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The outcomes of radiotherapy in patients with ovarian carcinoma

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Summary

Relapses of ovarian cancer have poor prognosis, overall survival (OS) after recurrence depends on patient's performance status, histological cell type, size and number of the relapse, and duration of the platinum-free interval. Pelvis, peritoneum, pleural effusion, liver, lung, lymph nodes, and central nervous system are the most frequent sites of relapse. The standard treatment for ovarian cancer is a combination of surgery and chemotherapy. This retrospective study aimed to describe incidence, characteristics, outcomes and prognostic factors of patients with ovarian cancer underwent radiotherapy. *Results:* In 47 with ovarian cancer underwent radiotherapy. Treatment modalities were radiotherapy 8- 56 Gy. After optimal treatment the authors observed complete remission in seven patients, and progression and/or metastases in 40 patients. The present study confirmed that patients with low advancement stage had better prognoses than patients with advanced disease, as confirmed by OS rates in groups T1 *vs.* T3 ($p = 0.066$) and T3 *vs.* T4 ($p = 0.066$). What was interesting was that the disease-free survival (DFS) in the group of patients with T3 cancer was longer than in the group of patients with T1 cancer. Time to marker progression (Ca 125) was longer in groups with FIGO Stage I *vs.* II and I *vs.* III ($p = 0.016$, $p = 0.044$), while the time to progression in FIGO Stage II cancer patients was shorter than in FIGO Stage III cancer patients. An interesting result was also obtained in the analysis of 36-month survival where a larger number of patients without the disease symptoms had T3 Stage cancer. New prospective studies, designed to include the aspects of target volumes, total doses and fraction doses, together with the use of state of the art planning techniques, and therapeutic instrumentation are required.

Key words: Cancer; Ovary; Radiotherapy; Brachytherapy.

Introduction

Ovarian carcinoma is currently the second most common cause of deaths for genital cancer in the Western countries. Standard management of ovarian carcinoma consists in combination of surgery and chemotherapy [1, 2]. Recurring ovarian carcinoma is associated with poor prognosis, with overall survival (OS) following a relapse being dependent on the overall condition of patients, histopathological type of tumor, size and number of relapse lesions, as well as time from last platinum-based chemotherapy [3].

Most common recurrence locations include pelvis, peritoneum, pleura, liver, lungs, lymph nodes, and central nervous system [3, 4]. About 70% patients with advanced-stage ovarian carcinoma respond to the first chemotherapy regimen; unfortunately, most of these patients experience disease recurrence, with median time to progression of about 18 months and median OS of about 24 months. The efficacy of chemotherapy delivered to these patients is lower than that of the first-line treatment; this means that only a small percentage of patients actually benefits from subsequent chemotherapy [5]. Currently, radiation therapy plays a less significant role, being used mainly as a next-line or palliative treatment.

The aim of this retrospective study was to assess the results of radiotherapy in ovarian carcinoma patients.

Materials and Methods

The study was conducted in ovarian carcinoma patients undergoing radiation therapy in the Department of Teleradiotherapy of the Oncology Center in Bydgoszcz between January 2009 and December 2013. The analysis covered patients with all stages of ovarian carcinoma, i.e. FIGO and TNM Stages I-IV (Table 1). The patients age ranged from 35 to 67 years. The most common cancer type as determined in histopathological assessment was adenocarcinoma and its histological variants. Lymph node metastases were confirmed in 22 patients while N0 Stage was identified in 18 patients. Tumor differentiation Grades G2 and G3 were determined in 12 and 18 patients, respectively (Table 2). Eleven patients underwent radiotherapy twice; three patients were irradiated three times while one patient underwent radiation treatment as many as five times. Radiotherapy was delivered to the pelvis in 25 patients, para-aortic lymph nodes in 12 patients, local lesions in 11 patients, and metastases in 13 patients; patients had a history of multiple surgical and/or systemic treatments.

Patients were treated in line with the accepted management standard; in most cases, this included combination treatment. Surgical treatment was undertaken in all 47 patients; of these, three

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Table 1. — *Patient's TNM and FIGO Stage.*

TNM Stage	Number of patients	FIGO Stage	Number of patients
T1	10 (21.2%)	I	7 (14.89%)
T2	13 (27.65%)	II	11 (23.40%)
T3	16 (34.04%)	III	23 (48.93%)
T4	2 (4.25%)	IV	4 (8.51%)
Tx	6 (12.7%)	X	2 (4.25%)

Table 2. — *Characteristics of patients with ovarian carcinoma.*

	Number of patients
Lymph node status	
Without lymph node involvement - N0	18 (38.29%)
With lymph node metasases - N1	22 (46.80%)
Unknown status - Nx	7 (14.89%)
Histopathological assesment	
Folliculoma	2 (4.25%)
Granulosa cell tumor	1 (2.12%)
Epitheliolid carcinoma	1 (2.12%)
Adenocarcinoma	12 (25.53%)
Adenocarcinoma endometroides	3 (6.38%)
Adenocarcinoma papillare serosum	3 (6.38%)
Adenocarcinoma serosum	1 (2.12%)
Adenocarcinoma clarocellulare	4 (8.51%)
Cystoadenocarcinoma	12 (12.53%)
Infitrartio carcinoma	3 (6.38%)
Carcinoma papillare	2 (4.25%)
Carcinoma serosum	1 (2.12%)
Carcinoma mucinosum	1 (2.12%)
Tumor differentation Grade	
Grade 2	12 (25.53%)
Grade 3	18 (38.29%)
Unknown status Gx	17 (36.17%)

patients required no adjuvant systemic treatment. The remaining patients received chemotherapy, most commonly platinum-based regimens in combination with taxoids.

