

Metastatic involvement of the urinary tract in patients with advanced ovarian carcinoma: lessons from the autopsy for an interdisciplinary treatment approach

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Summary

Purpose of investigation: Frequency and extent of metastases in urologic organs found at autopsy of ovarian carcinoma patients were evaluated. *Methods:* Autopsy reports from 170 patients who died of advanced ovarian carcinoma between 1975 and 2005 were studied. The distribution of abdominal metastatic sites with particular attention to the involvement of the urologic organs, and hydronephrosis was analyzed. *Results:* The distribution of metastatic sites was as follows: kidney (n = 6, 3.5%), urinary bladder (n = 38, 22.4%), and ureter (n = 20, 11.8%). In 36 patients, hydronephrosis was observed (21.2 %); of these patients, 20 (55.6%) also had ureteral involvement. All patients with ureteral involvement had hydronephrosis. *Conclusion:* Hydronephrosis in late stages of ovarian carcinoma, usually attributed to extrinsic compression of the ureter by an abdominal tumor, may also be explained by ureteral metastases. This fact must be considered in the clinical management of these patients, particularly in the restoration of luminal patency through an endoscopically placed internal ureteral stent.

Key words: Ovarian cancer; Urinary tract; Metastases; Hydronephrosis; Autopsy.

Introduction

In Western countries, ovarian carcinoma is the fourth most frequent cause of cancer death in women [1]. In most cases the disease is first diagnosed in advanced stages. Despite current multimodal therapies, most patients relapse and eventually succumb to the disease [2].

Since ovarian carcinoma, particularly in late- and end-stages of the disease, tends to relapse intraabdominally, urologic organs are often involved by metastases. In these situations, quality-of-life impairing symptoms such as renal failure, pain or fever associated with ureteral obstruction and hydronephrosis may occur, and therefore urologists are often involved in the palliative care of these patients.

The knowledge of metastatic extent in these late stages may improve the understanding of the disease and may assist physicians in the clinical management of these patients. In order to give an immediate and exact description of the morphologic extent of a disease in its late- and end stages, autopsy is the most appropriate and precise tool. Compared to studies in which the frequency and extent of distant metastases in patients with ovarian cancer were evaluated through postmortem examination [3-8], those which used only clinical data from living patients [9, 10] showed a consistently lower incidence of metastatically involved organs.

In this study, we evaluate the frequency and extent of metastases in urologic organs found at postmortem examination of ovarian cancer patients, paying particular attention to different factors influencing the course of disease, such as age, survival time and previous treatment. To the best of our knowledge, our study investigates the clinical and therapeutic implications of ureteral metastases for the first time in the literature.

Patients and Methods

Between 1975 and 2005, 22,023 autopsies on female subjects were performed at the Institute of Pathology of the University of Basel, Switzerland. Of these, primary epithelial ovarian cancer was diagnosed in 207 cases.

The autopsy reports and clinical records of these 207 patients were reviewed for the following information: date of diagnosis, age at death and survival time. The goal of our study was to evaluate the metastatic extent of ovarian carcinoma in a homogeneous group of patients who were clearly in the final stage of disease at the time of death, and to avoid inclusion of patients who were in earlier stages of the disease and who had ultimately died of other causes. Therefore, particular attention was paid to the analysis of the clinical data and the clinical course of each patient. According to these strict criteria, 37 cases had to be excluded from further analysis:

- In 16 cases the autopsy report described ovarian cancer in an early stage, and thus ovarian carcinoma was clearly not the cause of death, but rather an incidental finding.

- Nine patients had known metastatic ovarian cancer, but had other clearly identifiable causes of death based on prior clinical evaluation, which were confirmed by postmortem examination

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(accident, suicide, sepsis, liver cirrhosis due to chronic active hepatitis, cardiac disease and cerebrovascular disease).

– In six patients ovarian carcinoma tissue was found in the autopsy; however, these patients died within three weeks after primary surgery due to postoperative complications. The carcinoma tissue represented residual disease that could not be removed during debulking surgery.

