Accepted Manuscript

Stereotactic Body Radiotherapy For Oligometastatic Ovarian Cancer: A Step Towards A Drug Holiday

Roberta Lazzari, MD, Sara Ronchi, MD, Sara Gandini, PhD, Alessia Surgo, MD, Stefania Volpe, MD, Gaia Piperno, MD, Stefania Comi, MSc, Floriana Pansini, MSc, Cristiana Fodor, MSc, Roberto Orecchia, MD, Federica Tomao, MD, Gabriella Parma, MD, Nicoletta Colombo, MD, Barbara Alicja Jereczek-Fossa, MD, PhD

PII: S0360-3016(18)30609-6

DOI: 10.1016/j.ijrobp.2018.03.058

Reference: ROB 24903

To appear in: *International Journal of Radiation Oncology • Biology • Physics*

Received Date: 9 January 2018

Revised Date: 18 March 2018

Accepted Date: 28 March 2018

Please cite this article as: Lazzari R, Ronchi S, Gandini S, Surgo A, Volpe S, Piperno G, Comi S, Pansini F, Fodor C, Orecchia R, Tomao F, Parma G, Colombo N, Jereczek-Fossa BA, Stereotactic Body Radiotherapy For Oligometastatic Ovarian Cancer: A Step Towards A Drug Holiday, *International Journal of Radiation Oncology • Biology • Physics* (2018), doi: 10.1016/j.ijrobp.2018.03.058.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

STEREOTACTIC BODY RADIOTHERAPY FOR OLIGOMETASTATIC OVARIAN CANCER: A STEP TOWARDS A DRUG HOLIDAY

Roberta Lazzari, MD,[a,*] Sara Ronchi, MD,[b,*] Sara Gandini, PhD, [c] Alessia Surgo, MD,[a] Stefania Volpe, MD,[a, d] Gaia Piperno, MD,[a] Stefania Comi, MSc,[e] Floriana Pansini, MSc,[e] Cristiana Fodor, MSc,[a] Roberto Orecchia, MD,[d, f] Federica Tomao, MD[g], Gabriella Parma, MD[h], Nicoletta Colombo, MD,[h,i,§] Barbara Alicja Jereczek-Fossa, MD, PhD [a,d,§]

[a] Department of Radiation Oncology, European Institute of Oncology, Milan Italy.
[b]Department of Radiation Oncology and Medical Physics, Centro Nazionale Adroterapia Oncologica (CNAO), Pavia, Italy.
[c] Division of Epidemiology and Biostatistics Unit, European Institute of Oncology, Milan, Italy.
[d] Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy
[e] Department of Medical Physics, European Institute of Oncology, Milan Italy.
[f] Scientific Directorate, European Institute of Oncology, Milan Italy.
[g] Department of Gynecological, Obstetrical and Urological Sciences, "Sapienza" University, Rome, Italy
[h] Department of Gynecology, European Institute of Oncology, Milan, Italy.
[i] University of Milan-Bicocca, Italy.

* Roberta Lazzari MD and Sara Ronchi MD equally contributed to this work and should be considered as co-first authors.
§ Nicoletta Colombo MD and Barbara Alicja Jereczek-Fossa MD, PhD should be considered as co-last authors.

Sara Gandini PhD was responsible for the statistical analysis of the current work.

Corresponding author:
Stefania Volpe, MD Department of Radiation Oncology, European Institute of Oncology, Via Ripamonti 435, Milan 20141, Italy. Tel: +390257489037; E-mail: stefania.volpe@ieo.it

Acknowledgments:
This study was partially supported by the Fondazione IEO-CCM projects entitled:

- OLIG-ART: Ablative radiotherapy for oligometastatic cancer: When and how?", “Radioterapia di alta precisione con approccio stereotassico nelle neoplasie craniche ed extracraniche”, and "AXILL-ART: Biology-based radiotherapy volume definition for 1-2 macrometastatic sentinel lymph nodes without further dissection in breast cancer conservative surgery" and by a research grant from Accuray Inc. entitled “Data collection and analysis of Tomotherapy and CyberKnife breast clinical studies, breast physics studies and prostate study”.

A special thanks to Paola Romanelli MD, whose work is supported by the Fondazione for IEO-CCM; project entitled: OLIG-ART: Ablative radiotherapy for oligometastatic cancer: When and How?- Radioterapia di alta precisione con approccio stereotassico nelle neoplasie craniche ed extracraniche.

ACCEPTED MANUSCRIPT

CONFLICT OF INTEREST STATEMENT

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from (stefania.volpe@ieo.it).

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

STEREOTACTIC BODY RADIOTHERAPY FOR OLIGOMETASTATIC OVARIAN CANCER: A STEP TOWARDS A DRUG HOLIDAY

SUMMARY

This study including 82 patients showed that stereotactic radiotherapy for oligometastatic ovarian cancer is feasible, well tolerated and offers high local control. At 1 year, 1 out of 3 patients is free of progression and new treatments.

ABSTRACT

Purpose: To evaluate stereotactic body radiotherapy (SBRT) for metachronous oligometastatic ovarian cancer patients in terms of local control, delay of systemic treatment, survival outcomes and toxicity.

Materials and Methods: Retrospective data collection from a single institution. Inclusion criteria were: (1) oligorecurrent/oligoprogressive disease in ovarian cancer patients after/during systemic therapy; (2) surgery/other local therapies not feasible; (3) relative contraindication to systemic therapy, no more chemotherapy lines available or refusal of the patient. Tumor response and toxicity were evaluated using the Response Evaluation Criteria in Solid Tumors and the Common Terminology Criteria for Adverse Events (CTCAE) v4.03, A new systemic therapy regimen was started after SBRT treatment course in 57/109 cases (52.3%).respectively. Local progression free survival (LPFS), progression free survival (PFS) and overall survival (OS) were calculated via Kaplan-Meier method. Systemic treatment free interval (SFI) was calculated in cases without concomitant systemic therapy.