Disease recurrence was experienced by 44 patients, all of whom required combination treatment including next-line chemotherapy and/or radiotherapy and/or surgery. External beam irradiation was delivered at doses of 8-56 Gy in 47 patients, including 13 patients who received palliative radiation therapy for metastases. Radiotherapy consisted of irradiation of the tumor with appropriate margin at doses of 8-20 Gy in one to five fractions as part of palliative therapy.

In patients with confirmed metastases into the lymph nodes or pelvis or patients with local recurrence, target volume most commonly included the area from the L1 segment to the obturator foramina, laterally two cm from the pelvic walls on both sides, from 1/3 of pubic symphysis to the S2/S3 intervertebral joint in anteroposterior projection so as to include para-aortic, common iliac, external iliac, internal iliac presacral, and obturator lymph nodes.

In patients with confirmed metastases into para-aortic lymph nodes, target volumes most commonly spanned from the upper edge of the 12th thoracic vertebra down to the L5/S1 intervertebral joint, including a healthy tissue margin. The treatment was delivered at total doses of 30-56 Gy, with daily fraction dose of two to three Gy using six and 15 MeV energy sources. High-dose rate (HDR) brachytherapy was performed in seven patients at doses of 10-30 Gy divided into one to four fractions.

Repeated surgery was required by 32 patients, including six patients who were subjected to at least three surgical procedures. After completion of the treatment, response was observed in seven patients, with 40 patients experiencing progression and/or distant metastases. M1 stage was developed in 31 patients; 22 died of the disease while the fates of another three patients are unknown. Follow-up visits were held at four weeks after completion of radiotherapy and then at three-month intervals. Patient follow-up lasted at least 12 months. Three patients did not report to follow-up visits; further course of their disease remains unknown.

Statistical analysis

Statistical analysis of the was performed using Statistica, version 10.0. The association between OS rate, DFS rate, progression free survival rate, and prognostic factors was estimated using Kaplan-Mayer model. Differences between categorized groups were assessed with using the log-rank and Cox-Mantel tests. Proportions of survivors at 24 and 36 months were assessed using Chi-square test. Statistical significance was considered at $p < 0.05$.

Results

OS

Parameters affecting the likelihood of survival were analyzed in the entire group, including: T-staging, FIGO classification, tumor differentiation grade G, lymph node status, treatment history including surgery, first, second, third, next-line chemotherapy, induction chemotherapy, pelvic radiotherapy, local radiotherapy, para-aortic lymph node radiotherapy, radiotherapy of metastases, and brachytherapy. Log-rank test demonstrated borderline statistical significance for longer OS in patients with tumor advancement stage T1 as compared to T3 ($p = 0.066$) and higher OS rates in patients with T3 cancer as compared to patients with T4 cancer ($p = 0.064$) (Figure 1). A trend towards higher survival rates was also observed in patients with differentiation grade G2 as compared to patients with differentiation grade G3 ($p = 0.071$). No evidence was provided for N1 Stage (presence of lymph node metastases) having a negative impact on the survival as compared to N0; likewise, no effect of distant metastases was observed.

Log-rank and Cox-Mantel tests revealed no significant effects of the second-, third- and next-line chemotherapy on OS. The next stage of statistical analysis included the assessment of the effect of radiation therapy on ovarian carcinoma patients. No effect on OS was observed for pelvic radiotherapy, para-aortic lymph node radiation therapy (Figure 2), and brachytherapy ($p > 0.05$).

A trend towards shorter OS times was observed in patient undergoing local radiotherapy as compared to patients not subjected to such treatment ($p = 0.079$), particularly with respect to long-term survival (Figure 3).

In the entire study group, statistical significance (log-rank test) was determined for the effect of metastases radiotherapy on OS; patients undergoing such treatment were characterized by longer OS times than patients not subjected to the metastases-targeted radiotherapy ($p = 0.18$) (Figure 4).

