

# Hepatic Resection for Liver Metastases from Cervical Cancer Is Safe and May Have Survival Benefit

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**Abstract.** *The goal of this study was to evaluate the single-centre experience with hepatectomy for liver metastases from cervical cancer (CCLM). Fifteen patients who underwent such surgery at the Fundeni Clinical Hospital between January 2002 and April 2014 were retrospectively reviewed. Liver lesions diagnosed at more than 6 months from cervical cancer diagnosis were classified as metachronous lesions, while lesions occurring within the first 6 months were considered synchronous lesions. Two patients were diagnosed with synchronous CCLM, while the other 13 patients had metachronous. Early postoperative death occurred in a single patient with metachronous liver metastases and pelvic recurrence, but this was not related to liver surgery. The median overall survival for the entire cohort was 18 months from the time of liver resection; patients with metachronous lesions had an improved outcome when compared to those with synchronous lesions. In patients with metachronous liver metastases, prognostic factors associated with an improved outcome were the general biological status of the patient, grade of tumoural differentiation and absence of other abdomino-pelvic recurrences. In multivariate analysis, only the grade of differentiation was statistically significant. In conclusion, hepatic resection for liver metastases from cervical cancer can be performed safely, may prove effective, and should be part of the multimodal treatment.*

Although in developed countries incidence and mortality from cervical cancer have declined considerably, worldwide it still represents a major health problem, with 12,900 cases of

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invasive cervical cancer being diagnosed in 2015 in the USA, and the number of deaths increasing by 4,100 cases in the same year (1, 2). If detected in early stages, cervical cancer is curable (3) and simple screening methods, such as Papanicolau smear test, are generally available; however, recent data show that 8.3% of women with cervical cancer were diagnosed with primary metastatic disease between 2007 and 2015 (4). Since 50% of patients with locally advanced disease will experience relapse within the first 2 years after initial treatment (5, 6), optimizing treatment for recurrent disease represents an important problem. Although not frequently, synchronous and metachronous liver metastases from cervical cancer (CCLM) may occur and they are accompanied by a grim prognosis, with a median survival of 12 months (4). In light of these facts, it is worth mentioning that liver resection is becoming increasingly safer and it has a clearly established survival advantage for primary colorectal and neuroendocrine cancer; therefore, the question can be raised as to whether it may bring benefit for resection of CCLM.

## Patients and Methods

We retrospectively reviewed data of patients diagnosed with synchronous and metachronous CCLM at the Dan Setlacec Center of General Surgery and Liver Transplantation, Fundeni Clinical Hospital, between January 2002 and April 2014. Preoperative, intraoperative and postoperative data were collected retrospectively. The information included age when cervical cancer was diagnosed, International Federation of Gynecology and Obstetrics (FIGO) stage, neoadjuvant treatment, and initial surgery for cervical tumours, histopathological type, disease-free survival rate, treatment applied at recurrence, postoperative complications according to the Dindo-Clavien scale (7), and overall survival. Liver lesions diagnosed at more than 6 months from cervical cancer diagnosis were classified as metachronous lesions, while lesions occurring within the first 6 months were considered synchronous lesions. Informed consent was obtained from each patient before surgery and the Fundeni Clinical Institute Ethics Review Board approved the present study (approval number 32/2016).

Table I. Clinicopathological characteristics of patients with metachronous liver lesions from cervical cancer.

Patient	Age, years*	Stage	Grade	Primary surgery	Adj Tx	HP
1	37	II	3	Wertheim operation	Yes	Squamous
2	47	III	3	Wertheim operation	No	Squamous
3	65	II	2	Wertheim operation	Cisplatin	Squamous
4	43	II	3	Wertheim operation	No	Squamous
5	53	III	3	Wertheim operation	Yes	ADC
6	31	II	2	Wertheim operation	No	Squamous
7	40	I	2	Wertheim operation	Yes	ADC
8	54	II	3	Wertheim operation	Yes	Squamous
9	60	II	3	Wertheim operation	Yes	Squamous
10	50	III	2	Wertheim operation	Yes	Squamous
11	50	I	3	Wertheim operation	No	Squamous
12	47	IVA	3	Total exenteration	No	Squamous
13	67	II	3	Wertheim operation	No	Squamous

HP: Histotype, Adj Tx: adjuvant therapy, ADC: adenocarcinoma. \*At cervical cancer diagnosis.

*Statistical analysis.* The dates of death were obtained from the National Register of Population (<http://depabd.mai.gov.ro/>). The differences between different subgroups were analysed by the log-rank test. The Cox regression model was used to perform multivariate analysis of prognostic factors. A value of  $p < 0.05$  was considered statistically significant. The Kaplan–Meier method was used to calculate survival probabilities from the time of liver resection. Statistics and graphics were performed using SigmaPlot program, version 12 (STIRA Electronic S.R.L., Sighisoara, Romania)

## Results

From January 2002 until April 2014, 15 patients underwent surgery for CCLM at the Fundeni Clinical Institute. Only two patients were diagnosed with synchronous hepatic lesions (FIGO stage IVB cervical cancer), while the other 13 patients were diagnosed with metachronous liver lesions (FIGO stages II-IVA). The patient characteristics are shown in Tables I and II.

