resection', 'endometrioid', 'ovarian', 'endometrial' and 'non-colorectal' in combination with the Boolean operator 'AND'.

Results

During the 10-year period of the study (1 January 2000 to 31 December 2009), 617 patients underwent liver resection for a variety of different causes, of which colorectal cancer was the most common. Five patients underwent liver resection for endometrioid cancer during the study period, representing 0.8% of the total patient group. These patients' details are presented in Table 1. Patients 1–4 were given either adjuvant radiotherapy or

Table 1 Characteristics of patients undergoing liver resection for endometrioid carcinoma. Age refers to age at liver surgery

Patient number	Age, years	Cancer stage	Primary operation	Adjuvant treatment	Secondary operation	Follow-up, months	Status
1	59	Endometrial grade 2, stage IIIC	TAH + BSO + lymphadenectomy	Radiotherapy	Right trisegmentectomy + resection of diaphragm en bloc + prosthetic reconstruction	48	Alive, disease-free
2	65	Ovarian grade 3, stage IC	TAH + BSO + omentectomy	6 cycles carboplatin	Segment VI resection + cholecystectomy	61	Alive, disease-free
3	59	Endometrial grade 2, stage IIIA	TAH + BSO	6 cycles carboplatin	Right trisegmentectomy followed by video-assisted thoracoscopic left upper lobectomy as a separate procedure	66	Alive, disease-free
4	38	Mixed serous ovarian grade 3, stage IIIc	TAH + BSO + appendicectomy + omentectomy + paraaortic lymphadenectomy	6 cycles carboplatin Paclitaxel Gemcitabine	Right trisegmentectomy + lymphadenectomy + excision of nodule	8	Alive, pulmonary metastases
5	46	Endometriosis	TAH + BSO + appendicectomy	–	Right trisegmentectomy radical bile duct excision + lymphadenectomy	12	Alive, disease-free

TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy

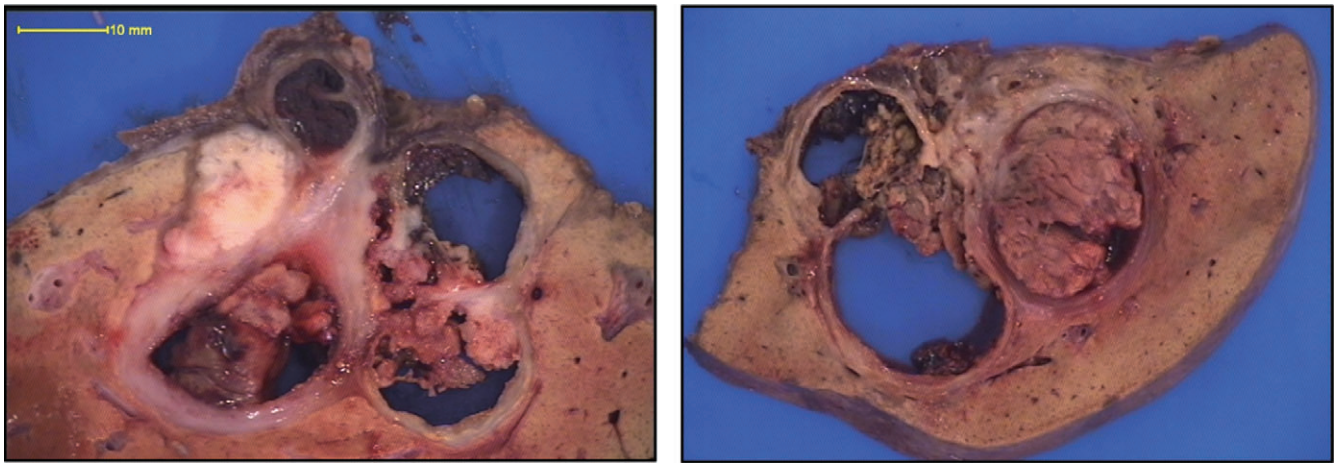

Figure 1 Macroscopic appearance of endometrioid adenocarcinoma: solid and cystic tumour arising in pre-existing hepatic and perihepatic endometriosis

chemotherapy after gynaecological surgery for the primary tumour. Patient 5 is believed to have developed endometrioid cancer against a background of endometriosis and did not have a primary gynaecological malignancy (Figures 1 and 2). No patient was given planned adjuvant chemotherapy following liver resection, but patient 4, who developed lung metastases, subsequently went on to receive palliative chemotherapy as part of a clinical trial.