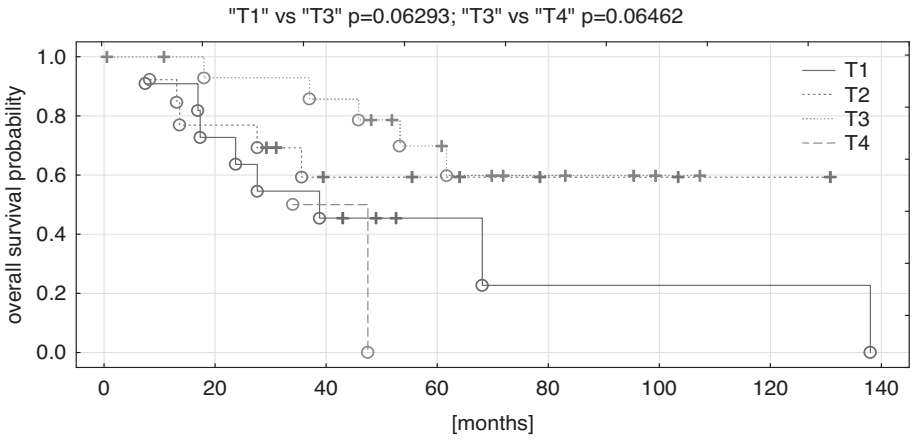

Figure 1. — Overall survival in patients with ovarian cancer in TNM stage.

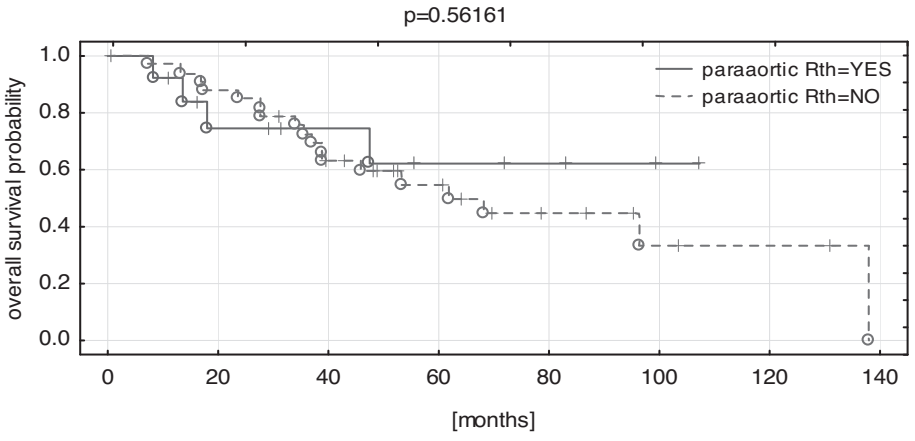

Figure 2. — Overall survival in patients with ovarian cancer with para-aortic lymph node radiotherapy *vs*. without radiotherapy.

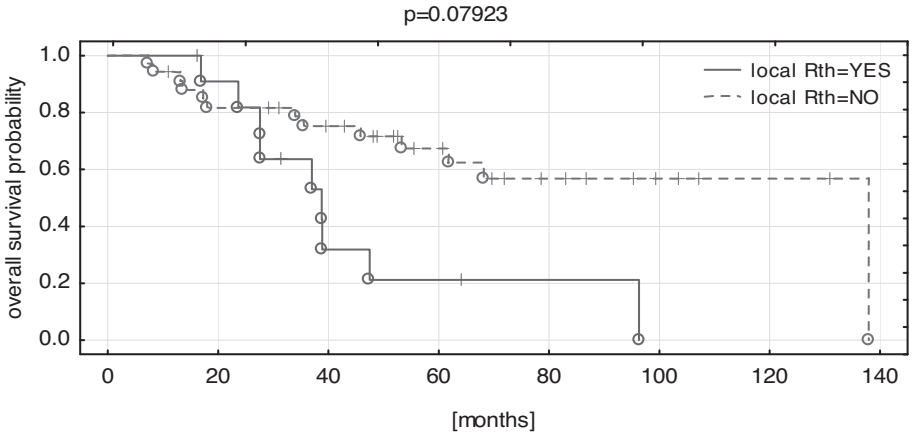

Figure 3. — Overall survival in patients with ovarian cancer with local radiotherapy *vs*. without radiotherapy.

The number of surgical procedures also affected OS at borderline statistical significance ($p = 0.06$, lower 95% CI limit -1.29235; upper 95% CI limit 0.04119).

DFS

The analysis of DFS time included the assessment of various parameters using the log-rank test to demonstrate that DFS was significantly longer in patients with tumor stage T3 as compared to patients with tumor stage T1 (p=0.03, lower 95% CI limit -2.62712, upper 95% CI limit 0.104210). Correlation of DFS with lymph node involvement proved to be very interesting. Statistically longer DFS times were observed in patients with confirmed lymph node metastases as compared to patients with clinical stage N0 ($p = 0.046$). Statistical evaluation was also performed for tumor differentiation grade confirming that

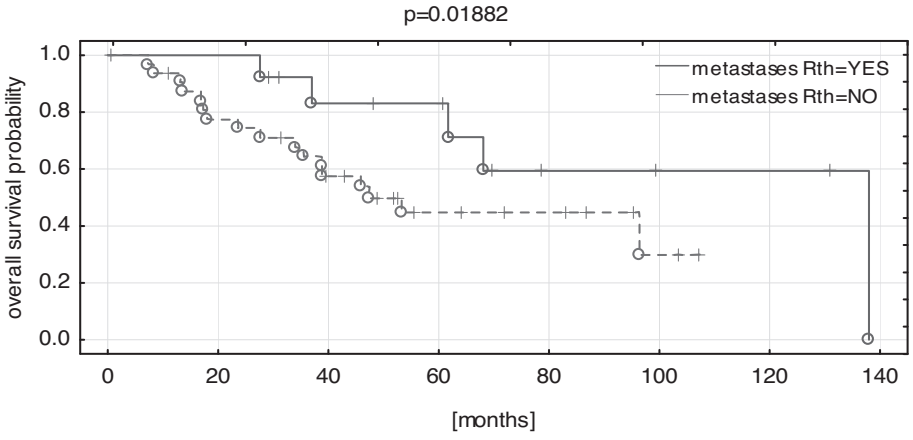

Figure 4. — Overall survival in patients with ovarian cancer with metastases radiotherapy *vs*. without radiotherapy.

