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The rate and role of diaphragmatic peritonectomy in optimal cytoreduction in patients with advanced stage ovarian cancer: a prospective study of 100 patients

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Background. Diaphragmatic peritoneal metastasis by advanced epithelial ovarian cancer is a very common holdback precluding optimal cytoreduction. The aim of this study was to determine the rate of diaphragmatic peritonectomy during optimal cytoreductive surgery and its role in postoperative morbidity and survival in patients with advanced ovarian cancer.

Materials and methods. 100 consecutive patients with advanced epithelial ovarian cancer underwent cytoreductive surgery and were followed up prospectively (January 2009 – March 2014). Characteristics of surgery, rate of diaphragmatic peritonectomy and post operative complications were assessed. The Kaplan-Meier method was used for survival analysis.

Results. The median age of the entire cohort at the time of primary cytoreduction was 58.5 years (23–83). Optimal cytoreduction was achieved in 73 cases out of 100 patients. From 73 patients in 30 cases (41.1%) upper abdominal procedures, specifically diaphragmatic peritonectomy, was performed to achieve the main goal of cytoreduction – no visible or palbable disease at the end of cytoreduction. Non-optimal cytoreduction was achieved in 27 cases. According to the Clavien-Dindo complication grading system grade I and grade II complications occurred more often in patients that underwent diaphragmatic surgery. The median overall survival from the time of diagnosis to the last follow-up or death was 28 months (range 0–63 months). The factors associated with the longest survival after primary cytoreductive surgery were the disease free interval from the primary cytoreduction of more than 19 months (n = 51) versus less than 19 months (n = 49) (95% confidence interval, 51.7–59.5; P = 0.013) and no visible or palpable residual disease at the end of cytoreduction (n = 73) versus visible or palpable residual disease (n = 27) (95% confidence interval, 52.7–61.2; P = 0.03).

Conclusions. Based on our prospective analysis of advanced ovarian cancer patients, diaphragmatic peritonectomy is feasible and safe, ensures better rates of optimal cytoreduction and should not be an obstacle towards better survival.

Key words: advanced ovarian cancer, diaphragmatic peritonectomy, cytoreduction

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INTRODUCTION

Advanced ovarian cancer is known to have a poor prognosis and it is believed that the explication for this is the lack of specific symptoms and sensitive diagnostic methods in the early stage (FIGO I/II) of ovarian malignancy (1). In fact, only 1/4 of women are diagnosed at the early stage of disease (2). The prognostic factors of advanced ovarian cancer are the size of residual tumor as well as sensitivity to platinum plus taxane-based chemotherapy after surgery (3). The Gynecologic Oncology Group (GOG) presently defines optimal debulking as the surgery when a residual tumor size is 1 cm or less in the maximal diameter, however, only debulking to an invisible tumor can be admitted as complete (4–7). Cytoreductive surgery seems to be the key towards prolonged survival in the patients with advanced epithelial ovarian cancer (EOC). Many studies as well as the Cochrane Gynecological Cancer Group meta-analysis have shown that cytoreduction resulting in the lowest residual disease prolongs survival in the face of metastatic EOC (6–7).

Metastatic disease in the upper abdominal region (diaphragm, splenic hilum) is very common among the patients with advanced epithelial ovarian cancer. Up to 40% of women with advanced ovarian cancer have bulky metastatic diaphragmatic disease, especially in the right hemidiaphragm. The common justification for not performing optimal cytoreductive surgery is the metastatic disease in the upper abdominal region that leads to poorer overall survival rates (8).

The objective of this study was to determine the rate of diaphragmatic peritonectomy during optimal cytoreductive surgery and its role in postoperative morbidity and survival in patients with advanced ovarian cancer.