Table 2 Embryonic derivatives of ovarian adenocarcinoma

Ovarian adenocarcinoma histological subtype	Mullerian derivative
Serous	Fallopian tube
Mucinous	Endocervix
Endometrioid (8%)	Endometrium
Clear cell	Endometrial glands during pregnancy

Discussion

The liver is a common site of metastasis for solid tumours. Although surgical resection is now considered standard treatment for resectable metastases from colorectal primaries, the data on liver resections for gynaecological, particularly endometrial, carcinoma are sparse.

In this series five women underwent resection of liver deposits of endometrioid adenocarcinoma. Four patients had metastatic

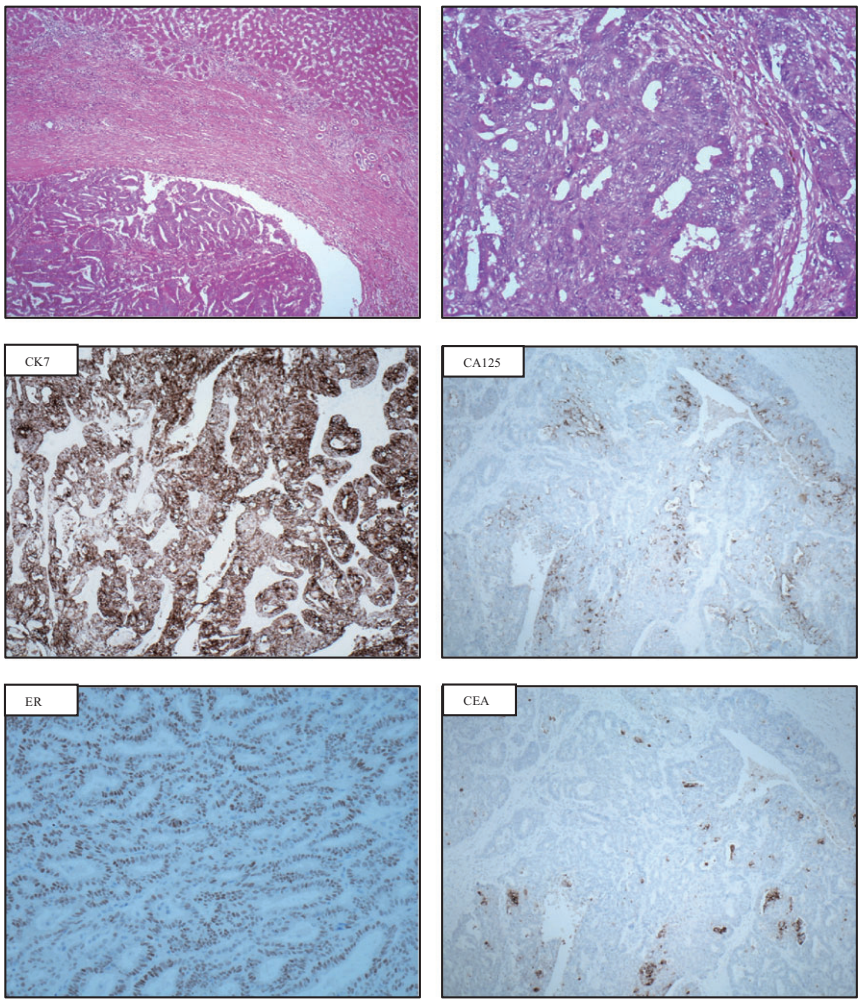

Figure 2 Histology of endometrioid adenocarcinoma arising in pre-existing hepatic and perihepatic endometriosis showing tumour (T) and surrounding liver (arrows) (upper two panels). Immunohistochemistry shows a classical pattern of staining: both cytokeratin 7 (CK7) and oestrogen receptor (OR) staining are diffuse; CA125 staining is patchy, and the squamous morules show focal carcinoembryonic antigen (CEA) staining. CK20 is negative (not shown)

disease from either ovarian or uterine primaries. The fifth patient is unusual as she is likely to have developed a focus of carcinoma arising from a hepatic deposit of endometriosis (Table 1). Hepatic endometriosis is an extremely rare entity of which fewer than 20 cases have been reported in the literature, although malignant transformation occurs in up to 23% of patients.[5,6]

The terminology used to describe gynaecological malignancies can be confusing to clinicians who are not used to dealing with these diseases. The fallopian tubes, uterus, wall of the vagina and the surface epithelium of the ovaries share a common embryonic origin. They develop from mesothelium lining, the gonadal ridge, which is invaginated to form the Müllerian ducts. When a neoplastic process arises in the epithelium of the ovaries, it resembles a variety of Müllerian-type differentiation, with histological subtypes representing the shared embryological derivatives of the ovarian surface epithelium (Table 2.)