*Synchronous liver metastases.* Stage IV B cervical cancer (presenting with unique liver metastases) was encountered in two patients. Both patients underwent Wertheim resection for the primary tumour and atypical minor resections for liver metastases. The age when diagnosed was 54 and 59, respectively. Both patients were submitted to neoadjuvant pelvic irradiation. Intraoperatively, unique liver metastases were found in both patients, measuring 1 and 5 cm, respectively, and these were completely resected, with negative margins. The postoperative course was uneventful, the patients being discharged the 10th and the 12th postoperative day, respectively. Histopathological studies of the resected liver revealed squamous cell metastases in both patients; in one patient, the tumour was considered well-differentiated, while in the second a poorly differentiated

subtype was found. The survival duration was 9 months and 89 months respectively, both patients having died of their disease by the end of the present study.

*Metachronous liver metastases.* The average patient age when cervical tumour was diagnosed was 50.4 years (range=31-671 years). All patients had been previously submitted to neoadjuvant irradiation therapy; surgery was performed after a mean interval of 1.5 months. Initial FIGO stage was I in two patients, II in seven patients, III in three patients and IVA in one patient. For patients diagnosed with FIGO stages I-III, the surgical procedure was Wertheim resection (12 patients), while total pelvic exenteration was performed in one patient for stage IVA cervical cancer. The main histopathological subtype was squamous cell carcinoma (11 patients), while uterine cervix adenocarcinomas were found in two patients. The average disease-free interval (DSI) before liver resection was 20 months. Eleven patients were diagnosed with single liver metastases, while the other two were diagnosed with four and two lesions, respectively. Four patients were submitted to major hepatectomies (more than three segments), while the other nine patients underwent minor hepatic resections. The median size of the liver lesions was 5.5 cm (range=1-cm). Five patients were considered to have well-differentiated tumours, while the other eight presented medium or poorly differentiated subtypes. Seven patients had concurrent extrahepatic disease.

The mean hospital stay was 12 days (range=4-58 days). According to the Clavien-Dindo classification, two patients presented grade 2 complications (pleural effusion in one patient and biliary fistula treated conservatively in the other), while another two patients experienced more severe complications: enteral or urinary fistulas after extended pelvic resections for synchronous pelvic recurrences

Table II. Intraoperative findings, types of liver resection and postoperative outcomes of patients undergoing liver resection for liver metastases from cervical cancer.

No	Age, years*	Liver metastasis size (cm)	Extra-hepatic disease	DFI <sup>#</sup>	Type of LR	Associated extrahepatic resection	Postoperative complications	Recurrence following LR (site, DFIL <sup>#</sup> )	Current status, survival after LR <sup>#</sup>
1	38	6	No	11	miH	None	None	Pelvic recurrence, cecum, 9	Dead, 20
2	50	6	Yes	32	MH	Nephrectomy, partial frenectomy	None	5	Dead, 10
3	67	15	Yes	23	MH (right)	None	None	Pelvic recurrence with extension to the sigmoid, 7	Dead, 23
4	45	6	Yes	26	MH	Partial pericardectomy, atypical pulmonary resection, diaphragm resection	None	Liver, 3	Dead, 5
5	54	4.5	No	16	miH	None	None	NA	Dead, 16
6	35	4	Yes	6.3	MH (right)	Right inferior lobectomy, diaphragm resection	Pleural effusion	Brain metastases, 11	Dead, 17
7	51	5	No	129	miH	None	-	None	Alive, 25
8	55	1.5	No	7	miH	None	-	None	Dead, 14
9	62	1	No	20	miH	None	-	None	Alive, 11
10	51	8	Yes	14	miH	Right inferior lobectomy, diaphragm resection	Biliary fistula	None	Alive, 30
11	54	2	Yes	42	miH	PRR <i>en bloc</i> with rectal resection	Enteral fistula, peritonitis, reoperation	111	Dead, 119
12	48	6	Yes	5	miH	PRR <i>en bloc</i> with partial cystectomy and distal ureterectomy	Urinary fistula, re-operation, sepsis	-	Dead, 0
13	70	2	Yes	25	miH	PRR <i>en bloc</i> with segmental enterectomy	-	-	Dead, 1

SCC: Squamous cell cancer, LR: liver resection, MH: major hepatectomy, miH: minor hepatectomy, WR: Wertheim resection, PRR: Pelvic recurrence resection, SCCm: squamous cell cancer metastases, DFI: disease-free interval, DFIL: disease-free interval after liver resection, NA: not achieved. \*At surgery for liver metastases. <sup>#</sup>In months.

(Clavien-Dindo grade 4 complications); both patients required re-operation; one of them died 10 days after re-intervention, while the second patient was still alive at the end of the present study.

The median overall survival rate for the patients with metachronous liver metastases was 18 months following liver resection. Three patients are alive, with no recurrence during the follow-up period and five patients developed recurrence.