MATERIALS AND METHODS

After the approval of the Vilnius Region Ethics Committee we prospectively included and followed one hundred consecutive patients with advanced EOC who underwent primary cytoreductive surgery in the Obstetrics and Gynecology Centre at Vilnius University Hospital Santariškių Klinikos (VUH SK) between January 2009 and March 2014. All the patients signed their informed consent before the surgery. Preoperatively patients underwent transvaginal ultrasound, chest X-ray, abdominal and pelvic computed tomography as well as serum CA 125 assay. Patients undergoing secondary cytoreduction or cytoreductive surgery with intraperitoneal heated chemotherapy (HIPEC) were excluded from our trial.

Data concerning demographic variables, the specific histologic diagnosis, grade, stage, surgical procedures, volume of the residual tumor, surgical time, estimated blood loss, complications and postoperative hospital stay were collected and analysed.

Surgical complexity score (SCS) which indicates the number and complexity of surgical procedures was calculated (9). Postoperative complications were graded according to the Clavien-Dindo classification of surgical complications (CDGS) (10).

All patients received platinum-based combination chemotherapy. Progression-free survival (PFS) was defined as the interval from the date of the diagnosis to the date of disease progression or last follow-up. Overall survival (OS) was defined as the interval from the date of the diagnosis to the date of death or last follow-up.

SPSS Statistical Version 17 (SPSS Inc., Chicago, IL) was used for all analyses. Survival estimates were determined with the use of the Kaplan-Meier method, and a P value of less than 0.05 was deemed statistically significant.

RESULTS

The clinical characteristics are listed in the Table. The median age at surgery time of the entire cohort was 58.5 years (23–83 years). Most patients presented at the time of surgery with stage III disease (83%). The tumors were mostly grade 3 (76%) and with papillary serous histologic diagnosis (87%).

The median estimated blood loss was 700 mL (range 65–3 000 mL), 5 patients required perioperative blood transfusions. The median length of a surgery was 215 minutes (range 99–465 minutes), with 11 surgeries lasting greater than 300 min. In all of these 11 operations diaphragmatic peritonectomy was a part of a procedure. The median length of hospital stay was 11 days (range 5–39 days) with no statistical difference between patients who experienced diaphragmatic peritonectomy or did not.

Table. Characteristics of primary cytoreduction

Clinical characteristic	No. of patients (n = 100)
Mean (±SD) age, years	54.7 ± 12.9
FIGO stage	
IIIC	83 (83%)
IV	17 (17%)
Tumor grade	
Grade I	5 (5%)
Grade II	19 (19%)
Grade III	76 (76%)
Histological subtype	
Serous	87 (87%)
Clear cell carcinoma	1 (1%)
Endometrioid	3 (3%)
Other	9 (9%)
Surgical characteristic	
Median intra-operative blood loss, ml (range)	700 (65–3 000)
Median duration of the surgery, min (range)	215 (99–465)
Median hospitalization days, d (range)	11 (5–39)
Median surgical complexity score (SCS) (range)	4.68 (2–12)
Hepato-biliar surgeon participation	43 (43%)
Optimal debulking	73 (73%)
Diaphragmatic peritonectomy	30 (30%)
Neoadjuvant chemoteraphy	30 (30%)

Optimal cytoreduction was achieved in 73 cases. Diaphragmatic peritonectomy was performed in 41.1% of those patients. In patients who experienced diaphragmatic surgery the surgical complexity score was twice higher (6.6 vs. 3.0, $p < 0.001$) and hepatobiliary surgeons had participated and provided aid to senior gynaecological oncologists more often (77% vs. 29%, $p < 0.001$), respectively.

Postoperative complications were assessed according to the Clavien-Dindo classification system. There were mostly grade I and II complications noted with no statistically significant difference between patients who underwent diaphragmatic peritonectomy or did not. There was one grade V complication with postoperative deaths within 8 days after surgery due to large bowel perforation and peritonitis in the patient who did not experience diaphragmatic peritonectomy. Postoperative pleural-effusion was diagnosed in 10% of patients with diaphragmatic surgery. The overall complication rate was 13%.