Results: Between May 2012 and December 2016, 82 patients/156 lesions underwent SBRT with a median dose of 24 Gy/3 fractions. Median follow-up was 17.4 months. Patients received a median of 3 systemic therapy regimens prior to SBRT. Concomitant systemic therapy was performed for 29

lesions (18.6%). Complete radiologic response, partial response, stabilization and progressive disease were observed in 91 (60%), 26 (17%), 24 (16%) and 11 (7%) lesions, respectively, out of 152 evaluable lesions. No G3-G4 acute or late toxicities were observed. Median SFI after SBRT was 7.4 months and 1 out 3 patients was disease free at 1 year after SBRT. Actuarial 2-year LPFS, PFS and OS rates were 68%, 18% and 71%, respectively. Pattern of failure was predominantly out-field.

Conclusions: SBRT for oligometastatic ovarian cancer showed good local control and toxicity profile. It might be an appealing alternative to other invasive local therapies in order to delay systemic therapy in case of chemorefractory disease or intolerance to systemic agents.

ACCEPTED MANUSCRIPT

INTRODUCTION

Ovarian cancer is the most lethal gynecological cancer. The role of radiotherapy (RT) remains controversial [1]. While whole abdominal irradiation (WART) is no longer considered a suitable adjuvant treatment due to unproven efficacy and relevant toxicity, indication to RT is mainly limited to the palliative setting. [2]. Recently, selective approaches with volume-directed involved-field radiotherapy (IFRT) showed promising results in case of limited recurrent disease [3-9]. The availability of more sophisticated imaging and the refinement of RT technology has allowed for the delivery of progressively higher doses to comparatively smaller target volumes with ablative-intent stereotactic body radiotherapy (SBRT). Oligometastatic state (up to 3-5 detectable metastases) is a transitional state between localized and widespread systemic disease in which local control may yield improved systemic control [10]. So far, SBRT applications have been incorporated in treatment algorithms for multiple disease sites (i.e. lung, prostate, breast) with local control rates ranging between 80 and 90% and excellent toxicity profile [11-16]. To the best of our knowledge, no dedicated report on SBRT for ovarian cancer has been published, the only available data deriving from oligometastatic patient series including all gynecological malignancies [17-22]. In this report we retrospectively reviewed our experience of SBRT for oligometastatic ovarian cancer patients in order to evaluate tumor outcome including post-SBRT systemic treatment free interval and toxicity.

METHODS AND MATERIALS

Study Protocol and Patient selection

This is a retrospective analysis of a series of oligometastatic ovarian cancer patients treated with SBRT at the Radiation Oncology Department of the XXXXXXXX. The study was part of a wider SBRT and image-guided RT research notified to the Ethical Committee of the XXXXXXXX (notifications 93/11 and 86/11).

Indication to SBRT was given following multisciplinary discussion during the institutional tumor board for gynecologic malignancies, according to the following criteria: (1) histologically-proven primary ovarian cancer; (2) oligorecurrent/oligoprogressive disease (< 5 new or enlarging metastases in an otherwise well-controlled disease state); (3) oligopersistent disease (< 5 persistent lesions after systemic therapy); (4) salvage surgery/other local therapies not feasible; (5) relative contraindication to further systemic therapy due to serious comorbidities, previous severe toxicity, no more chemotherapy lines available or refusal of the patient; (6) written informed consent for treatment and (7) for the use of the anonymized data for research or educational purpose. Patients with either bone or brain metastases were excluded.

The diagnosis was based on clinical examination and imaging studies. Total body staging included computer tomography (CT) or [18F] fluoro-deoxy-glucose positron emission tomography/CT scan (PET/CT). According to TNM classification [23], disease localization was divided in 2 categories: regional lymph node (LN) or distant metastasis (M).

All patients underwent debulking surgery at first diagnosis, and all except one had received systemic therapy prior to RT (chemotherapy, biological agents, target therapy or endocrine therapy). Additional surgical instances, thermoablation sessions or RT courses for other lesions were allowed and did not constitute exclusion criteria for the current study.

SBRT procedures

SBRT was performed using VERO™ and Cyberknife™ systems. All patients underwent supine CT simulation using suitable immobilization devices according to the site of the lesion. A iodinated contrast medium was administered prior to the CT simulation scan, patients with clinical contraindication to contrast medium as defined as per our institutional protocol underwent non contrast-CT examination. Additionally, whenever feasible, fusion PET/CT was performed with the same immobilization system used for CT simulation. In case of lung metastases, CT simulation

required a 4D acquisition for real time monitoring of the respiration signal. For all patients, simulation and SBRT were performed under free breathing.

For Cyberknife™ SBRT, the Multiplan treatment planning system (version 2.0.5, Accuray, Sunnyvale, CA) was employed. Xsight® Spine (Accuray, Sunnyvale, CA) detecting system was used. All patients were immobilized during CT simulation and SBRT bya customized external vacuum-type cast. The gross tumor volume (GTV) was contoured on the CT scan and a 2-mm margin was added to the GTV to obtain the planning target volume (PTV). The dose was prescribed to the 75-80% isodose using a nonisocentric and noncoplanar technique with 6 MV photons.

For VERO™ SBRT planning, Iplannet (version 4.5.3; BrainLab, Munich, Germany) was used. All patients were immobilized during CT simulation and SBRT using the Combifix (CIVCO Medical Solutions, Kalona, Iowa, Unites States of America) device with 7 infrared markers on the chest or abdomen wall. The GTV was contoured on the CT scan and a 3-mm margin was added to the GTV to compensate for the geometrical penumbra of the system. Treatment plans consisted of one or more noncoplanar 6MV photons dynamic arcs or multiple modulated fixed beams obtained with the micro-multileaf collimator (BrainLAB, Munich, Germany). Cone-beam CT (CBCT) was performed before every treatment session;, ExacTrac (BrainLab, Munich, Germany) system was used during beam delivery to monitor the position of patient on the basis of the infrared markers.