– Six patients were excluded because they had a second metastatic malignancy in addition to ovarian carcinoma, and the cause of death could not be clearly attributed to ovarian cancer.

Ultimately, 170 cases were available for analysis. Of these, serous carcinoma was the most common histologic type (n = 135, 79.4%). To confirm the histology reported in the autopsy findings, approximately 4,550 microscopic sections, averaging 20 sections/case, were reviewed by a specialized gynecopathologist. The distribution of the other histologic subtypes was as follows: endometrioid carcinoma (n = 20; 11.8%), mucinous carcinoma (n = 8; 4.7%) and clear cell carcinoma (n = 7; 4.1%).

We recorded data regarding ten intraabdominal metastatic sites: 1) parietal and visceral pelvic and abdominal peritoneum including omentum and diaphragm, 2) pelvic and abdominal lymph nodes, 3) bowel, 4) liver, 5) pancreas, 6) stomach and 7) spleen.

The urological organ sites were: 8) kidney, 9) urinary bladder and 10) ureter. We also noted additional information concerning hydronephrosis. For the latter eight organ sites, prerequisites were wall invasion or parenchymal involvement; that is, involvement of the serosal surface alone was not sufficient.

In order to correlate the autopsy findings with the clinical situations, the variables A) age at death, B) survival time and C) surgical therapy with curative intention were analyzed. For the last variable, 85 patients who had debulking surgery with curative intention (50% of the study group) were distinguished from patients who did not have this treatment. In 37 cases from the latter group, the diagnosis was first made at autopsy, and in 26 other cases the suspected diagnosis was made through radiologic studies or cytologic examination of ascites just a few weeks before death. In 22 cases the diagnosis was confirmed by exploratory laparotomy without any extensive cytoreduction, and tissue was only sampled for the purpose of making a histologic diagnosis. Ninety-eight patients received chemotherapy in the course of their disease. The application of chemotherapy, both in the adjuvant and palliative setting, was not specifically evaluated.

The study was carried out in accordance with the guidelines of the Ethics Committee of the University of Basel.

Statistical methods

The association between age at autopsy, survival time and surgical therapy with curative intention with the occurrence of metastases to organs of the urinary tract was calculated using a multivariate logistic regression model. Odds ratios with corresponding 95% confidence intervals were reported for these parameters. In the case of age and survival time, the odds ratio was expressed as the ratio of the odds from the 3rd to the 1st quantile of the corresponding distribution. Statistical analyses were performed with R Development Core Team software, version 2.5.0 (Vienna, Austria).

Results

Table 1 summarizes the clinical data and the frequency of metastatic disease at different sites in the 170 patients of the study group. The peritoneal cavity was the most

Table 1. — Ovarian carcinoma at autopsy: clinical data and metastatic involvement of organs of the abdominal cavity with special consideration regarding urologic organs.

Number of patients	170
Age at autopsy (years)	
median	73
range	36-98
Survival time (months)	
median	5
range	0-300
Treatment with curative intention	
no. of patients (%)	85 (50.0)
Metastatic sites in the abdominal cavity	
no. of patients (%):	
pelvic/abdominal peritoneum	168 (98.8)*
pelvic/abdominal lymph nodes	127 (74.7)
organ involvement:	
– bowel	95 (55.9)
– liver	81 (47.6)
– pancreas	12 (7.1)
– stomach	13 (7.6)
– spleen	27 (15.9)
Metastatic sites to urinary organs	
no. of patients (%):	
kidney	6 (3.5)
urinary bladder	38 (22.4)
ureter	20 (11.8)
hydronephrosis	36 (21.2)

* Distant metastases without peritoneal involvement were observed only in two cases: one patient had exclusively liver metastases, and another had isolated brain metastases.

frequently involved site. Only two patients had no peritoneal involvement at death.

Six patients had metastatic disease to the kidney (3.5%). All of these patients also had involvement of other intraabdominal organs. Only one patient had bladder involvement, another patient showed hydronephrosis and no patients had ureteral involvement.

