How can cytoreductive surgery (CRS) and hyperthermic intraperitoneal perioperative chemotherapy (HIPEC) be implemented in ovarian cancer therapy in Poland?
– A report from the 1st Kujawsko-Pomorski Days of Cytoreductive Surgery

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Abstract
Improving the long-term survival rates in patients with advanced peritoneal malignancy requires complex treatment including cytoreductive surgery (CRS) followed by perioperative chemotherapy (e.g. HIPEC or hyperthermic intraperitoneal chemotherapy). The rules for this kind of treatment were established by Paul Sugarbaker and his coworkers in the 1990s. Two schools of thought regarding ovarian cancer therapy can be distinguished. The first concentrates on attributing a major prognostic significance to chemotherapy. The second concept of treatment is surgically-oriented and tends to push the limits of radicality as far as is technically possible. This second group has grown extensively though it remains the minority despite many randomized trials that have recently been published indicating a relationship between a complete cytoreductive primary procedure and improved long-term survival. It is well known that the most important factor influencing overall survival is the achievement of no gross residual disease during primary surgery, and such efficacy of surgery in advanced ovarian cancer is linked with the experience level of the surgeon and the volume of such surgeries performed at the oncological center. This is the most important reason the chemotherapy approach still dominates. To counter this, we have, with the support of the Peritoneal Surface Oncology Group International, organized the conference called “Cytoreductive Surgery Days” in Bydgoszcz at the Lukaszczyk Oncological Center in Bydgoszcz.

Key words: cytoreductive surgery, HIPEC, ovarian cancer, peritoneal malignancy

Introduction
Improving the long-term survival rates in patients with advanced peritoneal malignancy requires complex treatment including cytoreductive surgery (CRS) followed by perioperative chemotherapy (e.g. HIPEC or hyperthermic intraperitoneal chemotherapy). The rules for this kind of treatment were established by Paul Sugarbaker and his coworkers in the 1990s [1, 2]. For more than years cytoreductive surgery has been used successfully to treat various types of advanced cancer such as rectal, gastric, or ovarian cancers [3-11]. Initially, such an extensive surgical procedure was not widely accepted and at many oncological centers the efficacy of this method was doubted. However, the use of this kind of surgery has now spread throughout the whole world and is proposed by all the leading oncological centers. This change in surgical approach is particularly prominent when it comes to the treatment of patients with ovarian cancer [6].
Chan et al. reviewed 24 non-randomized studies concerning HIPEC. In total, 1167 patients with advanced ovarian cancer were included. Morbidity rates ranged from 5% to 90%; major morbidity rates related to HIPEC ranged from 0% to 40%. In only two of the studies reviewed by Chan were the ranges higher than 20%. Oxaliplatin was used as a chemotherapeutic agent in these two studies. An increased rate of intraperitoneal bleeding requiring re-operation was observed for those patients included this pair of studies [12]. The median time period of disease-free survival for HIPEC in the 24 studies was 13 to 56 months for patients with primary tumors and 13 to 24 for those patients with disease recurrence. The overall survival periods ranged from 14 to 64 months and 23 to 49 months respectively. The survival rates at 5 years ranged from 35% to 70% for those patients with primary tumors, and 12% to 54% for those who had disease recurrence. Five different studies have demonstrated that more than 50% of patients with ovarian cancer survive 5 years. The mortality rates ranged from 0% to 5% for those patients with primary tumors and from 0% to 10% for those with disease recurrence [12]. Deraco has suggested that two schools of thought regarding ovarian cancer therapy can be distinguished [13-15]. The first concentrates on attributing a major prognostic significance to chemotherapy (high initial chemosensitivity of ovarian cancer cells is the most important basis for this kind of thinking). The second concept of treatment is surgically-oriented and tends to push the limits of radicality as far as is technically possible [13]. This second group has grown extensively though it remains the minority despite many randomized trials that have recently been published indicating a relationship between a complete cytoreductive primary procedure and improved long-term survival [8]. It is well known that the most important factor influencing overall survival is the achievement of no gross residual disease during primary surgery, and such efficacy of surgery in advanced ovarian cancer is linked with the experience level of the surgeon and the volume of such surgeries performed at the oncological center [13, 16]. Unfortunately, in the oncological centers in Poland the first group of practitioners (chemotherapy-oriented) dominates. In contrast to recent data supporting the surgical effort during the primary procedure, the majority of patients start adjuvant chemotherapy without complete or optimal (residual disease less than 1 cm) surgery. This is the most important reason the chemotherapy approach still dominates. To counter this, we have, with the support of the Peritoneal Surface Oncology Group International, organized the conference called "Cytoreductive Surgery Days in Bydgoszcz" at the Lukaszczyczk Oncological Center in Bydgoszcz.

