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Causes of postoperative mortality after surgery for ovarian cancer

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ABSTRACT

Residual disease after cytoreductive surgery is an important prognostic factor in patients with advanced stage epithelial ovarian cancer (EOC). Aggressive surgical procedures necessary to achieve maximal cytoreduction are inevitably associated with postoperative morbidity and mortality.

To determine causes of postoperative mortality (POM) after surgery for EOC all postoperative deaths in the southwestern part of the Netherlands over a 17-year period were identified and analysed by reviewing medical notes.

Between 1989 and 2005, 2434 patients underwent cytoreductive surgery for EOC. Sixty-seven patients (3.1%) died within 30 days after surgery. Postoperative mortality increased with age from 1.5% (26/1765) for the age group 20–69 to 6.6% (32/486) for the age group 70–79 and 9.8% (18/183) for patients aged 80 years or older. Pulmonary failure (18%) and surgical site infection (15%) were the most common causes of death. Only a quarter of deaths resulted from surgical site complications.

Our results suggest that causes of postoperative mortality after surgery for EOC are very heterogeneous. Given the impact of general complications, progress in preoperative risk assessment, preoperative preparation and postoperative care seem essential to reduce the occurrence of fatal complications.

1. Introduction

Treatment of patients with advanced stage epithelial ovarian cancer (EOC) is based on cytoreductive surgery and platinum-based chemotherapy. Prognosis mainly depends on FIGO (International Federation of Gynaecology and Obstetrics) stage and the extent of residual disease after primary cytoreductive surgery.[1–3]

Aggressive surgical procedures, necessary to achieve maximal cytoreduction, are associated with peri- and postoperative morbidity and mortality.[4–6] Extent of surgery, age, comorbidity and performance status are important predictors for short-term postoperative outcomes.[6,7]

Postoperative morbidity after primary cytoreductive surgery for advanced stage ovarian cancer is reported inconsistently, without standard definitions of postoperative morbidity. Unadjusted morbidity rates range between 11% and 67%.

Postoperative mortality (POM) is generally defined as death from any cause within 30 days of operation. POM rates after

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primary cytoreductive surgery for advanced stage EOC vary between 0% and 6.7%, with a mean POM rate of 2.8%.[8]

Little is known about the causes of postoperative mortality after surgery for EOC. Hospital series are generally too small whereas population-based studies lack clinical information. In an attempt to detect preventable complications, we decided to perform a retrospective chart review of all postoperative deaths in a region with 16 hospitals over a 17-year period.

2. Materials and methods

Information on all patients who died within 30 days after surgery for cancer of the ovary or fallopian tube was retrieved from the Rotterdam Cancer Registry. This registry was started in 1982 and reached complete coverage of the southwestern part of the Netherlands in 1989. Newly diagnosed cases of cancer are reported to the registry by pathology laboratories and by the hospital administration for discharge records. The region comprises one university hospital, four teaching hospitals and eleven non-teaching hospitals serving a population of 2.4 million inhabitants.

The study was approved by the Medical Ethical Committee of the Erasmus University Medical Center and was performed according to the standards outlined in the Declaration of Helsinki.

From 1989 through 2005, 3257 patients were diagnosed with EOC and in 2434 patients (75%) some form of resectional surgery, excluding diagnostic biopsies, had been performed. Fifty percent ($N = 1217$) of the patients were operated in a teaching hospital. For all patients who died within 30 days of surgery ($n = 76$, 3.1%), information was sent to the hospitals to obtain access to the medical records for review by two clinicians (CG and MdV). General case notes, surgical reports and pathology reports were reviewed. When available, autopsy records ($n = 8$) were also examined.

Preoperative patient characteristics included age, World Health Organisation (WHO) performance status, ASA classification, preoperative CA125 level and comorbidity status. Comorbidity was scored and categorised using a modification of the Charlson comorbidity index (CCI).[9] Type of surgery, surgical procedures, type of surgeon, type of hospital, duration of surgery, estimated blood loss and postoperative residual disease were registered. Optimal cytoreduction was defined as residual disease < 1 cm.[1,2] To assess the extent of surgical procedures, the surgical complexity score (SCS) described by Aletti and colleagues was adopted.[6] Based on number and complexity of the surgical procedures performed patients are assigned to one of three groups: low, intermediate and complex surgery (Table 3).