Dose volume histograms (DVHs) were calculated for PTV and organs at risk (OARs). The OARs constraints for SBRT published by Timmerman et al were applied in all treatment plans [24]. For patients who had received prior RT courses, the original treatment plans were retrieved in every case of suspected overlap with previous RT fields.. SBRT was usually given every other day.

After SBRT, patients were seen every 2-4 months either by a Radiation Oncologist or by a Gynecologic Oncologist, performing routine periodic re-evaluation with CT or PET/CT and tumor

markers dosage. Additional radiologic or PET/CT re-evaluation was requested in case of biochemical progression/clinical suspicion of disease progression.

Evaluation of outcomes and statistical methodology

Radiological response after SBRT was evaluated by the same imaging modality used for treatment planning (CT scan or PET/CT scan) and classified according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or PET/CT Response Criteria in Solid Tumors (PERCIST) [25,26]. Local disease relapse within the SBRT PTV was defined as in-field progression; distant disease relapse or relapse in proximity but outside the SBRT PTV was scored as out-field progression. Conversely, out-field LN relapses were dichotomized as either regional (i.e.: pelvic relapse after pelvic lymphnode treatment or paraortic relapse after paraortic lymphnode treatment) or extraregional (if relapse was outside the region treated with SBRT).

Patient characteristics were represented as frequencies and percentages for categorical variables and medians and ranges for continuous variables. The length of follow-up was calculated from the last SBRT day to the last follow-up visit. Progression free survival (PFS) was defined as the time interval between the last day of SBRT and the first diagnosis of progressive disease (any type of progression) or the last follow-up visit, in case no signs of progression were found. In-field progression free interval (local progression free survival: LPFS) and overall survival (OS) were calculated.

Systemic treatment free interval (SFI) was determined in patients without concomitant systemic therapy. It was the time between the last SBRT day and the date of initiation of new systemic therapy or the last follow-up visit, if no systemic therapy was started after SBRT. Treatment toxicity was evaluated using Common Terminology Criteria for Adverse Events (CTCAE) v4.03 [27].

Univariate and multivariate analyses were performed to quantify the impact of patient-, tumor-, and treatment-related factors on clinical outcomes. We carried out Log-rank tests and multivariate Cox-regression models, taking into account time-dependent variables. Several patients and tumor characteristics, recognized prognostic factors, previous treatments modality and RT parameters (i.e. Karnofsky Performance Status; treatment site; GTV volume in cm^3; biologically effective dose, BED) were evaluated in association with clinical outcome. Survival curves were estimated using the Kaplan-Meier method. All *P*-values were set at 0.05. Statistical analyses were performed with the SAS statistical software (version 9.2; SAS Institute Inc, Cary, NC).

RESULTS

Patients and disease characteristics

Between 5/2012 and 12/2016, 82 consecutive patients (156 lesions) were treated. Median age at the time of SBRT was 60.4 years **(Tab. 1)**. Primary histologies included high grade serous cell carcinoma, low serous cell, endometrioid, granulosa cell and other in 67%, 7.3%, 8.5%, 8.5% and 8.5% of cases, respectively. Information about breast cancer genes mutation status was available for 33 patients (40%). Patients received a median of 3 systemic therapy regimens prior to SBRT (range 0-9).

Treatment

Fifty-eight patients (70.7%) underwent a single SBRT course; of these, 41 (72%) had a single lesion, while in 16 (28%) more than 1 lesion (2 - 4) were treated concomitantly (synchronous SBRT) **(Tab. 1)**. Twenty-four patients (29.3%) received metachronous SBRT: in 21 (25.6%) and 3 (3.7%) patients, 2 and 3 SBRT were performed at different timing, respectively. In 77 (70.6%) and 32 (29.4%) SBRT courses, treatment was delivered either on a single lesion or synchronously on more than 1 lesion, respectively. For the whole cohort of patients, we evaluated overall 109 SBRT

courses/156 treated lesions. Median dose prescription was 24 Gy (14 - 45 Gy) given in 3 fractions (range 1 - 5); median Biologically Effective Dose was 43.2 Gy (range 28-112.5 Gy). Mean GTV was 6.77 cm^3 (range 0.19– 90.5 cm^3) **(Tab. 2)**.

Follow-up

No patient was lost at follow-up. Median follow-up was 17.4 months (range 2.2– 51.4 months). At the time of the analysis, 28 (34.1%) patients were alive with no evidence of disease, 40 (48.8%) were alive with clinically evident disease, and 14 (17.1%) patients had died of disease.

Treatment Outcome

Response

First radiological evaluation was available in 152/156 (94.4%) lesions. PET/CT was performed in 101/152 lesions (66%) As far as concerned responses classified as progression or stable disease, these were confirmed by PET in 17/35 lesions (49%). Response could not be assessed for three lesions since the patient had died before re-staging, while the remainder lesion could not be properly evaluated because of confounding uptake in the nearby bowel at the first PET/CT scan (but evaluable at subsequent follow-up). Complete radiological response, partial response, stabilization and progressive disease were observed in 91 (59.9%), 26 (17.1%), 24 (15.8%), 11 (7.2%) evaluable lesions, respectively. Median time to any progression was 5.6 months (95% Confidence Interval (CI) 3.5– 10.6) **(Fig. 1)**. Actuarial 1 year- and 3 year-PFS were 34% and 8%, respectively. Pattern of failure was mainly out-field **(Tab. 3)**. At last follow-up, in-field control was observed in 115 out of 153 evaluable lesions (75.2%). Actuarial 1-year and 3-year LPFS rates were 82% and 55%, respectively **(Fig. 2)**. 3-year OS rate was 71% **(Fig. 3)**. Loco-regional control was assessed for all the 78 treated LN lesions. At last follow-up, loco-regional control was maintained in 47/68 lesions

(60%); while disease progressions were distributed as follows: 7/31 cases were regional progression only (22%) and 24 were re-staged as both regional and extra-regional progressions (78%).