Cytoreductive surgery days in Bydgoszcz

The CRS and HIPEC conference in Bydgoszcz was organized as a two-day conference on the 14th and 15th of March 2013. The workshop (CRS and HIPEC) was scheduled for the first day. Four cytoreductive surgical procedures were performed simultaneously in 4 different operating theaters on 3 patients with primary advanced ovarian cancer and one patient with advanced rectal cancer. All patients were operated on by experienced multidisciplinary surgical teams. For the procedures performed on the ovarian cancer patients each team was made up of an oncological surgeon and gynecologist (M.O., K.P., P.R., T.R., L.W. and W.Z.). The operating teams were encouraged by two expert surgeons (J.-M.C. and M.D.), who were familiar with CRS and HIPEC. Throughout the operation these surgeons commented on the progress of the procedure. In all cases, complete cytoreductive surgery was achieved (CC-0 in 3 cases and CC-1 in one case). In one case, in which peritoneal diffuse dissemination was observed and mesentry of the small bowel was also involved, complete cytoreductive surgery (CC-1) was followed by the HIPEC procedure. In all cases, a partial or total peritonectomy was necessary to achieve completion of the surgical procedure. Furthermore, splenectomy with distal pancreatectomy proved necessary. In one case, parts of the diaphragm on the left side were involved and afterward were removed en bloc along with the spleen and the distal parts of the pancreas. The reconstruction of the diaphragm was undertaken and later pleural drainage was performed. In all the cases of ovarian cancer the bulky lymph nodes were removed from the pelvis and paracolic gutter (until the left renal vein). Partial intestinal resection was necessary in each case: two entailed right colectomies and one a subtotal colectomy with partial small bowel resection. In one case the intestinal continuity was restored with mechanical stamps; in another, intestinal continuity was achieved by mechanical stamps, but an ostomy was also applied because three different parts of the intestine were removed. In a third case a terminal colostomy was applied. The average operation time was 8 hours. After the operation each of the patients was admitted to the intensive care unit (ICU). During the surgical procedure and subsequent ICU treatment a total blood transfusion (an average of 6 units of packed red blood cells) and plasma transfusion (average 4 units) were
necessary. Parenteral nutrition was applied during the first or second day after the operation. The workshop demonstrated that cytoreductive surgery performed according to the Sugarbaker protocol is possible in Poland.

The next day, the 15th of March, the two key note lectures were presented, one by M.D. concerning the learning curve for CRS and HIPEC, and another by JM.C. concerning recent French national recommendations for advanced ovarian cancer surgery, focusing on the program of authorization at the oncological center for ovarian cancer therapy, and a program of labialization surgery and gynecological work with these types of cancer patients. The Take Home Conclusions regarding the promotion of the CRS and HIPEC procedures were simple and reasonable for the participants, namely, that CRS and HIPEC now constitute routine rather than special surgical procedures, and so we need to begin supporting training programs. Furthermore, it was concluded that only cancer centers specializing in this type of surgery should propose this kind of therapy.

Questions: the answers help to introduce the extensive cytoreductive surgery to routine gynecological oncological practice (experts in cytoreductive surgery, M.D., JM.C., responded)

1) At which time in the natural course of the disease is it most appropriate to apply HIPEC following surgery (upfront therapy or interval cytoreduction followed by NACT or consolidation of the treatment)?
   Upfront therapy (JM.C. and M.D.).