Stage of disease was established as defined by the International Federation of Gynaecology and Obstetrics (FIGO).[10] Tumour type was described according to the WHO guidelines. Tumour differentiation was classified as well (grade I), moderately (grade II) or poorly differentiated (grade III).

All peri- and postoperative complications were registered and classified according to the definitions of the National Surgical Quality Improvement Program.[11] This instrument divides complications into two broad categories, surgical and medical (Table 4). Cause of death was systematically described by applying the methodology proposed by Waljee and colleagues.[12] In this classification the complication that attributed most to the patient's death during a postoperative course has to be assigned.

All patient data were entered in a computerised relational database (Microsoft Access 2000). Tabulations and statistical testing (chi-square) were performed using SPSS 14.0 for Windows (Chicago, IL).

3. Results

During the study period the Rotterdam Cancer Registry recorded 76 patients (3.1%) who died within 30 days after surgery for ovarian cancer.

Fourteen patients had to be excluded because medical records were not available ($n = 9$) or incomplete ($n = 5$). In seven patients, final histological diagnosis was different from

Table 1 – Patient characteristics (n = 55).

	N	%
Age (years)		
20–69	18	33
70–79	22	40
>79	15	27
WHO performance score		
0	15	27
1	36	66
⩾2	4	7
ASA		
1	22	40
2	26	47
3	7	13
Comorbidity index		
0	21	38
1	18	33
2	9	16
>2	6	11
Unknown	1	2
FIGO stage		
I	8	14
II	2	4
III	29	53
IV	16	29
Residual tumour		
⩾1 cm	37	67
<1 cm	18	33
Differentiation grade		
I	5	9
II	18	33
III	27	49
Not specified	5	9
Morphology		
Serous	22	40
Mucinous	10	18
Clear cell	5	9
Endometrioid	5	9
Mixed mullerian	3	5
Undifferentiated	10	18

epithelial ovarian cancer, leaving a study population of 55 patients.

Patient characteristics are depicted in Table 1. The median age at operation was 75 years (range 42–97). Operative mortality increased with age from 1.5% (26/1765) for the age group 20–69 to 6.6% (32/486) for the age group 70–79 and 9.8% (18/183) for patients aged 80 years or older.

The WHO performance status was 0 or 1 in 51 patients (93%) and only 7 patients (13%) were classified with ASA 3.

Coronary artery disease (22%) and hypertension (16%) were the most frequent comorbid conditions (Table 2). Peripheral artery disease, diabetes, pulmonary disease and a prior malignant tumour were seen in 11% of patients. The CCI was >1 in 15 patients (27%). Mean CA125 level was 975 UI/ml (range 10–5977 UI/ml).

In 44 patients (80%) primary cytoreductive surgery was performed (Table 3). Two patients underwent interval debulking surgery, one patient was operated for staging purposes. Six patients needed emergency surgery (for bowel obstruction or perforation). In two patients ovarian cancer was accidentally diagnosed during surgery without previous suspicion (laparotomy for cervical neoplasia in one and hernia epigastrica repair in the other patient).

Residual disease was <1 cm in 18 patients (32%). The vast majority of patients (85%) were diagnosed with advanced stage disease (FIGO stage III/IV).

The operative procedure was classified as low complex surgery (SCS $\leqslant$ 3) in 47 patients (85%). Thirty-two patients (58%) were treated in a teaching hospital, including four patients operated on in the university hospital. Surgery was performed by a gynaecologic oncologist in 16 (29%) patients. Mean operative time was 135 min (range 24–258 min), mean estimated blood loss was 841 ml (range 100–3500 ml).