Thirty-eight patients had metastatic involvement of the urinary bladder (22.4%). Of these, six patients had no other intraabdominal organ involvement (15.8%) and ten patients had involvement of three or more other organs (26.3%).

Twenty patients of the study group had metastatic ureteral involvement (11.8%). Of these, only one patient had no other intraabdominal organ involvement (5.0%) and eight showed involvement of three or more intraabdominal organs (40.0%).

In 36 patients, hydronephrosis was observed at the time of autopsy (21.2 %). Table 2 shows the simultaneous

Table 2. — Ovarian carcinoma at autopsy: hydronephrosis and simultaneous involvement of urologic organs.

Ureteral obstruction/hydronephrosis	36
no. of patients (%)	(100)
+ ureteral involvement	20
	(55.6)
+ urinary bladder involvement	15
	(41.7)
+ urinary bladder and ureteral involvement	9
	(25.0)

involvement of the urologic organs in these patients. Of the patients, 55.6% also had ureteral involvement. Interestingly, all patients with ureteral involvement also showed hydronephrosis. Of the patients who had hydronephrosis, 22 patients had involvement of three or more intraabdominal organs (61.1%) and one patient had only peritoneal involvement but no other organ involvement (2.8%).

To analyze the factors that influenced the metastatic involvement of the urologic organs, multivariate analyses that took into account age at autopsy, survival time and surgical therapy with curative intention was performed (Table 3). Age at autopsy and survival time were shown not to be significant variables. Surgery with curative intention was a significant factor for the presence of hydronephrosis (odds ratio [OR], 3.06; 95% confidential interval [CI], 1.26 to 7.43; $p = 0.013$) but not for urologic organ involvement.

Table 3. — Multivariate analysis of factors influencing the metastatic spread pattern to urologic organs.

	OR (95% CI)	p value
<i>Kidney involvement:</i>		
age	0.30 (0.08-1.06)	0.062
survival time	1.24 (0.86-1.77)	0.246
surgery with curative intention	0.22 (0.03-1.63)	0.137
<i>Bladder involvement:</i>		
age	1.22 (0.65-2.30)	0.539
survival time	1.03 (0.84-1.25)	0.789
surgery with curative intention	2.10 (0.90-4.88)	0.085
<i>Ureteral involvement:</i>		
age	1.41 (0.61-3.25)	0.424
survival time	0.92 (0.67-1.28)	0.638
surgery with curative intention	2.01 (0.68-5.99)	0.209
<i>Hydronephrosis:</i>		
age	0.93 (0.49-1.77)	0.814
survival time	0.90 (0.69-1.18)	0.458
surgery with curative intention	3.06 (1.26-7.43)	0.013

OR: Odds Ratio; CI: Confidence Interval.

Discussion

Studies evaluating the anatomic-morphologic extent of ovarian cancer at the time of autopsy show considerable heterogeneities in their subject/sample composition and are therefore difficult to compare with each other [3-8]. Table 4 lists the data from the most recent studies with

Table 4. — Data on metastases from ovarian carcinoma to urologic organs found in four autopsy reviews (represented as percentages).

	Present study	Reed <i>et al.</i> [7]	Rose <i>et al.</i> [8]	Dvoretzky <i>et al.</i> [3]	All studies (mean)
Period when autopsies were performed	1975-2005	1972-1988	1958-1987	1958-1985	
no. of patients	170	73	381	100	724
Kidney	4	4	6	10	6
Urinary bladder	22	12	—	11	15
Ureter	12	16	3	24	14

special consideration to metastatic involvement of the urologic organs [3, 7, 8]. Relevant factors which contribute to the heterogeneity of the particular studies are the inclusion of less frequent types of ovarian cancer, such as germ cell and stroma cell tumors [3, 8] (which also leads to a considerably heterogeneous age distribution of the patient group analyzed, e.g., 5-84 years in a study by Rose *et al.* [8]) and inclusion of cases in which ovarian cancer was clearly not the cause of death [3, 6, 8] (e.g., patients had complete remission at the time of autopsy, or carcinoma tissue was found in the autopsy, although the disease was found in early stages). Furthermore, most other studies had been performed at a time when the currently accepted standards in histopathological diagnosis of metastatic disease secondary to the ovary had not yet been fully established [3, 6, 8]. If the current standards were to be applied to these older studies, this would probably lead to the exclusion of approximately 10% of the patients which had been included [4].