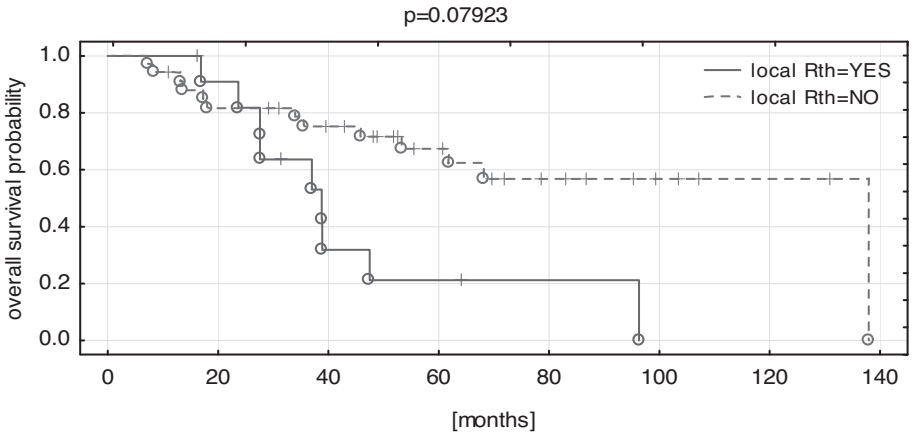

Figure 5. — Disease-free survival in patients with ovarian cancer with metastases radiotherapy *vs*. without radiotherapy.

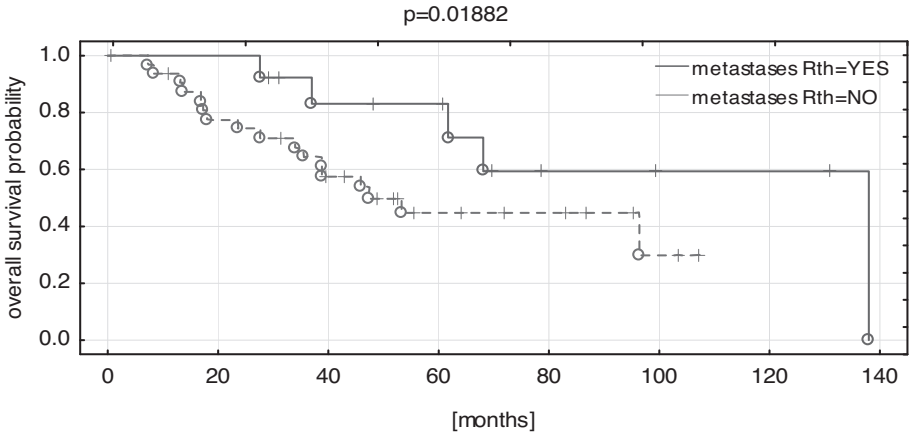

Figure 6. — Disease-free survival in patients with ovarian cancer with brachytherapy *vs*. without brachytherapy.

the DFS was longer in patients with tumor grade G2 as compared to patients with tumor grade G3 ($p = 0.27$).

With the Cox-Mantel test, a significant effect on DFS was demonstrated for first-line chemotherapy *vs*. no systemic treatment ($p = 0.007$). Patients treated with induction chemotherapy were characterized by shorter DFS as compared to patients not subjected to this treatment ($p = 0.002$).

The study did not demonstrate any effect of the second-, third-, and next-line chemotherapy on longer DFS; similarly, no effects were observed for pelvic radiation therapy, para-aortic node radiation therapy or local radiotherapy. A trend towards shorter DFS times was observed in the group of patients undergoing palliative radiation therapy for distant metastases as compared to patients not subjected to radiation therapy ($p = 0.08$) (Figure 5).

The next stage of statistical analysis included the assessment of the effect of brachytherapy on ovarian carcinoma patients. No effect on the DFS was observed ($p > 0.05$) However, curves in the Kaplan-Meier graph reveal a significant effect on local tumor control, particularly in the initial months, although no statistical significance has been reached (Figure 6). DFS time was longer in the group with minimum one surgical procedure as compared to no surgical procedures, with the difference at the border of statistical significance ($p = 0.055$).