In multivariate analysis, PFS was significantly better in cases of absence of residual tumor at first surgery (p=0.03, Hazard Ratio (HR) 0.54, 95% CI 0.30 – 0.99). while progression was significantly associated with the number of pre-SBRT systemic therapy lines.

Stage at primary diagnosis, number of SBRT-treated lesions, stage of SBRT-treated lesion (LN vs M), and time from last systemic therapy regimen before SBRT were associated with LPFS at univariate and multivariate analysis. In-field relapse risk was significantly associated with higher stage at diagnosis (III-IV versus I-II, p=0.0008, HR 7.49, 95% CI 2.32 – 24.16), number of treated lesions (p=0.0002, HR 2.02, 95% CI 1.39 – 2.92) and stage of SBRT-treated lesion, with M including non-locoregional LN versus regional LN (p=0.0008, HR 3.37, 95% CI 1.66– 6.84) **(Tab. 4)**. Time interval from the last chemotherapy of more than 7 months was associated with a better local control (p=0.02), also in a multivariate time dependent Cox regression model (p=0.02).

Deferral of systemic treatment:

A new systemic therapy regimen was started after SBRT treatment course in 57/109 cases (52.3%). For the SBRT with no concomitant systemic therapy, median SFI was 7.4 months (range 2.1– 49.3). In 26 cases (33.3%)/23 patients (28%), systemic therapy was deferred by at least 1 year. Considering the 22 patients who received concomitant systemic therapy (either hormonotherapy, chemotherapy or maintenance biological agent), indication to a new treatment regimen was given in 12 cases (55%), while 9 could maintain the ongoing regimen (41%). Of these, systemic treatment was interrupted in 3/9 cases (at 12 months after SBRT in 2 patients and after 6 months in 1): all of them were disease-free at last follow-up. Information on further systemic therapy was not available for 1/22 patient (4%).

Toxicity

SBRT was well tolerated. In 57 patients (69.5%) no acute or late toxicities were observed. No G3-G4 acute or late events were observed. Acute toxicity observed in 22 patients included G1-G2 gastrointestinal events (17 patients) and G1 fatigue (5 cases). Late toxicity (23 cases) included G1-G2 gastrointestinal events (16 patients), G1 genitourinary (4 events), other G1 events in 3 cases.

DISCUSSION

To the best of our knowledge, this is the largest series on oligometastatic ovarian cancer patients treated with SBRT. Our data show that SBRT may provide good local control, with more than one-third of patients being disease-free at 1 year. Moreover, we could achieve an interestingly durable systemic therapy free interval, which was especially relevant for heavily pre-treated patients or for those who had shown poor tolerance to chemotherapy. Additionally, not only toxicity rates were extremely low, but SBRT re-treatment may be proposed in case of further oligometastatic progression.

After it was first proposed in 1995 by Hellman and Weichselbaum [28], the concept of oligometastatic disease has been progressively investigated. The recognition of a continuous rather than a bimodal metastatic state (loco-regionally vs widely disseminated disease), with a distinct biological pattern and clinical outcome, has opened doors to the application of focal therapies in this subset of patients. In this context, SBRT has come to attention as a non-invasive alternative to surgery in the management of oligometastases, and a recent multi-national survey has endorsed its use with a strong level of recommendation [29] in cases with up to five metastases (range 2-5, limiting to three the number of lesions within a single organ). The potential role of SBRT in deferring systemic therapy has already been investigated in other oligometastatic tumors, with the concept of “drug holiday” or “androgen deprivation therapy (ADT)-free survival” [14,30-32]. Conversely, gynecological malignancies remain a largely unexplored field for SBRT applications in

the oligometastatic/oligorecurrent setting. Many published series include multiple subsites, and in only two SBRT studies ovarian cancer represent at least 50% of the selected population [20,22]. In our series of ovarian cancer patients, median SFI was 7.4 months. The longest SFI was 49.3 months with freedom from systemic therapy at 1 year in almost 30.5% of cases. Median SFI raised up to 13 months (range 6.3– 49.3 months) with a 1 year-deferral of systemic treatment in almost 58% of cases when SBRT was followed by other local therapies (including additional SBRT courses). This approach could also give a later possibility of rechallenge with cytotoxic systemic agents, enhancing therapeutic chances in these patients. In the current SBRT study, we chose to apply the linear quadratic (LQ) model. Although no direct data have been published on ovarian cancer series, the existing literature seems to support the validity of the LQ model for doses up to 18 Gy/fraction [33].

Our results permit to overcome the paradigm of the exclusive palliative role of RT in recurrent ovarian cancer, adding strength to the concept, previously introduced with IFRT, of RT as an active and definitive treatment option, to be integrated in a multidisciplinary strategy in order to maximally improve patients' clinical outcomes. Previous IFRT studies for limited recurrent ovarian cancer considered a variety of RT techniques and employed median doses of 45–60 Gy with either conventional fractionation or moderate hypofractionation. Albuquerque et al. [4] demonstrated that 5 years after IFRT high rates of local control (LRFS 70%) with a disease free survival (DFS) 33%. As already discussed by Chundury et al. [5], these results can be influenced by the fact that a high proportion of patients had previous optimal debulking of treated lesions or complete response to chemotherapy. The same authors have recently investigated the use of intensity modulated radiotherapy (IMRT) showing 2- and 3-year DFS of 11% and 8%, respectively, which are similar to our corresponding PFS rates (18% and 8%), while achieved a comparatively higher 3-year LPS (72% vs 55% in our series) [5]. Yahara et al. [6] found after external RT or brachytherapy a 3 year-LPFS of 96% and a 3 year- PFS of 39%, including in their analysis only patients with up to 2

lesions after ≤ 3 chemotherapy regimens. Interestingly, our analysis confirmed the significant association between these parameters and better LPFS and PFS. With the important limitation of making a comparison between such different techniques, doses and fractionations, we can assume that SBRT could be a reasonable alternative to IFRT, with the additional advantage of a very short overall treatment time.