Patient 1 had undergone previous surgical treatment for spinal cord compression caused by metastatic cancer at 8 months after primary tumour surgery. She received chemotherapy with Taxol and radiotherapy; however, 2 months later she was diagnosed with liver metastases, and wedge liver resection was performed. At 10 months following liver resection, pelvic metastatic tumour with extension to the cecum was found, and right hemicolectomy performed; she died 9 months later. Six months after liver resection, patient 3 had pelvic recurrence of cervical cancer with extension to the sigmoid, and Hartmann rectosigmoid resection was performed; 15 months later, she had recurrence in the right colon and invasive diaphragmatic metastases; *en bloc* tumoral resection,

right hemicolectomy with ileo-transverse anastomosis, and concomitant diaphragm resection was performed. The patient died 8 months later due to systemic recurrence.

In univariate analysis, the most important factors associated with improved survival in patients with metachronous liver metastases were the tumour grade of differentiation (G2 *versus* G3: median survival of 22.9 *versus* 15.5 months,  $p=0.021$ ) and the absence of extrahepatic recurrence (median survival of 19 months in patients submitted only to liver resection *versus* 10 months for those with multiple visceral resections,  $p=0.02$ ). An important aspect was that major hepatic resection was not associated with a poorer outcome when compared to minor hepatectomy ( $p=0.363$ ).

## Discussion

Liver metastases, either synchronous or metachronous, appear not to be a frequent situation in cervical cancer. The prognosis of patients with distant metastases or with disease recurrence not amenable to locoregional control is poor (8). A study by Kim *et al.* investigating the patterns of hepatic

involvement and the outcome of 1,665 patients with carcinoma of the uterine cervix detected liver metastases at follow-up in 20 patients. In nearly all patients, liver involvement was accompanied by uncontrolled locoregional disease or other extrahepatic metastases and prognosis was extremely poor – with a median survival of 10 months (6). In our study, liver metastases were associated with extrahepatic metastases in seven patients. Since no efficient management of such patients exists at the moment, and with response to chemotherapy being weak and usually short-lived (9-15), we hypothesize that surgery may bring survival benefit in selected patients, given the fact that liver resections are becoming safer (16).

Once survival benefit and safety of liver resection in patients with colorectal and neuroendocrine liver metastases became objectified and therapeutic standard, an increasing number of studies started exploring the possible benefit of liver resection for other primary tumour types, including gynaecological ones; data on CCLM are however very scarce, limited to case reports (17) or few patients incorporated in gynaecological or non-colorectal non-neuroendocrine resected metastases studies (18-20). The fact that liver resection proved beneficial even for patients with metastases from breast cancer (18, 21), which is by definition a systemic and aggressive disease, proved encouraging for attempting to define the benefit for malignancies with less hepatic tropism, such as cervical cancer.

In the study of Chi *et al.*, 2 out of the 12 patients had liver metastases originating from cervical cancer. Both had been initial IB stage squamous cell carcinoma, treated by radical hysterectomy and postoperative pelvic radiotherapy; liver metastases occurred after 18 and 32 months, respectively, following completion of the initial treatment, while survival after hepatectomy was of 50 months for the first patient, and 15 for the second (19).

In the series of Kamel *et al.* regarding the resection of liver metastases originating from gynaecologic primary tumour, 52 patients underwent liver resection, out of whom three had liver metastases from cervical cancer; for the entire cohort (including ovarian, uterine, cervical and fallopian tube metastases), a matched-paired analysis showed better survival for patients who underwent resection of liver metastases when compared to those who were treated otherwise (20). The median survival rate of 18 months obtained in our study for patients with metachronous liver metastases shows a considerable survival benefit. One of the two patients with synchronous metastases survived 89 months following liver surgery; the 15 patients with resected CCLM, analysed in the present study, even though small in absolute number, represents, to our knowledge, the largest published study dedicated to this pathology. In our series, 20 out of 35 patients with CCLM were excluded from the study due to the preoperative assessment that an R0 resection could

not be obtained; for the remaining 15 patients submitted to resection, complete resection was obtained in all of them.

Surgery proved to be safe, with only two patients experiencing severe complications, one of whom died, even though major hepatectomies were performed in four out of 15 patients; in addition, liver resection in three patients was accompanied by important resections in the upper abdomen and thoracic cavity, while in another three patients, extensive resections in the lower abdomen were required. It would seem that liver resection, even accompanied by other concomitant debulking procedures, might be safely offered to patients, especially in high-volume centres (21).

According to Tangjitgamol *et al.*, prognostic factors correlated with OS are the absence of extrahepatic disease, a longer disease-free survival, and the control of pelvic disease (22). Similarly, in our study, patients with disease confined to the liver benefited more from liver resection than those who underwent concomitant pelvic and abdominal debulking procedures, although these still proved to be feasible and safe. In addition, the degree of differentiation seemed to be a prognostic factor, with better survival for those with G2 *versus* G3 tumour.

## Conclusion

Liver resection for CCLM can be performed safely and may bring survival benefit. Patients who benefit most are those without extrahepatic disease, although concomitant resection of other sites of disease is safe, and in some patients may be followed by a long survival. Further prospective randomized studies are necessary in order to clearly establish the role of liver surgery in the multimodal treatment of metastatic cervical cancer.

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