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Early initiation of chemotherapy after primary surgery as an adverse prognostic factor in patients with ovarian cancer

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Summary

Objective: For patients with ovarian cancer (OC), the optimal time to initiate chemotherapy (TTC) after primary surgery is unknown. The aim of this study was to determine the effect of shorter TTC than 14 days on survival after primary surgery for OC among Polish women in 2011. *Materials and Methods:* All Polish women who underwent a surgical procedure for OC in the period from January 1, 2011 to December 31, 2011 recorded in the Polish National Health Fund Database (PNHFD) were included. The Cox proportional hazard regression analysis was used to compute the adjusted hazard ratio (HR). *Results:* The 25%, 50%, and 75% quantiles of intervals from surgery to TTC were 21, 30, and 43 days, respectively. In the multivariate analysis, it was observed that the adverse independent prognostic factors were: TTC ≤ 14 days [HR: 1.58 (95%CI: 1.24-2,01); $p = 0.0002$)] and a surgical procedure other than complex and very extensive excision of the upper part of the sex organs [HR: 2.02 (95%CI: 1.70-2.39); $p < 0.0001$]. The overall three-year survival rate for longer and shorter TTC than 14 days were 67.8% and 50.3%, respectively ($p < 0.0001$). *Conclusions:* This nationwide population-based cohort study revealed a significantly increased risk of death in patients with TTC ≤ 14 days after primary surgery compared with a TTC > 14 days. In order to explain the causes of this phenomenon, it is necessary to conduct a prospective study that randomizes patients to different time intervals. *Conclusions:* The early initiation of chemotherapy after a primary surgery within 14 days is not a favourable prognostic factor. The nationwide population-based cohort study showed that complex and very extensive excision of the upper part of the sex organs due to ovarian cancer significantly decreased risk of death. In patients with ovarian cancer with comorbidities, the use of chemotherapy shortly, within 14 days, after surgery had unfavourable impact on survival.

Key words: Ovarian cancer; Chemotherapy; Primary surgery; Prognostic factors.

Introduction

Around the world, it is estimated that more than 200,000 women develop ovarian cancer (OC) every year, and about 100,000 die of the disease [1]. OC is the fifth most common cancer in European women and the gynecologic cancer responsible for the most deaths. [2] According to the estimates of the GLOBOCAN database, the standardized incidence of OC in Poland, calculated for the year 2012, was 13.6/100,000 women; this is one of the highest rates in Europe. Similarly, the standardized death rate (SDR) of OC in Poland was 7.3/100,000, also one of the highest in Europe [3]. In 2012, the average value of indicators of the number of potential years of life lost due to the disease, potential years of life lost (PYLL) and period expected years of life lost (PEYLL), were 15.42 and 23.43 years, respectively [4].

A number of studies have shown that compliance with the recommendations of scientific societies improves the quality of care for patients with OC [5, 6]. However, in contrast to other cancers, the starting time of adjuvant chemotherapy after primary cytoreductive, or debulking, surgery has not been precisely defined for patients with OC. For example, in breast cancer patients, after local surgery with a lower load relative to the organism than primary debulking surgery for OC, systemic therapy should begin preferably within 2–6 weeks after surgery. [7]

Patients undergoing major surgery are exposed to metabolic and endocrine alterations in carbohydrate, protein, and insulin metabolism, often summarized as the catabolic response. Typical features of protein catabolism are stimulated rates of protein breakdown and amino acid oxidation, which lead to a net loss of body protein. Because protein encompasses both structural and functional components, the erosion of lean tissue delays wound healing, compro-

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mises immune function, and diminishes muscle strength after surgery [8].

Taking into account the catabolism of the postoperative period, commencing chemotherapy within too short a time interval from surgery could adversely affect regenerating the body after major surgery. The aim of this study was to determine the effect on survival of a time interval shorter than 14 days to the start of chemotherapy after primary surgery for OC among Polish women treated in 2011.