Kunos et al. [20] in their phase II study demonstrated a 100% local control rate and a median DFS of 7.8 months, using a dose prescription of 24 Gy in 3 fractions. Mesko et al. [22] found a median DFS of 10.8 months and a local control rate of 83%, using median prescription doses between 32.5 Gy in 5 fractions and 50 Gy in 4 fractions. Our local control rate (75%) and median PFS (5.64 months) were slightly lower when compared to both IFRT series and to Kunos' and Mesko's SBRT studies. Firstly, this might be at least partially explained by median dose of 24 Gy in 3 fractions which is lower than that prescribed by Mesko and in other IFRT series. This may underline the need of dose escalation [34-36], especially for the treatment of distant metastases (which were 50% of targets in our series, treated with the same median dose of 24 Gy in 3 fractions as loco-regional LN, but reaching lower local control rate of 70% vs. 81%). Corbin et al. reported that doses of either 50 Gy in 5 or 10 fractions or 36–48 Gy in 3 fractions yielded superior local control rates than 24–30 Gy in 3 fractions [34]. In our study, all distant metastasis treated with 36–45 Gy kept in field-control until last follow-up, while those treated with less than 36 Gy only in 65% of cases. Definitely, low toxicity and in-field progression observed in some patients open space for dose escalation. Differences in patient selection can also explain the difference between our findings and Kunos' results, Indeed, the majority of Kunos series patients had no prior systemic therapy (56%), were treated on ≤ 2 lesions (70%) and on loco-regional LN (66%). The latter feature in our study correlated with significantly better outcome: large part of patients with a PFS of at least 1 year were treated on a single lesion (90%), underwent 2 or less pre-SBRT systemic therapy regimens (63%)

and were treated on LN (74%), which were loco-regional LN (53%) and distant LN (21%). An overview of the currently available literature, as previously discussed, is provided in Table 5.

Our patients were widely heterogeneous (histological subtype, prior treatments, number of lesions). In several cases, they were referred to SBRT after the failure of multiple lines of systemic agents or when limited disease persisted after a previous polymetastatic state (negatively selected patients). Therefore we can hypothesize that a subgroup of patients, despite the low burden of disease at the time of SBRT, may not have been in a truly oligometastatic state and microscopic disease could have already become disseminated. Our analysis confirmed better outcomes in those patients with disease characteristics associated with limited-burden disease (presentation stage I-II, no residual tumor at first surgery, fewer previous systemic regimens performed, ≤ 2 lesions treated, only loco-regional LN involvement, time from last chemotherapy cycle > 7 months), thus strengthening the need for accurate patient selection and disease staging prior to the beginning of SBRT. We are well aware of the limitations of our study, which are mainly inherent to its retrospective nature (i.e. patient selection, potential under-reporting of toxicities). Additionally, as the proportion of patients who were re-staged with PET/CT was relatively high (66%), we acknowledge a possible underestimation of disease progression rates for those having PET-negative disease. Nevertheless, we could demonstrate that SBRT can be considered as a feasible and potentially effective treatment in the setting of oligometastic/oligorecurrent ovarian cancer. The identification of common patient selection criteria, together with the definition of fractionation and adequate treatment timing, are warranted in the upcoming future. Arguably, the incorporation of such parameters in structured prospective studies should contribute to improve the level of evidence of SBRT for ovarian cancer patients, and to break the paradigm of RT as a solely palliative treatment modality in this clinical scenario.

CONCLUSION

SBRT in oligometastatic/oligoprogressive ovarian cancer is safe and feasible and provides good local control at extremely low toxicity. In a good proportion of patients SBRT can allow for lasting treatment and toxicity free interval. Further prospective studies are warranted to identify which subgroup of patients may most benefit from this treatment. We believe that this experience could constitute a benchmark for SBRT application in oligorecurrent/oligoprogressive ovarian cancer and serve as well as an hypothesis-generating study for further clinical efforts. Specifically, the development of a prospective institutional trial is underway in order to help enhance the therapeutic index of SBRT (i.e. through the use of patient-reported-outcome tools) in a population of comorbid, heavily pretreated patients.

ACCEPTED MANUSCRIPT

REFERENCES

1) De Felice F, Marchetti C, Di Mino A, et al. Recurrent Ovarian Cancer: The Role of Radiation Therapy. *Int J Gynecol Cancer*. 2017; 27:690-695.
2) National Comprehensive Cancer Network. National Comprehensive Cancer Network Guidelines Version 1.2016 *Ovarian Cancer*. NCCN Web site. Available at: www.nccn.org
3) Brown AP, Jhingran A, Klopp A, et al. Involved-field radiation therapy for locoregionally recurrent ovarian cancer. *Gynecol. Oncol.* 2013; 130:300–305.
4) Albuquerque A, Patel M, Liotta M. et al. Long-term Benefit of Tumor Volume-Directed Involved Field Radiation Therapy in the Management of Recurrent Ovarian Cancer. *Int J Gynecol Cancer* 2016; 26:655-60.
5) Chundury A, Apicelli A, DeWees T, et al. Intensity modulated radiation therapy for recurrent ovarian cancer refractory to chemotherapy. *Gynecol Oncol*. 2016; 141(1):134-9.
6) Yahara K., Ohguri T., Imada H., et al. Epithelial ovarian cancer: definitive radiotherapy for limited recurrence after complete remission had been achieved with aggressive front-line therapy. *J Radiat Res.* 2013; 54:322–329.
7) Fujiwara K., Suzuki S., Yoden E., et al. Local radiation therapy for localized relapsed or refractory ovarian cancer patients with or without symptoms after chemotherapy. *Int J Gynecol Cancer* 2002; 12:250–256.
8) Machida S., Takei Y., Yoshida C., et al. Radiation Therapy for Chemotherapy-Resistant Recurrent Epithelial Ovarian Cancer. *Oncology* 2014; 86:232–238.
9) Lee SW, Park SM, Kim YM, et al. Radiation therapy is a treatment to be considered for recurrent epithelial ovarian cancer after chemotherapy. *Tumori* 2011; 97: 590-595.
10) Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol.* 1995; 13:8-10.