Thus ovarian endometrioid adenocarcinoma is thought to arise from deposits of endometriosis in the ovary; up to 10% of cases demonstrate a synchronous deposit of endometriosis and 10% show a synchronous endometrial carcinoma with the same histological features.[7] To date, the histological subtype of ovarian cancer has neither been identified as an independent prognostic variable nor influenced treatment.[8]

Endometrial carcinoma has four histological subtypes of which the endometrioid subtype is the most common, affecting 75–80% of patients. Unlike in ovarian carcinoma, it is an important independent variable for prognosis and potential treatment. Endometrioid endometrial adenocarcinoma has a better prognosis than the other subtypes (papillary serous, clear cell or carcinosarcoma) and tends to fail locally. These tumours can, however, metastasize to the lung, bone, brain or liver as solitary deposits amenable to resection, whereas other histological subtypes tend to

Table 3 Studies reporting outcomes post-resection of gynaecological hepatic metastases

Study	Number of patients in series with non-colorectal/non-neuroendocrine liver metastases	Characteristics of gynaecological metastases	Outcome(s)
Adam *et al*. 2006[1]	1452 over 21 years	126 (9%) gynaecological 65 ovarian 43 uterine 18 other (not reported)	Ovarian 50% 5-year overall survival Uterine 35% 5-year overall survival Overall 48% 5-year overall survival In favourable tumour type
O'Rourke *et al*.[17]	115 over 20 years (5% all resections for liver metastases at centres)	12 of 32 in genitourinary group 12 (12%) all ovarian	Genitourinary group 39% 5-year overall survival Grouped with renal, bladder, cervix and adrenal tumours
Weitz *et al*.[18]	141 over 21 years (1001 resections for other metastases in last 13 years)	19 (14%) of 39 in reproductive tumours group 12 ovarian 4 endometrial 2 cervical 1 fallopian 20 testicular	Reproductive tumours Actuarial cancer-specific 3-year survival 78% Yet to reach median survival
Ercolani *et al*.[20]	83 over 12.5 years	9 (11%) gynaecological 8 ovarian 1 endometrial	Genitourinary group 5-year survival: 42% Best outcome with median survival 52 months Grouped with renal and testicular tumours
Elias *et al*.[19]	120 over 12 years (22% of 538 liver resections over the same period)	6 (4%) gynaecological	Approximately 80% at 3 years

recur diffusely in the peritoneal cavity and to behave more like ovarian epithelial malignancies.[7]

Pathological genetic studies of ovarian cancer suggest a shared molecular origin for each histological subtype. Each is characterized by distinctive, although not unique, molecular defects in signal pathways that correlate with phenotype and may offer sites for targeted molecular therapy. Similar genetic abnormalities are seen in endometrioid adenocarcinoma arising from either the ovary or the endometrium.[8]

Liver metastases from ovarian or endometrial cancer at the time of presentation can represent true haematogenous spread or peritoneal seeding. Liver capsule metastases in ovarian cancer are considered to represent stage IIIB or C disease and parenchymal metastases from either primary to represent stage IV.[9] Since the introduction of platinum-based chemotherapy for gynaecological malignancies in the 1980s, overall survival in stage IV disease is less than 20% after optimal cytoreduction.[10] Resection of liver capsule metastases as part of cytoreductive surgery followed by chemotherapy for ovarian and endometrial malignancy has been shown to be feasible and may prolong survival.[2,11–13] In each of the first four patients in the current series, liver metastases occurred as a metachronous event following the completion of radiotherapy or chemotherapy. Chemosensitivity of the primary tumour may therefore not be a prerequisite for a successful outcome of liver resection. What is probably more important is evidence of stable pelvic disease after resection of the primary tumour. No patients with synchronous liver metastasis and endometrioid cancer have been treated or referred for treatment in this centre.