Eighty-seven intra- and postoperative complications were recorded according to the NSQIP definitions (Table 4). The main surgical complication was surgical site infection (36%). Pulmonary failure was the most frequent medical complication (33%). Seven patients required a reoperation, which was called for by postoperative bleeding in two patients, and by bowel perforation, gastric perforation, intraabdominal abscess, fascial disruption and peritonitis in the other five.

The main causes of death were surgical site infection (n = 8) and pulmonary failure (n = 10) (Table 5, Fig. 1). Death occurred within a mean of 13 days (range 0–30 days) after surgery. Pulmonary failure was a more common cause of death if surgery was performed by gynaecologic oncologists or in a teaching hospital. Surgical site complications were the most common cause of death in patients operated on by a general gynaecologist, general surgeon or in non-teaching hospitals. These differences were not statistically significant.

Table 3 – Procedures performed in the analysed patients and their surgical complexity score. Based on number and complexity of the surgical procedures performed patients are assigned to one of three groups: low-, intermediate and complex surgery. SCS = surgical complexity score.

Operative procedure	N	SCS
Hysterectomy	22	1
Salpingo-oophorectomy	49	1
Omentectomy	28	1
Lymphadenectomy (pelvic or para-aortic)	5	1
Small bowel resection	4	1
Large bowel resection	11	2
Colostomy	8	2

Complexity score groups.
SCS $\leqslant$ 3: low complex surgery.
SCS 4–7: intermediate complex surgery.
SCS $\geqslant$ 8: high complex surgery.

4. Discussion

This study is one of the first reports that focus on causes of death in patients who die in the postoperative phase after cytoreductive surgery for EOC. The main cause of death was pulmonary failure and only a quarter of deaths resulted from surgical site complications. Our results show that causes of death are very heterogeneous and the major importance of general complications such as thrombo-embolism (11%), pulmonary failure (18%) and cardiac failure (13%) suggests that interventions will rather rely on improvement of general postoperative care than on changes in surgical management.

Cytoreductive surgery is the cornerstone of treatment for advanced stage EOC but coincides with a considerable risk of morbidity and mortality. The 3.1% POM rate in our study

Table 2 – Prevalence of comorbid conditions according to the modified Charlson comorbidity index.

Comorbid condition	Index points	Number of patients[a]	(%)
Coronary artery disease[b]	1	12	22
Congestive heart failure	1	2	4
Cerebrovascular disease	1	5	9
Peripheral vascular disease	1	6	11
Hypertension	1	9	16
Dementia	1	2	4
Diabetes (mild or moderate)	1	6	11
Pulmonary disease	1	6	11
Renal disease	1	2	4
Any prior malignant tumour	2	6	11
Hepatic disease	3	2	4

[a] One patient may have several comorbid conditions.
[b] Including myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty and angina pectoris.

Table 4 – Peri- and postoperative complications according to National Surgical Quality Improvement Program definitions.

Surgical complications (45)		N
Haemorrhage (8)	Intraoperative	3
	Postoperative	5
Bowel laceration (7)	Large bowel laceration	2
	Small bowel laceration	5
Bowel obstruction		6
Surgical site infection (16)	Sepsis	8
	Intraabdominal abcess	1
	Peritonitis	2
	Urinary tract infection	3
	Superficial wound infection	2
Wound dehiscence/fascial disruption		1
Reoperation		7
Medical complications (42)		N
Cardiac (11)	Myocardial infarction	1
	Atrial and ventricular arrhythmias	2
	Unexplained cardiac arrest	3
	Congestive heart failure	5
Venous thrombo-embolism (7)	Deep venous embolism	2
	Pulmonary embolus	5
Pulmonary failure (14)	Pneumonia	7
	Prolonged ventilator assistance	5
	Unplanned intubation	2
Renal failure		4
Gastrointestinal bleeding		4
Stroke		2
Other (liver failure)		1

is comparable with other series,[8] despite the high proportion of elderly patients. At higher age, the operative risk tends to increase, which is confirmed by the 7.5% postoperative mortality in patients aged 70 years and older. Diaz-Montes and colleagues previously described a 2.3 times higher 30-day mortality rate for patients aged 80 years and older and suggested a higher frequency of emergency surgery.[13] In our series, of the 15 patients aged 80 years or older, 5 (33%) died after emergency surgery.