11) Alongi F, Arcangeli S, Filippi AR, et al. Review and uses of stereotactic body radiation therapy for oligometastases. *Oncologist* 2012; 17:1100-7.

12) Milano MT, Katz AW, Zhang H, et al. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. *Int J Radiat Oncol Biol Phys.* 2012; 83:878-86.

13) Decaestecker K, De Meerleer G, Lambert B, et al. Repeated stereotactic body radiotherapy for oligometastatic prostate cancer recurrence. *Radiat Oncol.* 2014; 12;9:135.

14) Jereczek-Fossa BA, Fanetti G, Fodor C, et al. Salvage Stereotactic Body Radiotherapy for Isolated Lymph Node Recurrent Prostate Cancer: Single Institution Series of 94 Consecutive Patients and 124 Lymph Nodes. *Clin Genitourin Cancer*. 2017; 15:e623-e632.

15) Jereczek-Fossa BA, Piperno G, Ronchi S, et al. Linac-based stereotactic body radiotherapy for oligometastatic patients with single abdominal lymph node recurrent cancer. *Am J Clin Oncol.* 2014; 37:227-33.

16) Jereczek-Fossa BA, Ronchi S, Orecchia R. Is Stereotactic Body Radiotherapy (SBRT) in lymph node oligometastatic patients feasible and effective? *Rep Pract Oncol Radiother*. 2015; 20:472-83.

17) Long B, Eskander RN, Tewari KS. Use of stereotactic radiosurgery in the treatment of gynecologic malignancies: A review. *World J Radiol.* 2014; 28;6:366-73.

18) Higginson DS, Morris DE, Jones EL, et al. Stereotactic body radiotherapy (SBRT): Technological innovation and application in gynecologic oncology. *Gynecol Oncol.* 2011;120:404-12.

19) Kunos C, Chen W, DeBernardo R, et al. Stereotactic body radiosurgery for pelvic relapse of gynecologic malignancies. *Technol Cancer Res Treat.* 2009; 8:393-400.

20) Kunos CA, Brindle J, Waggoner S, et al. Phase II Clinical Trial of Robotic Stereotactic Body Radiosurgery for Metastatic Gynecologic Malignancies. *Front Oncol* 2012; 5;2:181.

21) Kunos CA, Sherertz TM, Mislmani M, et al. Phase I Trial of Carboplatin and Gemcitabine Chemotherapy and Stereotactic Ablative Radiosurgery for the Palliative Treatment of Persistent or Recurrent Gynecologic Cancer. *Front Oncol.* 2015 Jun 5;5:126.

22) Mesko S, Sandler K, Cohen J, et al. Clinical Outcomes for Stereotactic Ablative Radiotherapy in Oligometastatic and Oligoprogressive Gynecological Malignancies. 2017; 27:403-408.

23) TNM Classification of Malignant Tumours – UICC. www.uicc.org/resources/tnm.

24) Timmerman RD. An overview of hypofractionation and introduction to this issue of seminars in radiation oncology. *Semin Radiat Oncol* 2008; 18:215-22.

25) Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009; 45:228–247.

26) Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. *J Nucl Med* 2009; 50:122S-125S.

27) CTCAE 4.03. Common Terminology Criteria for. Adverse Events (CTCAE). Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010). www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf.

28) Hellman S and Weichselbaum RR. Oligometastases. J Clin Oncol 1995 13:8-10.

29) Lancia A, Ingrosso G, Carosi A, et al. Oligometastatic cancer: stereotactic ablative radiotherapy for patients affected by isolated body metastasis. Acta Oncologica 2017; 56:1621-25.

30) Berkovic P, De Meerleer G, Delrue L, et al. Salvage stereotactic body radiotherapy for patients with limited prostate cancer metastases: deferring androgen deprivation therapy. *Clin Genitourin Cancer* 2013; 11:27-32.

31) Triggiani L, Alongi F, Buglione M, et al.: Efficacy of stereotactic body radiotherapy in oligorecurrent and in oligoprogressive prostate cancer: new evidence from a multicentric study. *Br J Cancer*. 2017 116:1520-1525.

32) Hong JC, Salama JK. The expanding role of stereotactic body radiation therapy in oligometastatic solid tumors: What do we know and where are we going? *Cancer Treat Rev.* 2017; 52:22-32.

33) Brenner D.J., Point: The linear quadratic model is an appropriate methodology for determining iso-effective doses at large doses per fraction, Semin Radiat Oncol, 2008; 18: 234-39

34) Salama JK, Hasselle MD, Chmura SJ, et al. Stereotactic body radiotherapy for multisite extracranial oligometastases: final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease. *Cancer* 2012; 118:2962–70.

35) Rule W, Timmerman R, Tong L, et al. Phase I dose-escalation study of stereotactic body radiotherapy in patients with hepatic metastases. *Ann Surg Oncol* 2011; 18:1081–7.