Time until Ca125 marker progression

The next stage of the study included the analysis of time until Ca125 marker progression. The analysis revealed longer times until Ca125 marker progression in patients with FIGO stage I cancer as compared to patients with FIGO stage II cancer (p=0.016) as well as in patients with FIGO stage I cancer as compared to patients with FIGO stage III cancer (p=0.044). What is interesting, as shown in the graph, patients with FIGO stage II cancer had shorter times to progression than patients with FIGO stage III cancer, although the differences were not statistically significant).

The next step of the statistical analysis made use of the log-rank and Cox-Mantel tests to determine the effects of pelvic, para-aortic nodes radiotherapy, local radiation therapy, brachytherapy and metastases-targeted radiotherapy in ovarian carcinoma patients. Shorter times to marker progression were observed in patients receiving palliative radiotherapy for distant metastases as compared to patients who were not subjected (did not require) such treatment; the result was at the border of statistical significance (p=0.060).

None of the other parameters subject to the analysis, such as first-, second,- or next-line chemotherapy had any significant effect on the time to Ca125 marker progression.

24- and 36-month survival

Spearman's analysis was employed to analyze OS and DFS 24 and 36 months after treatment. The study showed that in the group of patients who survived 36 months without any symptoms of the disease, Stage T3 was more common than Stage T1 or T2 ($p = 0.03$). The study showed that the group of patients who survived 24 and 36 months without disease recurrence included more patients with baseline confirmation of node metastases as compared to patients with N0 Stage ($p = 0.25$ and $p = 0.25$, respectively). Further analysis revealed that in the group of patients who survived 36 months without any symptoms of the disease, Stage G2 was more common than Stage G3, and the result was at the border of statistical significance ($p = 0.062$). A borderline significance trend was observed towards a higher percentage of patients who survived 36 months without any symptoms of the disease and who had not been subjected to metastases-targeting radiation therapy (p=0.073). Statistical analyses of OS of 24 months after the baseline treatment revealed that a higher number of patients survived in the group not subjected to local radiation therapy as compared to patients who underwent local radiotherapy (p=0.01). A similar situation was observed in relation to surgical treatment: a higher percentage of patients survived 24 and 36 months after the baseline treatment if they had undergone surgery, as compared to patients not subjected to surgery ($p = 0.01$ and $p = 0.036$, respectively).

Discussion

Recent years have witnessed a return to radiotherapy as adjuvant treatment of ovarian carcinoma. That was due to the dynamic advances in the techniques involving the planning and delivery of radiation beam treatments. The goal of radiotherapy is to treat the largest possible volume within the abdominal cavity with possibly lowest risk of early or delayed radiation-induced reactions and good protection of critical organs.

Treatment of ovarian carcinoma poses a significant challenge to radiotherapist as no standards are available regarding irradiation, including total dose, fraction doses or target volume outlines. This is particularly important as the number of reports on the subject is limited and dates back to 1980s and 1990s or is based on small patient groups and/or short follow-up periods [6-12].

The present study confirmed that patients with low advancement stage had better prognoses than patients with advanced disease as confirmed by OS rates in groups T1 vs T3 ($p = 0.066$) and T3 *vs.* T4 ($p = 0.066$). What is interesting, the DFS in the group of patients with T3 cancer was longer than in the group of patients with T1 cancer. Time to marker progression (Ca 125) was longer in groups with FIGO Stage I *vs.* II and I *vs.* III ($p = 0.016$, $p = 0.044$), while the time to progression in FIGO Stage II cancer patients was shorter than in FIGO Stage III cancer patients. An interesting result was also obtained in the analysis of 36-month survival where a larger number of patients without the disease symptoms had T3 Stage cancer.

The obtained results regarding cancer staging could have been affected by the number of patients in the study group; however, in the present Author's opinion, the difference in management protocols for patients with low FIGO and TNM stage cancers and advanced cancer patients might be of importance here. In addition, ovarian carcinoma is difficult to diagnose and stage which might significantly affect the obtained results.

Another parameter subject to the analysis was the lymph node involvement status. The study revealed longer disease-free progression times in N(+) patients as compared to N0 patients; in addition, the analysis could not confirm that lymph node metastases contributed to longer survival. This might confirm errors in the accuracy of disease staging and/or presence of micrometastases in N0 patients. The role of lymphadenectomy in patients with advanced ovarian car-

cinoma is unclear. Some authors recommend intraoperational removal of pelvic and para-aortic lymph nodes, highlighting that lymph node metastases are observed in 50-70% of ovarian carcinoma patients. The researchers point out that this is the only way allowing for actual disease staging, as well as for the removal of bulky lymph nodes, thus significantly affecting the PFS, although having no effect on OS, as studies show. One should remember that besides lymph node metastases that accompany the disease spread, isolated lymph node metastases are also possible. In these cases, consideration of different therapeutic approaches, including radiotherapy, is recommended [13, 14].

An important result was the lack of the effect of the next-line chemotherapy on the OS as well as on the DFS, indicating therapeutic nihilism and the need to search for novel methods for the treatment of ovarian carcinoma. While radiotherapy of the entire abdominal cavity is controversial, the use of radiation in recurrent cancer and/or palliative treatment seems to be the main indication for the use of this technique in ovarian carcinoma patients [15, 16]. On the other hand, the only randomized trial that confirmed an increase in the OS and the PFS, as well as a reduction in the rate of recurrences, was the study conducted by Sorbe in which patients with advanced ovarian carcinoma after induction chemotherapy were subjected to radiotherapy of the entire abdominal cavity with higher doses targeted to the pelvic region [17].