2) Can you imagine applying HIPEC in cases involving platinum-resistant tumors? HIPEC is a procedure that should be dedicated to platinum-sensitive cases (JM.C.).

3) Do you find that the prolongation of TTCH (time to chemotherapy) due to CRS and HIPEC has a clinical consequence for our patients? TTCH prolongation is no such marker following HIPEC, but the anti-cancer effect of hyperthermia and intraperitoneal effusion of chemotherapeutic drugs evokes the strongest anti-cancer effect (P.R.).

4) Is there a relationship between the range of CRS and tumor biology? It is thought that the success of the surgical effort and the prolongation of overall survival time is a result of favorable biological behavior and not just the completeness of the surgery. The recent data concerning the relationship between the aggressive phenotype of ovarian cancer (typified by high Ki67 expression and low CD8+T lymphocyte peritoneal infiltration) and the benefit of extensive surgery revealed that aggressive CRS provides a higher benefit for patients exhibiting the aggressive phenotype [17] (M.D.).

5) In your opinion, is being able to remove all the visible tumor implants the result of the favorable biological behavior of the tumor or rather of the experience of the surgeon? The achievement of complete surgery in the majority of cases (at least 75% of cases) is related to the proper selection of the patient based on the experience of the surgeon. The decision of whether to operate or not mainly depends on the type of cancer dissemination within the small bowel and its mesentery (M.D.).

6) How many surgical procedures does a surgeon have to perform in order to become an expert in CRS, and how many procedures a year should be performed by a surgeon who is an expert in CRS in order to maintain his or her surgical skills? Analyses of the learning curve indicate that it is necessary to perform at least 145 procedures of CRS and HIPEC in order to become a surgeon experienced with the procedure (M.D.).

   At least 20 procedures per year should be performed by a surgeon in order to maintain the necessary level of surgical skill. This number is thought to be the minimum necessary for labializations of surgeon. Furthermore, the surgeon must be employed in an authorized oncological center and in an authorized oncological center for ovarian cancer. 80 CRS procedures should be performed a year (JM.C.)

7) Is NACT (neo-adjuvant cancer therapy) a factor in facilitating optimal cytoreduction?
   It is logical, but it will be reasonable to reduce the usage of NACT to cases requiring support by NACT. In the majority of cases, the complete cytoreductive procedure is possible without NACT, but the adequate surgical experience is required (JM.C.).

8) Do you routinely use the peritoneal cancer index (PCI) proposed by Sugarbaker at the beginning of a surgery in order to assess the possible completeness of the cytoreduction? Yes, PCI is a strong predictor of overall survival [18] (M.D.).

9) On how many patients with ovarian cancer are you able to perform complete cytoreduction (at the level of CC score 0 or 1)? In at least 75% of cases (M.D.).

10) Can HIPEC cause an increased incidence of postoperative bleeding? Have you observed this? This correlation was observed by Pomel and colleagues. In this study HIPEC was used as a consolidation of therapy [19].

11) What kind of chemotherapeutic agents should be
used in HIPEC for ovarian cancer patients? Chan et al. reviewed 24 studies concerning the usage of HIPEC in patients with ovarian cancer. In 20 of the 24 studies reviewed by Chan and colleagues the platinum-based chemotherapy was used. In the majority of cases Cispaltin was applied [12].

12) Is secondary cytoreductive surgery (SCS) also linked with the best overall survival? Yes it is; in my recent paper presenting a group of 108 patients with ovarian cancer relapse and complete and optimal SCS, it was linked with statistically significant prolongation of overall survival time after the first relapse (optimal SCS vs non-optimal SCS ranged from 35 vs 15 months) [20] (J.-M.C.).

13) What kind of steps can be distinguished for peritoneectomy? First the omental bursa should be opened. The incision should be made 2-3 cm from the left side of the central vein. Furthermore, the sub-diaphragmatic part of the central vein should be visual, and the caudal lobe of the liver should be mobilized at first (M.D.).