36) Corbin KS, Ranck MC, Hasselle MD, et al. Feasibility and toxicity of hypofractionated image guided radiation therapy for large volume limited metastatic disease. *Pract Radiat Oncol* 2013; 3:316–22.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Table 1. Patient, tumor and treatment characteristics (N=82 patients, n= 156 lesions, n=109 SBRT courses)

Patient, tumor and treatment characteristics	**n (%)**
Age (range) Median (range)	 60.4 (37.5-84.13)
Karnofsky Performance Status 60 - 80 90 100	 5 (6) 18 (22) 59 (72)
Primary histology Serous-high grade Serous-low grade Endometrioid Granulosa cell tumor Other	 55 (67.1) 6 (7.3) 7 (8.5) 7 (8.5) 7 (8.5)
Grade 1 2 3 4 Unknown	 2 (2.4) 11 (13.4) 60 (73.2) 1 (1.2) 8 (9.8)
FIGO stage at diagnosis I II III IV Unknown	 6 (7.3) 11 (13.4) 52 (63.4) 12 (14.6) 1 (1.2)
BRCA status Negative BRCA1 positive BRCA2 positive Unknown	 18 (22) 8 (9.8) 7 (8.5) 49 (59.6)
Baseline Platinum Sensitivity Sensitive (PFI > 12 months): Partially sensitive (PFI: 6 – 12 months): Resistant/Refractory (PFI: <6 months):	 48 (58.5) 24 (29.3) 10 (12.2)
Number of SBRT treatment courses per patient during time 1 2 3	 58 (70.7) 21 (25.6) 3 (3.7)
Number of treated lesions per treatment course 1 2 3 4	 77 (70.6) 22 (20.2) 5 (4.6) 5 (4.6)
Number of treated lesions (per patient) 1 2 3 ≥4	 40 (49) 23 (28) 11 (13.4) 8 (9.6)

ACCEPTED MANUSCRIPT

Interval between diagnosis of primary tumor and SBRT Mean (range) in years Median	 6.31 (0.48-22.3) 5.21
Treatment characteristics prior to SBRT	**n (%)**
Previous treatments: Surgery Chemotherapy/biological agents Endocrine therapy Thermoablation RT for ovarian cancer RT only for previous breast cancer	 82 (100) 81 (98.8) 20 (42.4) 4 (4.9) 19 (23.2) 5 (6.1)
Number of previous systemic therapy regimens (median; range)	 3 (0 – 9)
Platinum-based chemotherapy regimens (median; range)	 2 (0 – 6)
Number of surgical instances (median; range)	 1 (1 – 7)
Pre-SBRT Platinum Sensitivity Sensitive (PFI > 12 months) Partially sensitive (PFI 6 – 12 months) Resistant/Refractory (PFI < 6 months)	 36 (33) 36 (33) 37 (34)

Abbreviations: BRCA: Breast Cancer Gene; FIGO, International Federation of Gynecologists and Obstetrics; PFI, platinum free interval; RT, Radiotherapy; SBRT, Stereotactic Body Radiotherapy

ACCEPTED MANUSCRIPT

Table 2. SBRT Treatment characteristics by lesions (n=156)

Characteristics	n (%)
Classification of SBRT-treated lesion	
Oligorecurrent	78 (50)
Oligoprogressive	47 (30)
Oligopersistent	31 (20)
SBRT treatment	
VERO system (Mitsubishi-Brainlab)	126 (80.8)
CyberKnife (Accuray)	30 (19.2)
SBRT treatment group/per lesion	
Abdomen Pelvis	123 (79)
Regional lymph node	78
Distant lymph node	15
Visceral metastases	30
Abdominal cavity: 14 lesions	
Liver: 14 lesions	
Other: 2 lesions	
Thorax	26 (17)
Distant lymph node	12
Visceral metastasis:	14
Lung: 6 lesions	
Pleura: 8 lesions	
Head and Neck	7 (4)
Previous radiotherapy in the site of treated lesion	
Yes	5 (3.2)
No	151 (96.8)
Concomitant systemic therapy/per lesion	
No	127 (81.4)
Yes	29 (18.6)
Chemotherapy	9 (5.8)
Endocrine therapy	20 (12.8)
Number of fractions	
Median, range	3 (1 - 5)
Total dose and fractionation/per lesion	
24 Gy (8 Gy x 3 fr)	89 (57)
25 Gy (5 Gy x 5 fr)	35 (22.4)
30 Gy (10 Gy x 3 fr)	10 (6.4)
Other regimens	22 (14.1)
BED in Gy (α/β=10 Gy)	
Median	43.2
Range	28 – 112.5
GTV volume (cm^3)	
Mean	6.77
Median	3.15
Range	0.19 – 90.5

Abbreviations: BED, Biologically Effective Dose; GTV, Gross Tumor Volume; LN, regional lymph nodes; M, distant metastases; SBRT, Stereotactic Body Radiotherapy

Table 3. SBRT Treatment outcome (n= 82 patients, n=156 lesions)

Outcome	**n (%)**
Follow-up duration, months	
Median (range)	17.4 (2.2– 51.4)
Status at the last observation (December 2016, n=82 patients)	
NED	28 (34.1)
AWD	40 (48.8)
Died of disease	14 (17.1)
Radiological and/or FDG-PET/CT response to SBRT at first assessment (n=156 lesions, 152 evaluable):	
CR	91 (59.9)
PR	26 (17.1)
SD	24 (15.8)
PD	11 (7.2)
Radiological and/or FDG-PET/CT response in the lesions treated with SBRT only with no concomitant systemic therapy (n=127 lesions, 123 evaluable)	
CR	76 (61.8)
PR	17 (13.8)
SD	19 (15.5)
PD	11 (8.9)
Disease progression after first SBRT course (n=82, 81 evaluable)	
Yes	60 (74.1)
No	21 (25.9)
Site of first progression (n=60)	
In-field only	2 (3.5)
Out-field only	54 (90)
In-field+ Out-field	4 (5.5)
In field progression (at any time)/per lesion (n=153)	
Yes	38 (24.8)
No	115 (75.2)
Local control at last follow-up (n= 153)	
Yes	115 (75.2)
No	38 (24.8)
Local control at last follow-up in the lesions treated with SBRT only with no concomitant systemic therapy (n=127, 124 evaluable):	
Yes	90 (72.6)
No	34 (27.4)
Systemic treatment free-interval (months) after SBRT courses with no concomitant systemic therapy:	
Mean, Median	10.5 ,7.4
Range	2.1 – 49.3
Systemic treatment free-interval (months) after single SBRT courses not followed by intermediate SBRT/other local therapies before new systemic regimen or last follow-up:	
Mean, Median	9, 6
Range	2.1 – 33.4
Systemic treatment free-interval (months) after SBRT courses followed by intermediate SBRT/other local therapies (on different disease sites) before new systemic regimen or last follow-up:	
Mean, Median	15.8, 13

