



Stereotactic Body Radiotherapy for Lymph Node Relapse in Ovarian Cancer

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Abstract

Purpose: To evaluate the effectiveness and toxicity of stereotactic body radiotherapy (SBRT) for lymph node relapse in patients with ovarian cancer.

Material and Methods: Between August 2008 and March 2015, 11 patients were treated with SBRT on 20 lymph nodes of previous ovarian cancer. All patients at the time of ovarian cancer diagnosis were submitted to surgery and at least one line of chemotherapy (range, 1-3). Median age was 64 years (range, 49-74), and primitive histology was sero-papillar and endometrioid carcinoma in 8 (72%) and 3 (28%) patients, respectively. Median time between first diagnosis and lymph node relapse was 79 months (range, 16-171). Lymph node recurrence was documented with PET-CT as the only site of disease. Response was evaluated with PERCIST (PET Response Criteria in Solid Tumors) criteria.

Results: Median follow-up was 24 months, median Gross Tumor Volume (GTV) 5.35 cc (range, 1.5-18.3), median Planning Target Volume – obtained adding an isotropic margin of 5 mm to the GTV– 15.6 cc (range, 4.2-85.7). The lymph node relapsing sites were 14 (70%) sub-diaphragmatic (i.e., pelvic and lumbo-aortic), and 6 (30%) mediastinal. Fractionation schemes were 5 x 8Gy in 10 (50%), 5 x 7Gy in 2 (10%), 5 x 6Gy in 3 (15%) and 5 x 5Gy in 5 (25%) lymph nodes. Outcome, evaluated with PET-CT 3 months after SBRT, showed a complete metabolic response in all treated lesions. Local control (LC) at 2- and 5 years was 73% +/- 12 and 48% +/- 20, respectively and median duration of LC was 57 months. Outcome resulted related to administered doses. In fact, at the univariate analysis, LC was significantly better in 5 x 8Gy group versus 5 x < 8Gy group (p = 0.004). Cancer specific survival and overall survival at 2- and 5 years were 87% +/- 11 and 73% +/- 16 and 78% +/- 14% and 65% +/- 16, respectively. We did not register acute or late toxicity after SBRT.

Conclusions: All ovarian cancer patients submitted to SBRT for lymph node relapse had a durable complete metabolic response without toxicity. Outcome was related to higher doses. The good rates of cancer specific and overall survivals were probably associated to an accurate patient selection that identified true oligometastatic lesions suitable for an ablative local therapeutic approach as SBRT.

Keywords: Stereotactic body radiotherapy; Ovarian cancer; Oligometastases

Introduction

Oligometastatic disease is considered an intermediate state between localized and systemic cancer [1]. There is rising evidence that patients with a limited number of metastases have a better prognosis than those with extensive disease. The increasing ability to detect and cure earlier state metastatic cancer mandates the expansion of staging and classifying metastases in the TNM system [2] (e.g. patients with a solitary metastasis in a single organ are defined M1, whereas oligometastases, limited to 1 organ, number < 5 and < 5 cm in total, are defined M2).

Ablation of solitary metastases (e.g. M1, M2) is in the domain of surgeon and radiation oncologists. Stereotactic Body Radiotherapy (SBRT) is an emerging approach in the treatment of single lesions that combines the complex dose distributions of intensity modulated radiation therapy with the accuracy, reproducibility, and high doses of external beam radiotherapy. Dose is usually divided in 1-5 fractions given in one week. Body immobilizers may be used to maintain spatial relationships during treatment sessions. The precision of this technique allows delivery high dose of radiotherapy to the tumor while sparing surrounding normal tissue. Recent published data show that epithelial ovarian cancer recurs in 17-35% of the patients with early disease and in 30-75% patients with advanced disease [3]. Relapses of disease have a poor prognosis and are almost always fatal. Frequency of nodal involvement among relapses is well known, but isolated lymph

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node recurrence is less described in literature [4,5]. Generally, these patients are treated with surgery and/or chemotherapy. In our study we evaluated the local control (LC), overall survival (OS) and toxicity in 11 consecutive patients with previous diagnosis of ovarian cancer who have relapsed in localized lymph node and was submitted to SBRT.