Historical reports have shown no 5-year survivors after hepatic resection for parenchymal gynaecological metastases.[14] Only two reports of hepatic resection in endometrioid endometrial cancer have been published.[2,15] One of these involved a grade 2 and the other a grade 3 case and primary surgical treatment was total abdominal hysterectomy and bilateral salpingo-oophorectomy followed by pelvic radiotherapy.[15] Disease-free survival was 15 months and 70 months, respectively. Both patients underwent trisegmentectomy followed by adjuvant chemotherapy.[15] One patient went on to develop a single brain metastasis 19 months after liver resection, for which she underwent surgical resection and radiation.[2] She went on to survive for 33 months after liver resection. The other patient unfortunately experienced pulmonary recurrence 8 months after a combined and bilateral pulmonary wedge resection and died of disease 2 months after the second recurrence.[15]

However, more recent experience reports longterm survival after resection of hepatic metastases. These cases are published within retrospective series of liver resections for non-colorectal non-neuroendocrine (NCNN) liver metastases (Table 3).[16–20] Unfortunately, these studies do not report histological subtypes. Weitz *et al*. reported on 16 patients, of whom 12 had ovarian and four had endometrial disease.[18] Specific survival times were not mentioned. The series was grouped with patients with resected liver metastases from testicular carcinoma and reported to have the best outcome of liver resection cases for NCNN hepatic metastases, with 63% of patients disease-free at 3 years and an actuarial 3-year cancer-specific survival of 78%. The authors also noted no effect of the disease-free interval on the prognosis, unlike in the non-reproductive tract liver metastases resected in their series.[17]

The series reported by Adam *et al.*[16] and Ercolani *et al.*[20] also describe favourable survival for primary gynaecological tumours. The series from Adam *et al.* describes the largest number of liver resections for gynaecological metastases. Their multi-institutional series of 1452 NCNN liver resections included 126 (9%) cases of either ovarian or uterine primaries, with an overall 5-year survival of 48%. Five-year survival for ovarian primaries (50%) exceeded that for endometrial primaries (35%), although no *P*-value was given.[16] Ercolani *et al.* grouped eight ovarian and one endometrial patient with liver metastases with renal and testicular liver metastases patients and demonstrated the best outcome for tumour type in their series, with a 5-year survival rate of 42%.

The most recent series reported by O'Rourke *et al.*[17] failed to find a relationship between tumour type and survival. These authors published the outcomes of 12 patients with ovarian liver metastases along with those of 20 other patients with liver metastases from renal, bladder, cervical and adrenal primaries and reported a 5-year survival rate of 39%.

These are highly selected series of patients that represent only a minority of total liver resections for metastases performed in specialist hepatobiliary units. In each series gynaecological metastases account for fewer than 10% of cases and are often included for tumour type uni- or multivariate analysis with testicular, renal or even bladder and adrenal liver metastases.

It is impossible to determine whether the liver surgery itself is of benefit. However, common to all series are low rates of morbidity and mortality and prolonged overall and disease-free survival rates that seem better than those for historical controls.

In conclusion, recent publications on hepatic resection for isolated metastases from gynaecological primaries would support hepatic resection in the face of isolated liver metastases. Preoperative factors such as fitness for surgery, co-morbidity and prognostic indicators such as the presence of disseminated disease and the resectability of hepatic lesions must be taken into account. To date, no such guidance exists for liver metastases from gynaecological primaries. However, the criteria used for the resection of colorectal metastases may be applied: (i) the patient must be medically fit enough to undergo major abdominal surgery; (ii) no unresectable extrahepatic tumours demonstrable on preoperative imaging must be present, and (iii) grossly negative resection margins leaving an adequate volume of functional liver must be achievable. This patient series demonstrates a successful outcome following hepatic resection for liver metastases from endometrioid primaries, with a longest disease-free survival of 66 months. The authors advocate that patients with isolated hepatic deposits and stable primary disease should be referred to specialist hepatobiliary units for assessment for hepatic resection. Such treatment should be considered as part of multimodal therapy and should be delivered in consultation with specialist gynaecological cancer specialists.

Conflicts of interest

None declared.