The median OS for the entire cohort was 28 months (range 0–63 months). Median OS after optimal cytoreduction was reached by 92% of patients and after non-optimal cytoreduction by 68% of patients ($p = 0.03$). The median PFS for the entire cohort was 19 moths (range 2–63 months). Based on a Kaplan-Meier survival analysis, the factors associated with the longest survival after primary cytoreductive surgery were the disease free interval from the primary cytoreduction of more than 19 months (n = 51) versus less than 19 months (n = 49) (95% confidence interval, 51.7–59.5; P = 0.013) and no visible or palpable residual disease at the end of cytoreduction (n = 73) versus visible or palpable residual disease (n = 27) (95% confidence interval, 52.7–61.2; P = 0.03; Fig. 1).

DISCUSSION

Many studies have proved that optimal cytoreduction resulting in the lowest or no residual disease had prolonged survival of advanced EOC (6–7). The most common extra pelvic metastatic site of advanced stage epithelial ovarian cancer is the diaphragm, especially right hemidiaphragm (11). Einekel et al. have published that the involvement of diaphragm was diagnosed in 91% of the women (12). In advanced epithelial ovarian cancer diaphragmatic metastasis is often a holdback

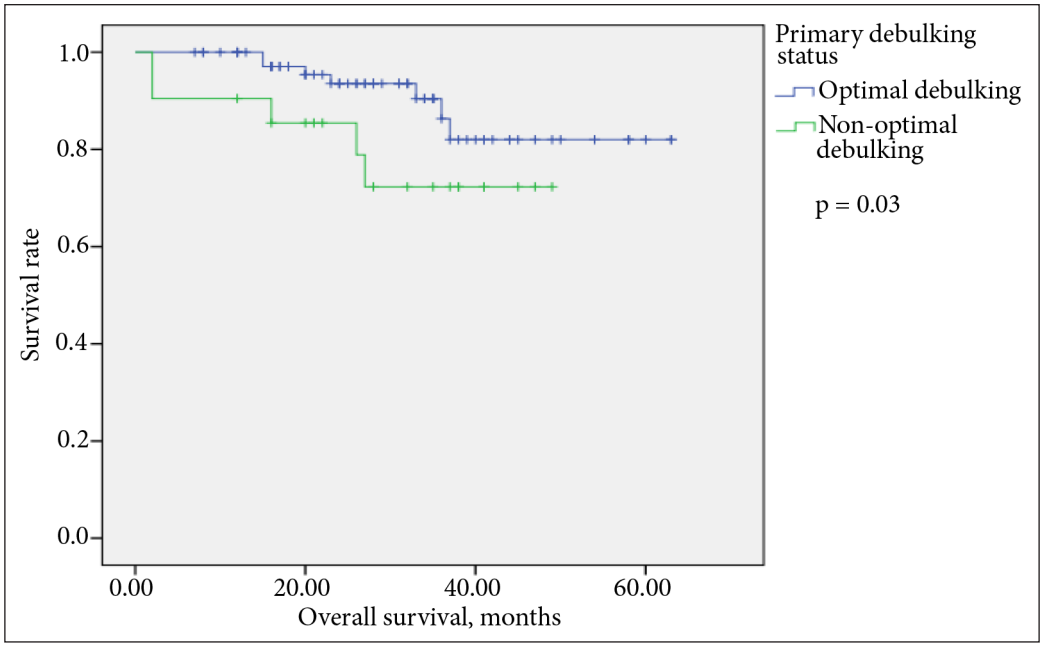

Fig. 1. Overall survival after optimal cytoreduction vs. non-optimal cytoreduction

to an optimal cytoreduction (13). Unfortunately common justification for not performing optimal cytoreductive surgery is the metastatic disease in the upper abdominal region (8), hence, it is really important to perform this radical surgery meticulously.