Material and Methods

Eligibility

Patients who entered the study were enrolled from August 2008 and March 2015. Inclusion criteria were a history of ovarian cancer and limited lymph node relapse (M1, M2) showed by diagnostic imaging: computed tomography (CT) and ¹⁸F-FDG positron emission tomography (PET)-CT scan.

Treatment planning

Treatment set-up was performed with a multi-slice CT, 2.5 mm thick with 0 mm gap between scans were acquired. A stereotactic body frame with a rigid body fixation system and a fiducially box were used. The use of contrast was evaluated case by case. Gross tumor volume (GTV) was defined as the radiologically visible tumor. Clinical target volume (CTV) was coincident with GTV and planned target volume (PTV) was designed as GTV/CTV plus an additional isotropic margin of 5 mm. After dosimetric and physic calculations for each treatment, the GTV/CTV was re-contoured in the image slices obtained with a verification CT (i.e. PTV must include both GTV/ CTV using the image fusion of the first CT and the verification CT). Coplanar dynamic arcs were conformed around PTV, typical field-shape margin was 2 mm, and micro-multileaves (MLC) set-up changed every 10 degrees to follow the possible variations on target profile through the beam eye view system. Treatment was delivered with a 5-MV X-rays linear accelerator with external dynamic MLC. Before each SBRT fraction, accuracy of treatment was evaluated with daily MV portal imaging. The SBRT dose was prescribed to the isocentre and the minimal coverage accepted dose was 90% with a maximum dose not exceeding 110%. Five consecutive daily fractions were delivered.

Response, toxicity evaluation and statistical analysis

Response was assessed with PET-CT using PET Response Criteria in Solid Tumors (PERCIST 1.0) [6]. Local control was achieved if there was a lack of progression (i.e., any metabolic response or stable metabolic disease). All patients were evaluated with PET-CT 3 months after the end of SBRT, and at 4 months interval thereafter.

Acute toxicity was scored according to the National Cancer Institute Common Terminology Criteria for Adverse Effects Version 4 (CTCAE v 4.0). Late toxicity was recorded according to the Radiation Therapy Oncology Group-RTOG and European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring.

A software package (MedCalc 11.1 Broekstraat 52, B-9030 Mariakerke Belgium) was used for statistical analysis. Overall survival and duration of local control were estimated for the entire population using the Kaplan-Meier product-limit method [7].

Results

Eleven patients with 20 lymph node recurrent lesions were treated with median follow-up of 24 months. Fractionation schemes were 5 x 8Gy in 10 (50%), 5 x 7Gy in 2 (10%), 5 x 6Gy in 3 (15%) and 5 x 5Gy in 5 (25%) lymph nodes. Doses were prescribed considering the organ

Table 1: Lesion characteristics.

Total lymph nodes	20 (100%)
Site:	
Pelvic	4 (20%)
Lumbo-aortic	10 (50%)
Mediastinal	6 (30%)
GTV median	5.35 cc (range, 1.5 – 18.3)
PTV median	15.65 cc (range, 4.2 - 85.7)
SBRT doses:	
5 x 8Gy	10 (50%)
5 x 7Gy	2 (10%)
5 x 6Gy	3 (15%)
5 x 5Gy	5 (25%)

GTV: Gross Tumor Volume; PTV: Planning Target Volume; SBRT: Stereotactic Body Radiotherapy

Table 2: Prognostic factors for local control (LC) probabilities at univariate analysis.

	LC at 2 years (%)	LC at 5 years (%)	p value
Site			
Sub-diaphragmatic	57 +/- 17	28 +/- 11	0.08
Mediastinal	100	100	
Dose			
5 x 8Gy	100	66 +/- 27	0.004
5 x < 8Gy	24 +/- 20	24 +/- 20	

at risk constraints, so higher doses were used in about one half of the treated lesions. At the time of ovarian cancer diagnosis, all patients were submitted to surgery and at least 1 line of chemotherapy (range, 1-3). Median age was 64 years (range, 49-74), primitive histology was sero-papillar and endometrioid carcinoma in 8 (72%) and 3 (28%) patients, respectively. Median interval time between first diagnosis and lymph node relapse was 79 months (range, 16-171). Table 1 shows the lesion characteristics.