The present study could not confirm the effect of radiotherapy on OS; however, it revealed good local control and positive impact on the DFS, particularly when the irradiation volume included para-aortic lymph nodes. The study results might have been affected by the total doses delivered during the treatments: some authors recommend doses as high as 45-60 Gy being delivered to bulky lymph node tumors in salvage therapy, while suggesting that even these doses might be insufficient [7, 10, 18, 19].

Blanchard *et al.* [13] analyzed a group of 640 ovarian carcinoma patients, 27 (4.2%) of whom developed isolated recurrences in lymph nodes. In 23 patients, the recurrence was correlated with an increase in the level of the Ca125 cancer marker. Most commonly, the recurrence was observed in retroperitoneal lymph nodes, followed by supraclavicular, mediastinal, mesenteric, and axillary lymph nodes. The treatment of recurrence episodes was varied. In 48% of cases, the disease recurrence was observed more than two years after cancer diagnosis. Mean OS was 68 months (12-210 months), while mean OS after lymph node recurrence was 26 months. Authors demonstrated no differences in two-year survival rates following a lymph node recurrence in the group of early recurrences (< 24 months) *vs.* the group of delayed recurrences (> 24 months) (59% and 47%, respectively). According to the authors, patients benefit most from radiotherapy in cases of isolated recurrence or recurrence in lymph nodes, particularly para-aortic lymph nodes [13].

Fujiwara *et al.* [20] assessed a group of isolated or multiple recurrences after disease spread was ruled out. The mean number of recurrences per patient was two (1-5), with a total of 44 recurrence foci in 20 patients. Patients were qualified to radiotherapy with total doses of 40-68 Gy administered in 1.6-2.0 Gy fractions. Tumor regression was observed immediately after treatment completion in 42 recurrences, with 39 recurrences responding within two to three months after the start of radiotherapy. The percentage of tumor regressions was higher in patients with lesions smaller than five cm and in cases when recurrences occurred in lymph nodes. However, according to the authors, disease progression outside radiation target volume occurred in most patients.

The study conducted by Tinger *et al.* [16] included 80 patients with ovarian carcinoma remission after at least one laparotomy and chemotherapy including one to 20 cycles of platinum-based agents. Some patients were subjected to radiotherapy targeting more than one site of recurrence and/or metastasis; in 64 patients, radiation was delivered to abdominal cavity, while 11 brain metastases and five metastases into other organs were also observed. Authors were able to achieve therapeutic response in 73% of patients, with complete resolution of symptoms, i.e. tumor mass and/or Ca 125 levels in 28% of patients. Partial response was observed in 45% of patients, while 11% of patients experienced progression during radiotherapy. Survival rates over periods of one, two, three, and five years after diagnosis were 89%, 73%, 42%, and 33%, respectively. Respective survival rates after completion of radiotherapy were 39%, 27%, 13%, and 10%, according to authors' estimates [16].

Many studies unambiguously point to the important role of radiotherapy in palliative treatment of ovarian carcinoma, particularly in metastases to the brain, bones, and lymph nodes [21]. Clinical symptoms may be related to recurrence within pelvis minor, as well as to metastases to the brain, lungs, and other locations. In their analysis of available literature, Delaney *et al.* [21] estimated that disease spread is observed in 38% of patients, with palliative radiotherapy indicated in 11% of patients. As shown by the studies, complete resolution of complaints is achieved after irradiation in 50-70% of patients [12, 15, 16, 20]. In about one-third of patients, the effect is maintained for about one year. The recommended total dose is about 30-45 Gy, depending on the general condition of the patient, cancer type and treatment history [3, 22].

Many authors recommend radiotherapy in palliative treatment of e.g. brain metastases, incidence of which has increased in recent years. Whole brain irradiation increases survival in ovarian carcinoma patients [3, 13].

Corn *et al.* [15] applied this treatment in 32 patients, demonstrating clinical response in 23 individuals. Of those, the response was maintained until death in 71% of cases.

The present study confirmed the importance of radiotherapy in palliative treatment, as patients subjected to this type of treatment had longer survival, although their DFS times

were shorter than in patients not subjected to radiotherapy due to distant metastases, obviously due to the stage of the disease. In addition, the study suggested that the control of 24-month survivals was better in the group of patients undergoing palliative radiotherapy, as compared to patients subjected to local radiotherapy. This indicates better radiotherapeutic control in the treatment of metastases as compared to local disease. The outcome might have been impacted by the fact that patients undergoing local treatment had history of multiple failures of other therapies (either surgical or systemic), where the treatment of metastases using irradiation was usually a primary treatment, commonly administered as a part of combination therapy.