It is worth mentioning that every 10% decrease in a residual tumour is a 5.5% increase in the median survival time. Bristow et al. illustrated how optimal debulking can influence the median survival time: in centres where the optimal cytoreduction was achieved in more than 75% of cases the median survival time was 33.9 months, whereas in the centres where optimal debulking was less than 25% the median survival time was 22.7 months (5). We have demonstrated that optimal cytoreduction increases the median overall survival by 24% compairing to non-optimal cytoreduction. These results are consistent with the study of Aletti et al., he have proved that 5-year overall survival increases by 38% for the patients that undergo diaphragmatic surgery in order to achieve optimal cytoreduction (53% vs. 15%, $p < 0.0001$) (14).

In our study we have achieved an optimal cytoreduction in 73% of the patients with the aid of diaphragmatic peritonectomy (Fig. 2) in almost every second patient. Hepatic mobilization was performed in all patients who received diaphragmatic peritonectomy to reach the appropriate diseased area and to avoid liver ripping complications. As a consequence, due to additional complex procedures, the duration of surgery had increased and gynaecological oncologist required more assistance from hepato-biliar surgeons.

Furthermore, in our trial the rate of postoperative complications was higher among the patients with diaphragmatic surgical procedures, however, the complications were not severe (grade I or II). The most common complication among the patients with diaphragmatic peritonectomy was pleural effusion (10%). According to a literature review the rates of pleural effusion range from 10% to 59% for the patients with diaphragm surgery in stage IIIC/IV ovarian cancer (14). In our study

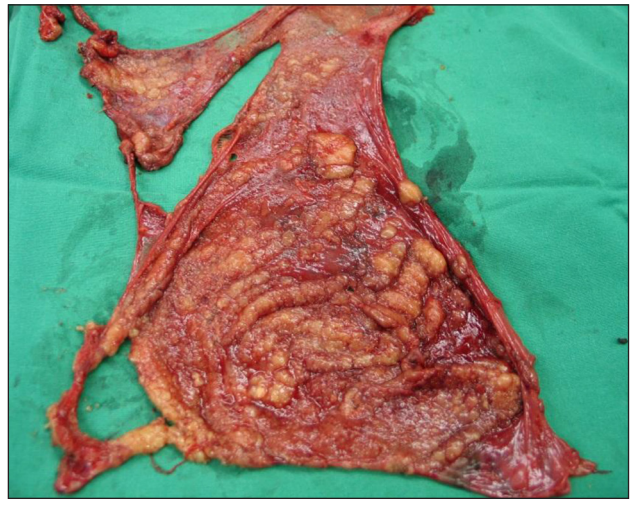

Fig. 2. Metastases on diaphragmatic peritoneum

the pleural space was opened in 10 (33.3%) cases during diaphragmatic surgery whereas the rates occurred in other studies ranged from 7 to 52% (15). Other complications among the patients who received diaphragmatic surgery were quite rare (postoperative dynamic ileus, severe anaemia and wound infection) and were managed conservatively. Besides, the diaphragmatic peritonectomy has not increased the length of hospital stay.

The patients who underwent optimal cytoreduction in our study were younger compared to the patients who did not, respectively 54.7 vs. 60.4 years. In other studies optimal debulking during the cytoreductive surgery also correlated with a younger patient's age (16). A possible explanation for this could be that surgeons feel more comfortable by attending to perform more complex procedures in the patient that has no comorbidities, generously has more factors for a favourable outcome (lower ASA score, higher serum albumin levels, etc.) (17–21).

We could only regret that we could not achieve optimal debulking in 27% of the patients, though it was a high risk group of patients with large tumor load and death of one patient occurred postoperatively in this group due to large bowel perforation and peritonitis. Therefore we should respect and remember the EORTC-GCG/NCIC trial results on neoadjuvant chemotherapy and interval debulking (22–23) because this approach could be an option for patients with high tumor burden.

CONCLUSIONS

In the present study we have presented that diaphragmatic surgery was associated with more complex surgical procedures, longer operative time and required specific skills, and an interdisciplinary team, though did not lead to longer hospitalization time and higher postoperative morbidity rate. Moreover, our prospective trial has demonstrated that diaphragmatic peritonectomy procedures are essential for ensuring optimal cytoreduction, better progression free survival and overall survival in cases of advanced epithelial ovarian cancer and that complex procedures should be performed as a part of an interdisciplinary team under supervision of a gynaecologic oncologist. Hence, in order to improve the gynaecological surgeon's technical skills in the diaphragmatic region and upper abdomen we suggest being a participating surgeon in an organ explantation team. Fellowship in a training centre could be an option too.