Table 5 – Tabulation of causes of death.

Cause of death	N (%)
Surgical site complications	13 (23.6)
Haemorrhage	5
Surgical site infection	8
Pulmonary failure	10 (18.2)
Pneumonia	3
Prolonged ventilator assistance	5
Unplanned intubation	2
Cardiac complications	7 (12.7)
Myocardial infarction	1
Unexplained cardiac arrest	2
Congestive heart failure	4
Venous thrombo-embolism	6 (10.9)
Deep venous embolism	2
Pulmonary embolus	4
Other	19 (34.5)
Bowel obstruction	1
Gastrointestinal bleeding	3
Renal failure	1
Stroke	1
Liver failure	1
Treatment refusal	1
Progressive disease	7
Infection during chemotherapy	1
Unknown	3

Residual disease after primary cytoreductive surgery is an import prognostic factor in advanced stage epithelial ovarian cancer[1,3] and the ability to achieve optimal cytoreduction is related to surgeons specialty and type of hospital.[1,14–16] One would expect a higher postoperative mortality after more extensive surgery and for audit purposes the SCS should be used to allow meaningful comparisons.[6]

Whether the causes of death were accurately determined might be questioned. Due to the retrospective nature of this study and an autopsy rate of only 15%, we had to rely on stan-

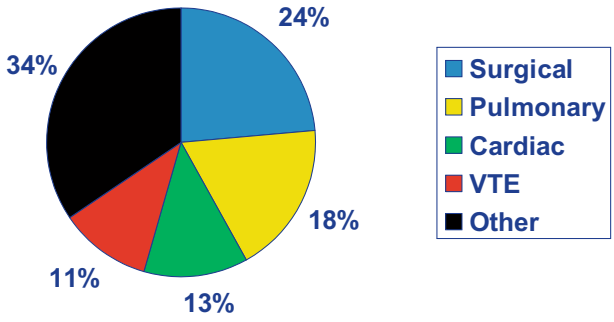

Fig. 1 – Pie chart with distribution of the identified causes of death. Surgical = surgical site complication; pulmonary = pulmonary failure; cardiac = cardiac complication and VTE = venous thrombo-embolism.

dard case notes. Accurate prospective recording of comorbidity, extent of surgery and postoperative complications seem important to develop preventive measures. Aletti and colleagues recently developed a prediction model for morbidity and mortality after primary cytoreductive surgery for advanced stage ovarian cancer. Albumin, ASA and complexity of surgery were identified as predictors for 30-day morbidity. Predictors for 3-month mortality were age and ASA.[6] Our study corroborates the importance of comorbidity and performance status. Sixty-two percent of the patients were known with some comorbid condition and in 65% performance status was influenced at the time of cancer diagnosis. Prediction models may identify patients who can benefit from alternative treatment strategies such as neoadjuvant chemotherapy or optimise physical performance before surgery, for example, by improving the nutritional status.

For several reasons, postoperative mortality appears to be a poor quality indicator for gynaecological surgery. First, it is a rare event, considering that an average hospital would encounter only one case every four years. Second, results depend on the extent of surgery performed and fatal complications tend to be non-surgery related.

It also remains remarkable that in our series most surgical procedures were low complex and that in two-thirds of patients tumour removal was suboptimal. Several authors suggested that surgery for ovarian cancer should be centralised in specialised hospitals.[14,17] Others suggest that results can be improved by a consultant gynaecologic oncologist.[15] To reduce postoperative mortality, the latter option will be less effective. To ensure optimal care all aspects, diagnostics, selection, surgery and postoperative care need to be of high standard.

In conclusion, clinical evaluation of adverse events remains an essential method to improve the quality of care. Nonetheless, postoperative complications will inevitably occur after surgery for ovarian cancer. To some extent, age and comorbidity can predict the postoperative risk but even in elderly patients cytoreductive surgery should be considered given the poor results of alternative options.

Conflict of interest statement

None declared.

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