References

1. Cancer Research UK. Cancer Research UK Statistics. http://info.cancerresearchuk.org/cancerstats/types/uterus/incidence/. [Accessed 4 July 2010].
2. Chi DS, Fong Y, Venkatraman ES, Barakat RR. (1997) Hepatic resection for metastatic gynaecologic carcinomas. *Gynecol Oncol* 66:45–51.
3. Foster JH, Berman MM. (1977) Solid liver tumors. *Major Problems in Clinical Surgery* 22:1–342.
4. Harrison LE, Brennan MF, Newman E, Fortner JG, Picardo A, Blumgart LH *et al*. (1997) Hepatic resection for non-colorectal, non-neuroendocrine metastases: a fifteen-year experience with ninety-six patients. *Surgery* 121:625–632.
5. Nezhat C, Kazerooni T, Berker B, Lashay N, Fernandez S, Marziali M. (2005) Laparoscopic management of hepatic endometriosis: report of two cases and review of the literature. *J Minim Invasive Gynecol* 12:196–200.
6. Sanchez-Perez B, Santoyo-Santoyo J, Suarez-Munoz MA, Fernandez-Aguilar JL, Aranda-Narvaez JM, Gonzalez-Sanchez A *et al*. (2006) [Hepatic cystic endometriosis with malignant transformation.] *Cir Esp* 79:310–312.
7. Hoskins WJ Perez CA, Young RC. (2000) *Principles and Practice of Gynecologic Oncology*, 3rd edn, Philadelphia PA: Lippincott Williams & Wilkins.
8. Cho KR. (2009) Ovarian cancer update: lessons from morphology, molecules, and mice. *Arch Pathol Lab Med* 133:1775–1781.
9. Benedet JL, Bender H, Jones H III, Ngan HY, Pecorelli S. (2000) FIGO staging classifications and clinical practice guidelines in the management of gynaecologic cancers. FIGO Committee on Gynaecologic Oncology. *Int J Gynaecol Obstet* 70:209–262.
10. Aletti GD, Podratz KC, Cliby WA, Gostout BS. (2009) Stage IV ovarian cancer: disease site-specific rationale for postoperative treatment. *Gynecol Oncol* 112:22–27.
11. Lim MC, Kang S, Lee KS, Han SS, Park SJ, Seo SS *et al*. (2009) The clinical significance of hepatic parenchymal metastasis in patients with primary epithelial ovarian cancer. *Gynecol Oncol* 112:28–34.
12. Merideth MA, Cliby WA, Keeney GL, Lesnick TG, Nagorney DM, Podratz KC. (2003) Hepatic resection for metachronous metastases from ovarian carcinoma. *Gynecol Oncol* 89:16–21.
13. Landrum LM, Moore KN, Myers TK, Lanneau GS Jr, McMeekin DS, Walker JL *et al*. (2009) Stage IVB endometrial cancer: does applying an ovarian cancer treatment paradigm result in similar outcomes? A case–control analysis. *Gynecol Oncol* 112:337–341.
14. Wolf RF, Goodnight JE, Krag DE, Schneider PD. (1991) Results of resection and proposed guidelines for patient selection in instances of non-colorectal hepatic metastases. *Surg Gynecol Obstet* 173:454–460.
15. Tangjitgamol S, Levenback CF, Beller U, Kavanagh JJ. (2004) Role of surgical resection for lung, liver, and central nervous system metastases in patients with gynaecological cancer: a literature review. *Int J Gynecol Cancer* 14:399–422.
16. Adam R, Chiche L, Aloia T, Elias D, Salmon R, Rivoire M *et al*. (2006) Hepatic resection for non-colorectal non-endocrine liver metastases: analysis of 1452 patients and development of a prognostic model. *Ann Surg* 244:524–535.
17. O'Rourke TR, Tekkis P, Yeung S, Fawcett J, Lynch S, Strong R

et al. (2008) Longterm results of liver resection for non-colorectal, non-neuroendocrine metastases. *Ann Surg Oncol* 15:207–218.

18. Weitz J, Blumgart LH, Fong Y, Jarnagin WR, D'Angelica M, Harrison LE *et al*. (2005) Partial hepatectomy for metastases from non-colorectal, non-neuroendocrine carcinoma. *Ann Surg* 241:269–276.

19. Elias D, Cavalcanti de Albuquerque A, Eggenspieler P, Plaud B, Ducreux M, Spielmann M *et al*. (1998) Resection of liver metastases from a non-colorectal primary: indications and results based on 147 monocentric patients. *J Am Coll Surg* 187:487–493.

20. Ercolani G, Grazi GL, Ravaioli M, Ramacciato G, Cescon M, Varotti G *et al*. (2005) The role of liver resections for non-colorectal, non-neuroendocrine metastases: experience with 142 observed cases. *Ann Surg Oncol* 12:459–466.