The present study could not confirm the effect of brachytherapy on DFS. On the other hand, brachytherapy helped to achieve good local control, particularly within the first months after initiation of the treatment. The outcome might have been affected by the number of subjects, as clinical experience demonstrated an important role of brachytherapy in the treatment of ovarian carcinoma, particularly in advanced diseases including infiltration of uterine body and/or cervix and/or vaginal wall, as well as in helping to achieve good local control of the disease and/or antihemorrhagic effect [23].

The results presented herein as well as those reported by other authors suggest an important impact of adjuvant treatment in ovarian carcinoma patients, while indicating that radical surgery remains the imperative treatment goal as having an important effect on local control of the disease and increase in survival.

The results obtained in the present study should be subjected to further analyses in larger groups of patients; however, they may reflect inaccurate staging of the disease in patients in whom clinical presentation suggested a low stage and thus affected the extent of the procedure and impacted the overall survival and DFS.

Introduction of novel techniques of radiation planning facilitates irradiation of the largest possible volume within the abdominal cavity with the possibly lowest risk of early or delayed radiation-induced reactions in critical organs. The available techniques of intensity-modulated radiation therapy (IMRT), RapidArc, or tomotherapy may provide maximum protection of critical organs such as kidneys, liver, and intestines while ensuring precision and short treatment times when combined with image-guided radiation therapy (IGRT) [24-27].

It seems that the views on the role of radiotherapy in ovarian carcinoma treatment should be revised. The marginal use of radiotherapy should be extended by indications in the treatment of residual disease, post-surgery or post-chemotherapy residues, isolated inoperable metastases, recurrences, as well as in irradiation of the entire abdominal cavity in patients not qualified and/or resistant to chemotherapy or not consenting for other treatment methods. It should also be kept in mind that this treatment may be combined with intraoperative radiotherapy (IORT) in an increasing number of sites, providing an interesting alternative in the treatment of this disease [22, 26, 28].

Conclusion

In conclusion, the main limitation of the present study was the fact of its being a retrospective study in a small group of ovarian carcinoma patients. On the other hand, according to the Author's knowledge, this is one of few studies dealing with the role of radiotherapy in the treatment of ovarian cancer.

New prospective studies, designed to include the aspects of target volumes, total doses, and fraction doses, together with the use of state of the art planning techniques and therapeutic instrumentation are required. Other problems remaining to be solved are to determine the time point at which radiotherapy should be considered, whether the treatment should be administered in a standalone or combined fashion (together with chemotherapy and/or IORT and/or surgery), and what would be the appropriate order of therapeutic actions.

References

[1] Reinfuss M., Czepko A., Lesiak J., Kojs Z.: "Napromienianie chorych na raka jajnika technika "wędrujących pasków". Wstępna ocena tolerancji i skuteczności". *Nowotwory*, 1989, *39*, 53. [Article in Polish]

[2] Urban A., Miszczyk L.:" Rak jajnika- diagnostyczny i terapeutyczny problem ginekologii onkologicznej". *Cotenporary Oncol.*, 2003, *7*, 294. [Article in Polish]

[3] Teckie S., Makker V., Tabar V., Alektiar K., Aghajanian C., Hensley M., Beal K.: "Radiation therapy for epithelial ovarian cancer brain metastases:clinical outcomes and predictors of survival". *Radiat. Oncol.*, 2013, 8, 36.

[4] Zieliński J., Krzakowski M.: "Onkologia Kliniczna tom II". 1st ed. Krzakowski M. (ed). Warsaw: Borgis, 2001, 141.

[5] Nagai Y., Inamine M., Hirakawa M., Kamiyama K., Ogawa K., Toita T., *et al.*: "Postoperative whole abdominal radiotherapy in clear cell adenocarcinoma of the ovary." Gynecol. Oncol., 2007, *107*, 469.

[6] Dembo A.: "Abdominopelvic radiotherapy in ovarian cancer. A 10-year experience". *Cancer*, 1985, *55*, 2285.

[7] Goldhirsch A., Greiner R., Dreher E., Sessa C., Krauer F., Forni M., *et al.*: "Treatment of advanced ovarian cancer with surgery, chemotherapy, and consolidation of response by whole-abdominal radiotherapy". *Cancer*, 1988, *62*, 40.

[8] Buser M., Bacchi A., Goldhirsch R., Greiner R., Diener P., Sessa C., *et al.*:" Treatment of ovarian cancer with surgery, short-course chemotherapy and whole abdominal radiation". *Ann. Oncol.*, 1996, 7, 65.

[9] Wong R., Milosevic M., Sturgeon J., Pintilie M., Fyles A., Levin W.: "Treatment of early epithelial ovarian cancer with chemotherapy and abdominopelvic radiotherapy: results of a prospective treatment protocol". *Int. J. Radiat. Oncol. Biol. Phys.*, 1999, *45*, 657.

[10] Hacker N., Berek J., Burnison C., Heintz P., Juillard G., Lagasse L.: "Whole abdominal radiation as salvage therapy for epithelial ovarian cancer". *Obstet. Gynecol.*, 1985, *65*, 60.