Materials and Methods

A nationwide population-based study was conducted in Poland, which has approximately 38 million inhabitants. Healthcare services in Poland are financed by the National Health Fund, which is tax-supported and provides universal, equal, and unlimited access to medical care, including hospitalization.

The computer system of the Head Polish National Health Fund (PNHF) created a module called the Diseases Register, enabling the analysis of data related to the treatment of oncological diseases. The module is based on network technology and allows for the extraction and data analysis of all patients diagnosed with cancer (C00-D09) from January 1, 2002. The Diseases Register of the PNHF was used to identify all women in Poland who underwent surgery and chemotherapy due to OC between January 1, 2011 and December 31, 2011. The authors chose an exemplary period of one year, excluding the first two years after the reform of the Polish healthcare system carried out on July 1, 2008. The PNHF contains a validated database of patients with diagnosis codes, the date of the procedures, and procedure billing codes for their medical expenses.

The PNHF has codification data for all procedures performed on patients who underwent at least one cycle of chemotherapy with paclitaxel/platinum analogs (carboplatin or cisplatin) within 12 months after a surgical procedure. To calculate the survival data, the starting point was the date of initial provision with an indication of OC. The dates of death were obtained from the Central List of Insured Persons of PNHF. For each eligible patient, the authors obtained the year of diagnosis and type of hospital in which they were treated.

In Poland, according to the British model, a homogeneous group of patients was introduced on July 1, 2008. OC-directed surgical procedures were coded as M11, M12, M13, M14, M15, M20, and M21. The authors excluded the minor surgical procedure M15, which is an invasive diagnostic procedure, such as hysteroscopy or ovarian biopsy. The full description of the surgical procedure codes is shown in Table 1.

Exclusion criteria were no surgical procedure performed, no chemotherapy or given a treatment other than the standard (according to the then current recommendations of the Polish Gynecological Society) [9] paclitaxel/platinum analogs, lack of information on chemotherapy administration, neoadjuvant chemotherapy given (initial chemotherapy prior to definitive surgery), and chemotherapy initiated more than 12 months after surgery.

Each patient was monitored from the date of the surgical procedure until the date of death or the end of follow-up (March 4, 2015). Survival time was calculated as the number of months from the date of surgical procedure until death or end of follow up, whichever came first. Patients who survived past the end of follow-up (March 4, 2015) were censored and contributed the time from their surgery date to the end of follow up to the analyses of overall survival.

The patients were divided into two groups, according to the time of chemotherapy initiation after primary surgery (TTC): the early group of patients who received chemotherapy ≤ 14 days after primary surgery (TTC ≤ 14 days) and the late group of patients who received chemotherapy > 14 days after primary surgery (TTC > 14 days).

The chi-squared test was used to compare the frequency distributions of categorical variables. All hypothesis tests were two-sided. In the Cox proportional hazards analyses, the authors modeled the overall mortality hazard ratios (HRs) of patients who received early treatment (TTC ≤ 14 days) compared to late group patients (TTC >14 days). Kaplan–Meier graphs were plotted for overall survival of patients with respect to TTC less than and greater than 14 days. All statistical analyses were performed using Statistica software release 12 SAS release 9.3. Statistical significance was defined as a p-value less than 0.05.

Results

The authors identified 5,577 women with OC treated in 2011 in the PNHF database. A total of 3,144 individuals underwent OC-directed surgical procedures. Among these women, 43.5% (1,369/3,144) received at least one cycle of chemotherapy with paclitaxel plus a platinum analog (cisplatin or carboplatin) after OC-directed surgical procedures, thus providing a total of 1,369 patients to be included in the study population.

The reasons for exclusion were no chemotherapy given (26.6%; 837/3,144), chemotherapy other than the current recommendations of the PSG (8.8%; 278/3,144), neoadjuvant chemotherapy given (19.5%; 615/3,144), and chemotherapy initiated more than 12 months after the primary surgical procedure (0.005%; 15/3,144). A further 0.009% (30/3,144) of patients who underwent surgery due to OC were also diagnosed with breast cancer (C50) and followed the chemotherapy regimens recommended for breast cancer. This group of patients was excluded from the analysis. Table 2 provides the demographic characteristics.