At PET-CT control, 3 months after the end of SBRT, a complete metabolic response in all treated lesions was observed. Local control at 2- and 5 years was 73% +/- 12 and 48% +/- 20, respectively with a median duration of 57 months. Outcome resulted related to administered doses. In fact, at the univariate analysis, LC was significantly better in 5 x 8Gy group versus 5 x < 8Gy group (p = 0.004; see (Table 2 and Figure 1). After SBRT we did not register in-field relapse, 5 (45%) patients with primary sub-diaphragmatic (i.e. pelvic and lumbo-aortic) lymph node disease had out-field progression,

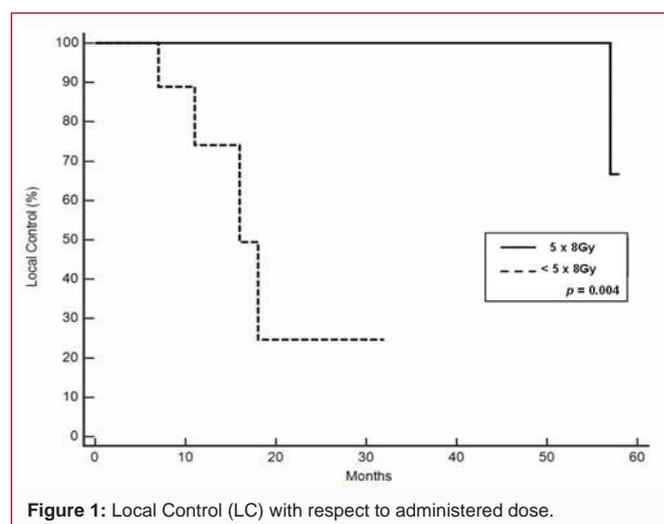


Figure 1: Local Control (LC) with respect to administered dose.



Figure 2A: PET-CT basal evaluation showed recurrent left external iliac lymph node (yellow arrow).

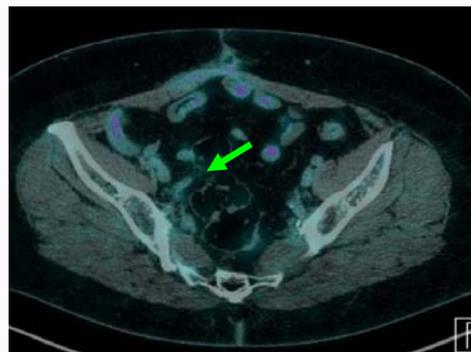


Figure 2C: PET-CT control at 3 months showed a complete metabolic response (green arrow).

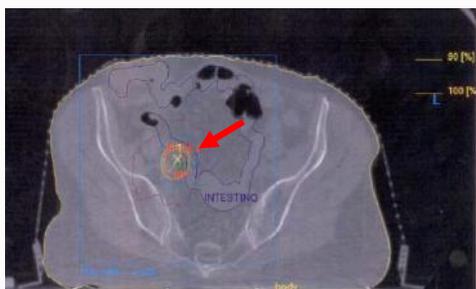


Figure 2B: Planning target volume with isodose lines (red arrow).

one a pelvic lymph node relapse, and remaining four a peritoneal localization. One (9%) patient with primary mediastinal lymph node disease recurred out-field on new mediastinal lymph node. The two cases with nodal progression received another SBRT, while the other four patients with peritoneal diffusion were submitted to salvage chemotherapy. Cancer specific and overall survivals at 2- and 5 years were 87% +/- 11 and 73% +/- 16 and 78% +/- 14 and 65% +/- 16, respectively. We did not register acute or late toxicity after SBRT.