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DIAFRAGMOS SRITIES PERITONEKTOMIJŲ DAŽNIS IR REIKŠMĖ ATLIEKANT OPTIMALIĄ CITOREDUKCIJĄ IŠPLITUSIU KIAUŠIDŽIŲ VĖŽIU SERGANČIOMS PACIENTĖMS: 100 PACIENČIŲ PROSPEKTYVINIS TYRIMAS

Santrauka

Įvadas. Metastazės diafragmoje yra dažna kliūtis, užkertanti kelią optimaliai citoredukcijai gydant išplitusį kiaušidžių vėžį. Šio tyrimo tikslas – nustatyti diafragmos srities peritonektomijų dažnį atliekant optimalią citoredukciją pacientėms, sergančioms išplitusiu epiteliniu kiaušidžių vėžiu, bei tiesiogiai su šia procedūra susijusias komplikacijas.

Darbo metodika ir medžiaga. 100 pacienčių, kurioms atlikta citoredukcinė operacija dėl išplitusio epitelinio kiaušidžių vėžio, buvo stebėtos prospektyviai nuo 2009 m. sausio iki 2014 m. kovo mėnesio. Tyrimo metu buvo analizuojami atliktų operacijų ypatumai, diafragmos srities peritonektomijų dažnis ir pooperacinės komplikacijos. Išgyvenamumo rodikliai vertinti pagal Kaplan-Meier kreives.

Rezultatai. Pirminės citoredukcinės operacijos metu tiriamosios grupės amžiaus mediana buvo 58,5 metų (nuo 23 iki 83 metų). Optimali citoredukcinė operacija atlikta 73 iš 100 pacienčių. Diafragmos srities peritonektomija, atlikta 30 pacienčių iš 73 (41,4 %), padėjo pasiekti optimalią citoredukciją, tai yra buvo pašalinti visi čiuopiami ar matomi naviko židiniai. 27 pacientėms atlikta neoptimali citoredukcinė operacija. Remiantis Clavien-Dindo chirurginių komplikacijų klasifikacija, I ir II laipsnio komplikacijos dažniau pasitaikydavo pacientėms, kurioms buvo atlikta diafragmos srities peritonektomija. Vidutinis bendras išgyvenamumas nuo diagnozės nustatymo iki paskutinio susitikimo su paciente ar jos mirties buvo 28 mėnesiai (intervalas 0–63 mėnesiai). Ilgesnį išgyvenamumą po pirminės citoredukcinės operacijos lėmė šie veiksniai: ilgesnis nei 19 mėnesių išgyvenamumas be ligos atkryčio (n = 51), palyginti su trumpesniu nei 19 mėnesių išgyvenamumu be ligos atkryčio (n = 49) (95 % pasikliauties intervalas, 51,7–59,5; p = 0,013), taip pat visų čiuopiamų ar matomų naviko židinių pašalinimas (n = 73), palyginti su matomais ar čiuopiamais naviko židiniais po citoredukcinės operacijos (n = 27) (95 % pasikliauties intervalas, 52,7–61,2; p = 0,03).

Išvados. Remiantis atlikto tyrimo rezultatais galima teigti, kad diafragmos srities peritonektomija buvo dažna ir saugi citoredukcinės operacijos dalis, leidžianti pasiekti didesnį optimalių citoredukcijų dažnį, todėl ji neturėtų būti kliūtis užtikrinant ilgesnį pacienčių, sergančių išplitusiu kiaušidžių vėžiu, išgyvenamumą.

Raktažodžiai: išplitęs kiaušidžių vėžys, diafragmos srities peritonektomija, citoredukcija