The authors compared the type of surgical procedure in the groups TTC ≤ 14 days and TTC >14 days (Table 3). They observed significant differences in the type of surgery performed in the two groups ($Z=3.93$, $p < 0.0001$). They found no differences between the two most common types of treatment (M11 and M12) in terms of three-year survival (log-rank test, $p > 0.05$).

The 25%, 50%, and 75% quantiles of the time interval from surgery to TTC were 21, 30, and 43 days, respectively. Among the 1,369 women who received chemotherapy, 10.7% (147/1,369) began treatment within 14 days of primary surgery, while 89.3% (1,222/1,369) initiated chemotherapy 14 days after primary surgery. The number of patients who did not complete six cycles of chemotherapy was not significantly different between TTC ≤ 14 days and TTC > 14 day groups ($p = 0.3701$) (Table 3).

The three-year survival rate for all 1,369 patients was

Table 1. — *Description of codes of ovarian cancer directed surgical procedures according to the system of Homogeneous Groups of Patients (HPG) using by Polish National Health Fund.*

Code of HGP	Short description of surgical procedures HGP	Used ICD-9 codes to encode the procedure HGP
M11	Comprehensive treatment of the upper part of the reproductive system in patients without serious comorbidities (including extended radical hysterectomy or pelvic exenteration).	68.61; 68.62; 68.71; 68.76; 68.77; 68.8
M12	Very extensive treatment of the upper part of the reproductive in patients without serious comorbidities (including radical hysterectomy or laparoscopically assisted vaginal hysterectomy).	68.42; 68.51
M13	Extensive treatment of the upper part of the reproductive (including simple hysterectomy or laparoscopic bilateral salpingo-oophorectomy or unilateral salpingo-oophorectomy.	65.26; 65.41;65.49;65.519; 65.53;65.54; 65.61; 65.62; 65.63; 65.69; 65.73; 65.76; 66.51; 66.75; 66.93; 68.24; 68.311; 68.312; 68.391; 68.41; 68.51; 68.59; 69.23; 69.492; 69.493
M14	Moderate treatment of upper part of reproductive system (including laparoscopic unilateral salpingo-oophorectomy or ovarian wedge resection).	54.11; 54.21; 65.01; 65.09; 65.12; 65.13; 65.21; 65.22; 65.23; 65.24; 65.25; 65.292; 65.293; 65.31; 65.39; 65.52; 65.71; 65.74; 65.81; 65.89; 65.95; 66.01; 66.02; 66.11; 66.21; 66.22; 66.29; 66.31; 66.4; 66.521; 66.61; 66.62; 66.69; 66.71; 66.72; 66.92; 68.17; 68.22; 68.232; 68.233; 68.234; 68.291; 69.1; 69.211; 69.222; 69.223; 69.3; 69.41; 69.42; 69.491; 69.499
M20	Comprehensive treatment of the upper part of the reproductive in patients with serious comorbidities (diabetes mellitus, coronary artery disease, atrial fibrillation, etc.).	68.61; 68.62; 68.71; 68.76; 68.77; 68.8 with serious comorbidities, among others ICD-10 codes: E01.0; E01.1; E01.2; E03.2; E05; E10; E11; E14; F05.1; F31.2; F72.9; G20; G30.9; G40; G41; I11.0; I11.9; I12.0; I12.9; I13; I20; I34; I48; I50.1; I50.9; N19; K27.9; J45; Z95.2 etc.
M21	Very extensive treatment of the upper part of the reproductive in patients with serious comorbidities (diabetes mellitus, coronary artery disease, atrial fibrillation, etc.).	68.42; 68.51 with serious comorbidities, among others ICD-10 codes: E01.0; E01.1; E01.2; E03.2; E05; E10; E11; E14; F05.1; F31.2; F72.9; G20; G30.9; G40; G41; I11.0; I11.9; I12.0; I12.9; I13; I20; I34; I48; I50.1; I50.9; N19; K27.9; J45; Z95.2 etc.