[11] Fyles A.W., Dembo A.J., Bush R.S., Levin W., Manchul L.A., Pringle J.F., *et al.*: "Analysis of complications in patients treated with abdomino-pelvic radiation therapy for ovarian carcinoma". *Int. J. Radiat. Oncol. Biol. Phys.*, 1992, *22*, 847.

[12] Gelblum D., Mychalczak B., Almadrones L., Spriggs D., Barakat R.: "Palliative benefit of external-beam radiation in the management of platinum refractory epithelial ovarian carcinoma." *Gynecol. Oncol.*, 1998, *69*, 36.
[13] Blanchard P., Plantade A., Pages C., Afchain P., Louvet C., Tournigand C., de Gramont A.: "Isolated lymph node relapse of epithelial ovarian carcinoma: Outcomes and prognostic factors". *Gynecol. Oncol.*, 2007, *104*, 41.
[14] Pereira A., Perez-Medina T., Magrina J., Magtibay P.M., Millan I., Iglesias E.: "The role of lyphadenectomy in node-positive epithelial ovarian cancer". *Int. J. Gynecol. Cancer*, 2012, *6*, 22.
[15] Corn B., Greven K., Randal M., Wolfson A., Kim R., Lanciano R.: "The efficacy of cranial irradiation in ovarian cancer metastatic to the brain: analysis of 32 cases". *Obstet. Gynecol.*, 1995, *86*, 955.
[16] Tinger A., Waldron T., Peluso N., Katin M.J., Dosoretz D., Blitzer P., *et al.*:" Effective palliative radiation therapy in advanced and recurrent ovarian carcinoma". *Int. J. Radiat. Oncol. Biol. Phys.*, 2001, *51*, 1256.
[17] Sorbe B.: "Consolidation treatment of advanced (FIGO stage III) ovarian carcinoma in complete surgical remission after induction chemotherapy: a randomized, controlled, clinical trial comparing whole abdominal radiotherapy, chemotherapy, and no further treatment". *Int. J. Gynecol. Cancer*, 2003, *13*, 278.
[18] Petit T.,Velten M., d'Hombres A., Marchal C., Montbarbon X., Mornex F., *et al.*:" Long term survival of 106 stage III ovarian cancer patients with minimal residual disease after second-look laparotomy and consolidation radiotherapy". *Gynecol. Oncol.*, 2007, *104*, 104.
[19] Dowdy S., Metzinger D., Gebhart J., Srivatsa P., haddock M., Suman V.: "Salvage whole-abdominal radiation therapy after second-look laparotomy or secondary debulking surgery in patients with ovarian cancer". *Gynecol. Oncol.*, 2005, *96*, 389.
[20] Fujiwara K., Suzuki S., Yoden E., Ishikawa H., Imajo Y., Kohno I.: "Local radiation therapy for localized relapsed or refractory ovarian cancer patients with or without symptoms after chemiotherapy". *Int. J. Gynecol. Cancer*, 2002, *12*, 250.
[21] Delaney G., Jacob S., Barton M.: "Estimation of an optimal radiotherapy utilization rate for gynecologic carcinoma". Cancer, 2004, *101*, 671.
[22] Biedka M., Żmuda E.: "Możliwe zastosowanie radioterapii u pacjentek z rakiem jajnika". *Oncol. Radiotherapy*, 2013, *3*, 18.
[23] Murakami N., Kasamatsu T., Sumi M., Yoshimura R., Harada K., Kitaguchi M., *et al.*: "Vaginal tolerance of CT based image-guided high-dose rate interstitial brachytherapy for gynecological malignancies". *Radiat. Oncol.*, 2014, *9*, 31.
[24] Rochet N., Jensen A., Sterzing F., Munter M.W., Eichbaum M.H., Schneeweiss A., *et al.*: "Adjuvant whole abdominal intensity modulated radiotherapy (IMRT) for high risk stage FIGO III patients with ovarian cancer (OVAR-IMRT-01)-pilot trial of phase I/II study". *BMC Cancer*, 2007, *7*, 227.
[25] Rochet N., Kieser M., Sterzing F., Krause S., Lindel K., Harms W., *et al.*:" Phase II study evaluating consolidation whole abdominal intensity-modulated radiotherapy (IMRT) in patients with advanced ovarian cancer stage FIGO III-The OVAR-IMRT-02 Study". *BMC Cancer*, 2011, *11*, 41.
[26] Mahantshetty U., Jamema A., Engineer R., Deshpande D., Sarin R., Fogliata A., *et al.*: "Whole abdomen radiation therapy in ovarian cancers:a comparison between fixed beam and volumetric arc based intensity modulation". *Radiat. Oncol.*, 2010, *5*, 106.
[27] Shetty U., Shankar S., Engineer R., Chopra S., Gupta S., Maheshwari A., *et al.*: "Image-guided intensity-modulated whole-abdominal radiation therapy in relapsed epithelialovarian cancers: A feasibility study". *J. Can. Res. Ther.*, 2013, *9*, 17.
[28] Biedka M., Śpiewankiewicz B.: "Zastosowanie radioterapii śródoperacyjnej w nowotworach wywodzących się z narządów płciowych kobiet". *Curr. Gyncol. Oncol.*, 2012, *3*, 215.

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