Discussion

Lymph node metastases are well known in the course of ovarian carcinoma, with prevalence among metastatic between 50 and 70% in clinical and necroscopic studies [8]. Isolated lymph node relapses are rarely described, indeed, nodal metastasis usually occurs along with the appearance of peritoneal carcinomatosis, solid organ metastasis, such as pleura, liver or lung. Blanchard in his retrospective analysis on 640 patients with ovarian cancer, showed a rate of 4.2% of isolated lymph node recurrence after primary therapy [5]. Patients were treated with surgery, chemotherapy or conformal radiotherapy with a median OS of 26 months. In oligometastatic cancer patients, SBRT is an emerging ablative treatment option which can be effective in delaying disease progression especially in limited lymph node relapse. To reduce selection biases and to identify the true oligometastatic patients, diagnosis of oligometastasis should be carefully made using both CT scan and PET-CT.

Using this accurate diagnostic selection in a group of 40 oligometastatic prostate cancer patients with 47 isolated lymph node metastases, we obtained a high LC rate with SBRT (98% of LC and no disease recurrence in 40% of cases) [9]. In ovarian cancer few experiences of SBRT in the treatment of recurrent or non-operative disease are reported. Higginson submitted to SBRT patients with isolated lung metastasis, paraaortic nodes, or vaginal cuff recurrences after primary surgery and adjuvant therapy, and with a median follow-

up of 11 months, reported 79% locoregional control, 43% distant failure, and 50% overall survival [10]. Kunos included only three cases in their experience but involved patients with multiple local and distant recurrences treated with multiple courses of chemotherapy, prior radiation, and/or surgeries. One patient after primary surgery and chemotherapy was submitted to SBRT for a third relapse of her cancer and obtained a stabilization of disease without evidence of progression for 9 months. Another patient was free of disease at 10 months after SBRT used for a persistent vaginal lesion following primary debulking, several chemotherapy courses, and external pelvic radiotherapy. A third patient who underwent SBRT after multiple treatments (i.e., surgery, chemotherapy and radiotherapy) had stable disease at 6 months follow-up with no more than grade 2 acute toxicities. [11]. Finally, Deodato described four cases of SBRT in ovarian cancer, 3 patients were without evidence of disease at 37, 31, and 19 months after undergoing SBRT to presacral lymph nodes, hepatic lesions, and supraclavicular nodes, respectively. One patient was alive with disease at 18 months after SBRT dosing to anterior mediastinal and left internal mammary nodes [12]. So considering the few data published in this field, our series can be relevant because analyse the subset of ovarian cancer patients with only oligometastatic lymph node recurrence. Outcome resulted related to administered doses. In fact, at the univariate analysis, LC was significantly better in 5 x 8Gy group versus 5 x < 8Gy group ($p < 0.004$). In our analysis, outcome seems less satisfying in patients with sub-diaphragmatic (i.e., pelvic and lumbo-aortic) disease because of a peritoneal progression also in absence of in-field relapse. We observed that patients with supra-diaphragmatic (mediastinal) lymph node localization had a higher rate of LC respect to those with sub-diaphragmatic disease. Sub-diaphragmatic nodal relapse in ovarian cancer can be closely related to the synchronous presence of microscopic peritoneal disease that cannot be evidenced by PET-CT. In fact, the 4 patients who developed peritoneal carcinomatosis had a previous sub-diaphragmatic lymph node localization treated with SBRT. At univariate analysis, sub- versus supra-diaphragmatic localization did not result statistically significant probably for the relatively low number of recruited patients. To our knowledge, this is one of the largest experience analysing the role of SBRT in oligometastatic ovarian cancer patients affected by isolated node metastasis. SBRT is safe, effective, and minimally invasive in the eradication of limited nodal metastases. At PET-CT control all patients obtained a complete metabolic response and maintained their in-field metabolic remission until last evaluation, furthermore we did not report acute or late toxicity (Figure 2). Outcome was related to higher doses. The good rates of cancer specific and overall survivals were probably associated

to an accurate patient selection that identified true oligometastatic lesions suitable for an ablative local therapeutic approach as SBRT.

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