ICD-9: The International Classification of Diseases -9; HGP: Homogeneous Groups of Patients.

Table 2. — *Patient characteristics (n=1,369).*

Factors	No. of patients	%
Operative procedure:		
• M11	566	41.3
• M12	321	23.5
• M13	188	13.7
• M14	122	8.9
• M20	129	9.4
• M21	44	3.2
Completion of adjuvant chemotherapy (6 cycles):		
• No	349	25.5
• Yes	1020	74.5
Time to initiation of chemotherapy (TTC) Median (range)	30 (0-351)	
Type of chemotherapy:		
• Paclitaxel + cisplatin	231	16.9
• Paclitaxel + carboplatin	1138	83.1

TTC: time to initiation of chemotherapy after primary surgery; M11: comprehensive treatment of the upper part of the reproductive system in patients without serious comorbidities (including modified radical hysterectomy or pelvic exenteration); M12: extensive treatment of the upper part of the reproductive system in patients without serious comorbidities (including enlarged hysterectomy or laparoscopically assisted vaginal hysterectomy); M13: extensive treatment of the upper part of the reproductive system (including simple hysterectomy or laparoscopic bilateral salpingooophorectomy or unilateral salpingooophorectomy; M14: moderate treatment of the upper part of the reproductive system (including laparoscopic unilateral salpingooophorectomy or ovarian wedge resection); M20: comprehensive treatment of the upper part of the reproductive system in patients with serious comorbidities (diabetes mellitus, coronary artery disease, atrial fibrillation, etc.); M21: very extensive treatment of the upper part of the reproductive system in patients with serious comorbidities (diabetes mellitus, coronary artery disease, atrial fibrillation, etc.).

65.9 %. Among the 1,369 patients, the prognostic impact of time to the initiation of chemotherapy was investigated by evaluating factors associated with overall survival using univariate and multivariate analyses (Table 4). The univariate analysis showed that the following three prognostic factors significantly correlated with long-term, overall survival: completion of six cycles of chemotherapy (p = 0.0029), M11 or M12 surgical procedure performed (p < 0.0001), and TTC longer than 14 days (p < 0.0001) (Figure 1). The authors observed that the 25% and 50% quantiles of the interval from surgery to TTC were significant for OS (respectively, p = 0.0024 and p = 0.0357). This effect was not observed for the TTC 75% quantile (p = 0. 4778). Using multivariate analysis, time of the initiation of chemotherapy ≤ 14 days after primary surgery, not completing six cycles of chemotherapy, and a procedure other than comprehensive and very extensive treatment of the upper part of the reproductive system in patients without serious comorbidities (M11 and M12) [HR: 1.62 (1.27-2.06), p < 0.0001; HR:1.55 (1.19-2.03) p = 0.0012 and HR: 2.02 (1.70-2.40), p < 0.0001, respectively] were independent adverse prognostic factors (Table 4).

Table 3. — *Comparison of surgical procedures in patients who received initial chemotherapy within 14 days after the primary surgical procedure and patients who received initial chemotherapy more than 14 days after the primary surgical procedure and the impact on survival.*

Code of surgical procedure	TTC >14 days		Three-year	TTC ≤ 14 days		Three-year	*p*-value
	N	%	survival %	N	%	survival %	
M11	532	43.5	74.6	34	23.1	67.6	0.1288
M12	281	23.0	78.3	40	27.2	67.5	0.2983
M13	153	12.5	56.2	35	23.8	25.7	**0.0094***
M14	102	8.4	42.2	20	13.6	30.0	0.2405
M20	119	9.7	69.7	10	6.8	40.0	**0.0486***
M21	35	2.9	60.0	8	5.5	87.5	0.5713
Total	1222	100%	69.4	147	100%	52.4	**<0.0001***
Completion of adjuvant chemotherapy (6 cycles):							
No	316	25.9%		33	22.4		0.3701[#]
Yes	906	74.1%		114	77.6%		