Most other studies fail to adequately consider the different factors which have a significant effect on the course of the disease, such as age at death, survival time and relevant treatment factors such as previous surgical therapy [3, 6-8]. In contrast, our study was undertaken to correlate the frequency and sites of metastasis, paying particular attention to these important factors. In order to avoid heterogeneity, only epithelial ovarian cancers (which comprise 90% of all ovarian cancers [1]) were included. Furthermore, we analyzed only cases in which the death of the patient was directly due to ovarian carcinoma in its final stage. We did not consider the effect of chemotherapy, since the chemotherapy regimens changed considerably during the study period. Due to the drastic decrease in the performance of autopsies in the last years at our institution, there were too few patients to make a relevant statement which could be applied to currently used chemotherapy regimens and agents.

On the whole, our results concerning metastatic sites oscillate around the previously reported results (Table 4). Our study shows that in late stages of ovarian carcinoma, other abdominal organs are also usually involved when metastatic disease to the urologic organs is present. In comparison with other urological organs, renal involvement is relatively rare (in 3.5% of cases). Neither age nor duration of disease are useful to predict any involvement of the urological organs or the presence of hydronephrosis.

It is a widely lamented fact that autopsy rates have seriously decreased in many countries [11-14]. One reason for the lack of interest in performing autopsies is the belief that autopsy findings do not add much relevant information which could improve the management of living patients [11]. We refute this belief, and to support this, we provide the following example. Renal failure and pain associated with ureteral obstruction and/or hydronephrosis are frequent symptoms in the course of a malignant disease in its late stages. In our study hydronephrosis was found in 21% of the patients who died of ovarian cancer. It has been well documented that

restoration of luminal patency through an endoscopically placed internal ureteral stent (IUS) is a difficult procedure in patients with advanced metastatic ovarian cancer [15, 16]. This is usually attributed to extrinsic compression of the ureter by tumor, although this is not true in all cases. In many cases, the tumor mass in the pelvic cavity is not massive enough ("frozen pelvis") to explain this symptom through extrinsic compression alone. Interestingly, 55% of cases in our study with ureteral obstruction also had metastatic involvement of the ureter. As also shown by Dvoretzky *et al.* [3], metastatic involvement of the ureter was always associated with ureteral obstruction. Even small metastases to the ureter can result in significant narrowing of the ureteral lumen and therefore can cause difficulties when inserting an IUS.

We believe that this clinical situation is perceived differently by gynecologic oncologists and urologists. According to urologists, the insertion of an IUS in women is considered as a minor intervention and relatively easy to perform. Therefore, IUSs are often inserted or exchanged under local anesthesia. This seems to be in contrast to what gynecologists hear from their patients: for many women with end-stage ovarian carcinoma and IUS, any manipulation in local anesthesia is frequently reported to be extremely painful and traumatic. A possible explanation for this increased perception of pain in this group of patients could be our finding of significant ureteral metastases. We therefore advocate inserting or changing an IUS in patients with advanced ovarian carcinoma under regional or general anesthesia.

This study demonstrates the need for cooperation and exchange between the different disciplines involved in the care of palliative patients. Furthermore, we show that autopsy findings are an important clinical tool for the exact evaluation of oncologic diseases and their metastatic spread. It would be interesting to further investigate whether other intraabdominal cancer entities cause similar metastatic patterns to urologic organs as seen with ovarian carcinoma.

Conclusion

Autopsy findings may assist the clinician in the clinical management of living patients. Hydronephrosis in late stages of ovarian carcinoma, usually attributed to extrinsic compression of the ureter by abdominal tumor, may also be explained by ureteral metastases. This fact must be considered in the treatment of these patients, particularly in the restoration of luminal patency through an endoscopically placed internal ureteral stent.

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