Peritonectomy should be started from removal of peritoneum from the diaphragm, because this part of cytoreductive surgery is linked with a majority of cases of such complications as pre-operative bleeding from the liver space or diaphragm. When the peritonectomy is begun from the diaphragm, the surgeon has the possibility of observing the diaphragm and checking homeostasis potentially until the end of the CRS procedure (J.-M.C.).

14) How often do you restore intestinal continuity with a rectal stamp during CRS? If at all possible, the intestinal continuity should be restored during the same procedure (M.D.). If possible the Hartman procedure should be avoided (J.-M.C.).

15) Is a terminal colostomy instead of restoration of intestinal continuity prior to HIPEC a reasonable procedure to avoid fistulas? In some cases, yes, but this procedure should be used only in special cases, although the data from the literature is contradictory. Di Giorgio et al. have proposed opting for terminal colostomy during the primary surgery and postponing restoration of intestinal continuity for a second look [21]. Generally the restoration of intestinal continuity is not possible in every case and it requires an additional surgical procedure, so it would seem better to restore the intestinal continuity before the HIPEC procedure (M.D.).

16) How often do you observe pancreatic fistula following distal pancreatectomies? It is a rare complication. According to the data from different studies it has appeared in no more than 2% of cases.

17) What kind of treatment do you recommend in such a case? Drainage, intra-venous somtosatins, and parenteral nutrition.

18) In every case of advanced ovarian cancer do you perform CRS in the upper abdomen, cleaning the following areas: omental bursa (OB), surface of the pancreas, lesser omentum, caudate lobe, celiacnodes (CNs), portal node, and triad nodes spread? Raspagliesi revealed that in about 65% of cases, the OB area was found to be involved in advanced ovarian cancer. In order to achieve complete cytoreduction (real optimal debunking) these peritoneal metastases located within the OB area are removed and their removal is linked with the prolongation of long-term survival [22].

19) How often do you perform lymphadenectomies during primary or secondary CRS? Lymphadenectomies are performed at the end of cytoreductive surgery. Bulky nodes are removed routinely (J.-M.C.).

20) What is the range of lymphadenectomies that you perform (para-aortic and pelvic... celiac? Routinely until the left renal vein (J.-M.C.)

21) Have you observed increasing incidence rates of perioperative bleeding following HIPEC? No, but the low rate of complication is related to the surgical experience and the passage through the learning curve. To achieve the desired parameters for this type of surgical procedure, including an incomplete cytoreduction rate less than 10.2%, G3-5 morbidity at the level of 28.5%, and mortality rates at the level 2.2%, a surgeon should perform 149 procedures. The individual learning curve differs from the institutional learning curve, but both should be elucidated. What constitutes the critical point on the learning curve differs for various oncological centers and ranges from 55 to 222 procedures [15, 23] (M.D.).

22) Are the majority of complications related to the extensiveness of the surgery or to HIPEC? The most common adverse post-operative events are: pleural effusion, pneumonia, abscess, infection, urinary infection, urinary retention, bleeding, biliary fistulas, gastrointestinal fistulas, and pancreatic fistulas. G3-G5 morbidity rate ranges are no more than 25% of cases and the procedure-related mortality is no more than 5% [15] (M.D.)
Conclusions

- Removal of all visible tumor implants is crucial for the long-term outcome and this has been proven in a randomized trial.
- Completeness of cytoreduction in peritoneal malignancy is not a direct consequence of a favorable biological behavior but of surgical experience [24, 25].
- Standardization of therapy requires the organization of high-volume cancer centers (specialized institution).
- The efficacy of CRS and HIPEC in patients with both advanced ovarian cancer and ovarian cancer relapse based on a non-randomized trial.
- It seems important to establish the randomized trials presenting HIPEC as an acceptable alternative to the current standards of care for the adjuvant treatment of advanced ovarian cancer.

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References