** A statistically significant probability value (log rank test, p <0.05); [#] Chi square test; TTC: time to initiation of chemotherapy after primary surgery; M11: comprehensive treatment of the upper part of the reproductive system in patients without serious comorbidities (including modified radical hysterectomy or pelvic exenteration); M12: extensive treatment of the upper part of the reproductive system in patients without serious comorbidities (including enlarged hysterectomy or laparoscopically assisted vaginal hysterectomy); M13: extensive treatment of the upper part of the reproductive system (including simple hysterectomy or laparoscopic bilateral salpingo-oophorectomy or unilateral salpingo-oophorectomy; M14: moderate treatment of the upper part of the reproductive system (including laparoscopic unilateral salpingo-oophorectomy or ovarian wedge resection); M20: comprehensive treatment of the upper part of the reproductive system in patients with serious comorbidities (diabetes mellitus, coronary artery disease, atrial fibrillation, etc.); M21: very extensive treatment of the upper part of the reproductive system in patients with serious comorbidities (diabetes mellitus, coronary artery disease, atrial fibrillation, etc.).*

Table 4. — *Univariate and multivariate overall survival analysis of prognostic factors for patients with ovarian cancer who received chemotherapy after primary surgery.*

Factors	Univariate analysis			Multivariate analysis	
	No. of patients	Three-year survival (%)	*p*-value	Hazard ratio (95 % CI)	*p*-value
Completion of six cycles of chemotherapy					
Yes	1020	70.7	**0.0029***	1.55 (1.19-2.03)	**0.0012***
No	349	57.0			
Paclitaxel + cisplatin *vs.*	231	69.3	0.2365		
Paclitaxel + carboplatin	1138	67.7			
Type of surgery					
M11 + M12 *vs.*	887	75.2	**<0.0001***	2.02 (1.70-2.40)	**<0.0001***
others	482	53.5			
TTC ≤ 14 days *vs.*	147	52.4	**<0.0001***	1.62 (1.27-2.06)	**<0.0001***
>14 days	1222	69.4			
TTC ≤ 21 days *vs.*	369	61.0	**0.0024***		
> 21 days	1000	70.0			
TTC ≤ 30 days *vs.*	697	65.4	**0.0357***		
> 30 days	672	69.8			
TTC ≤ 43 days *vs.*	1035	67.5	0.4778		
> 43 days	334	67.7			

* A statistically significant probability value (p <0.05), TTC: time to initiation of chemotherapy after primary surgery, M11: comprehensive treatment of the upper part of the reproductive system in patients without serious comorbidities (including modified radical hysterectomy or pelvic exenteration); M12: extensive treatment of the upper part of the reproductive system in patients without serious comorbidities (including enlarged hysterectomy or laparoscopically assisted vaginal hysterectomy).

Discussion

The present findings based on the data from the PNHF show that, among women with OC who underwent chemotherapy, considerable variability existed in the implementation of this treatment. The authors found that patients who initiated therapy earlier than 14 days after the primary surgery procedure were more likely to die than were patients with TTC later than 14 days. In addition, the earlier initiation of chemotherapy after the primary surgery procedure was an independent adverse prognostic factor in this cohort.

Studies in animal models showed that surgery increased the angiogenesis process [10], the production of oncogenic growth factors, and immunological disorders [11]. Surgery might suppress cytotoxic T-cell and natural killer cell activity, enabling the growth of micrometastases [12]. This mechanism could lead to faster tumor growth. The longer

interval between surgery and adjuvant chemotherapy proved to increase the risk of proliferation and the spread of residual cancer cells. Chemotherapy was more effective when the tumor was smaller. Mathematical modeling suggested that the drug sensitivity of tumors was related to their spontaneous mutation rate, which was a function of time [13]. Therefore, the early start of postoperative chemotherapy could be more effective in eliminating the remaining cancer cells [14].

In a univariate analysis, Flynn *et al.* [15] found, in a group of 472 patients with OC, women who started chemotherapy within three weeks after primary surgery showed shorter progression-free survival than women who started later. However, the group treated earlier showed a significantly higher percentage of patients with large-volume residual tumors (>2 cm). In a multivariate analysis, this effect was not confirmed as an independent adverse prognostic factor. Authors of this study suggested that patients treated earlier had shorter progression-free survival, probably due to differences in the volume of their residual disease after primary surgery.

In the present study, the authors observed a similar effect. Patients in the group with shorter TTC underwent a greater amount of surgery, suggesting a large volume of residual disease (less radical surgical procedures such as M13 and M14). In contrast, although the percentage of M20 procedures, which describes surgery in patients with comorbidities, was insignificantly lower in the TTC<14 group, the use of chemotherapy shortly after surgery had an unfavorable impact on survival in this group. This could underline the adverse impact of administering chemotherapeutic agents during the postoperative enhanced catabolism period. In previously published studies to address this area, some authors found that the time of the chemotherapy initiation after primary surgery did not have a significant impact on survival. For example, in a multicentric Italian study, and in one study of from a US center, time of chemotherapy initiation had no effect on survival [16–18]. However, in other studies, some investigators have indicated that delaying the initiation of chemotherapy after primary surgery by more than six weeks was an adverse prognostic factor in patients with OC. A prospective GOG trial considered adjuvant cisplatin and cyclophosphamide, with or without doxorubicin, and the effect of delaying the initiation of treatment and outcome for 349 patients with Stage III OC. The investigators categorized patients by week of chemotherapy initiation and found that women who began therapy after week six had lower survival rates than those treated earlier [19]. Similarly, as observed by Wright *et al.* [20], among patients > 65 years with Stage III/IV OC based on the Surveillance, Epidemiology, and End Results-Medicare database, women who initiated chemotherapy six weeks after surgery had poorer overall and OC-specific survival than did women who did not delay treatment.

The concept for this study arose from the authors' desire to answer the following question: does the initiation of chemotherapy during the highest postoperative catabolism period jeopardize a patient's prognosis? This study demonstrated that there was little evidence for any standard that stipulated a strict time interval within which treatment should be initiated; however, beginning treatment within the highest postoperative catabolism period was discussed. Of particular importance in patients after oncological surgeries was protein catabolism, which stimulated rates of protein breakdown and amino acid oxidation, leading to a net loss of body protein. Observations made in patients with critical illness indicated that muscle wasting occurred early and rapidly during the first week and was more severe among patients with multi-organ failure [21]. Metabolically healthy patients lost 40–80 grams of nitrogen after elective abdominal surgery, which was equivalent to 1.2–2.4 kg of wet skeletal muscle. Patients with burns or sepsis experienced daily losses of up to 800 grams of muscle mass. Protein loss in type 2 diabetic patients after colorectal cancer surgery was shown to be 50% greater than in non-diabetics [8].

The main strengths of this study were the population-based cohort approach, and the large population from an actual, complete follow-up for mortality through the Polish Civil Registry System. The accuracy of these findings depended on the quality of the registry. However, the PNHF contained validated data, as reported by hospitals under pain of financial penalties and audits, which was sufficient for quality monitoring in gynecological oncology. In turn, the main limitation of the study was the lack of complete data containing the FIGO Stage of OC and the size of the residual disease after primary surgery, which are not currently collected by the PNHF. It is possible, that having the complete information on stage and residual disease could be helpful to explain away the observed differences in this study between groups of patients with longer and shorter TTC.

In conclusion, this nationwide population-based cohort study revealed a significantly increased risk of death in patients in which the initiation of chemotherapy occurred within 14 days after primary surgery compared with a TTC > 14 days. In real practice, the time of chemotherapy initiation after primary surgery can be dependent on various factors, such as the cooperation between institutions or the speed of recovery after aggressive debulking surgery. The adverse effects of the early administration of chemotherapy observed here were explained. In order to determine if they are dependent on differences in faster qualifications in patients with unfavorable prognostic factors after suboptimal debulking surgery, or whether they arise from the adverse effects of the administration of chemotherapy during the greatest postoperative catabolism, it is necessary to conduct a prospective study that randomizes patients to different time intervals.

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