ACCEPTED MANUSCRIPT

Range	6.3 – 49.3

Abbreviations: AWD, Alive With Disease; CR, Complete Response; FDG-PET/CT, [^{18}F]-fluoro-deoxy-glucose positron emission tomography/computer tomography scan; NED, Non Evidence of Disease; PD, Progression of Disease; PR, Partial Response; SD, Stable Disease; SBRT, Stereotactic Body Radiotherapy.

ACCEPTED MANUSCRIPT

Table 4. Multivariate regression Cox models for progression

Analyses	Variables included in the model	HR	Low 95%CI	Up 95%CI	P-values
Per patients	Residual tumor at first surgery	0.54	0.30	0.99	0.05
Per lesions	Rtage III-IV vs I-II	7.49	2.32	24.15	0.0008
	N. of treated lesions	2.02	1.39	2.9	0.0002
	M vs LN	3.37	1.66	6.84	0.0008
	Time from the last chemotherapy >7months	2.39	1.18	4.84	0.016

Abbreviations: CI: Confidence Interval; HR: Hazard Ratio; LN, regional lymph nodes; M, distant metastases;

ACCEPTED MANUSCRIPT

TABLE 5. Published clinical series including patients treated with radiotherapy for oligorecurrent/oligoprogressive ovarian cancer

Author, year of publication	Ref	n	Primitive Site of Disease	Pre-RT chemotherapy courses, median (range)	Site of recurrence	RT modality	Total Dose (median)	Median follow-up (range)	PFS	LRFS	OS
Brown et al, 2013	3	102	Ovary: 100%	3 (0-9)	Nodal: 49% pts Extranodal: 51%	IFRT	Definitive IFRT: 59.2 Gy (73 pts) Post-operative: 54.5 Gy (16 pts) Post-induction CT (13 pts)	37 (1-123) months	5-year: 24%, 38% pts without ED at after a median f-up of 38 months (range:7-122)	5-year: 71%	5-year: 40%
Albuquerque et al, 2016	4	27	Ovary: 100%	10	Extraperitoneal local recurrences	EBRT only: 18 pts (67%) EBRT+BRT: 7 pt (26%) BRT only: 2 pts (7%)	50.4 (40-60) Gy Post- R0/R1 surgery: 17 pts; Salvage/Post R2 surgery: 10 pts)	2.5 years	5-year (actuarial): 33%	5-year (actuarial):70%	5-year (actuarial): 30%
Chundury et al, 2016	5	33 pts, 49 lesions	Ovary: 100%	3 (1-12)	Abdomen/pelvis: 34 pts (69.4%) Thorax: 3 pts (6.1%) Other sites: 12 pts (24.5%)	IMRT	50.4 (45-70) Gy	23.7 (1.0-105.8) months	2-year (actuarial): 11%	2-year (actuarial): 82%	2-year (actuarial): 63%
Yahara et al, 2013	6	27 pts	Ovary: 100%	Not stated	Abdomen/pelvis	EBRT only (3D-CRT): 25 pts (93%) EBRT+BRT: 1 pt (4%) BRT only: 1 pt (4%)	60.0 (50.0-61.2) Gy	25 (3-95) months (surviving pts)	2-year: 39%	2-year: 96%	2-year: 56%
Kunos et al, 2012	20	50 pts	Ovary: 50% Uterus: 28% Uterine Cervix: 18% Vulva: 4%	Not stated	Abdomen/pelvis: 44 pts (88%) Thorax: 6 pts (12%)	SBRT, Cyberknife	24 Gy, 8 Gy/fraction (mainly to the 70% isodose line)	15 (1-31) months	7.8 months (95% C.I.)	15-months: 100%	20.2 months (95% C.I.)
Mesko et al, 2017	22	28 pts, 47 lesions	Ovary: 15 pts Endometrium: 8 pts Cervix: 2 pts Vagina: 2 pts Carcinosarcoma:	2 (0-9)	Abdomen/pelvis: 53% Thorax: 21% Unspecified: 26%	SBRT	40 (16-54) Gy	12.8 months	10.8 months	Not stated	Not stated

			1 pt								
Current study, Lazzari&Ronchi et al, 2018		82 pts, 156 lesions	Ovary: 100%	3 (0-9)	Abdomen/pelvis: 123 pts (79%) Thorax: 26 pts (17%) Head and Neck: 7 pts (4%)	SBRT	24 Gy, 8 Gy/fraction	17.4 months	2-year (actuarial): 18%	2-year (actuarial): 68%	2-year (actuarial): 71%

Abbreviations: BRT: Brachytherapy, EBRT: External Beam Radiotherapy, IFRT: Involved-Field Radiotherapy, LRFS. Local Recurrence Free Survival, OS: Overall Survival, PFS: Progression Free Survival, Pts: Patient, Ref: Reference, RT: Radiotherapy SBRT: Stereotactic Body Radiotherapy

ACCEPTED MANUSCRIPT

Fig. 1: Kaplan–Meier curve for progression-free survival (PFS) of the 82 patients over time (full line). Confidence interval (C.I.)= 95% (dashed line).

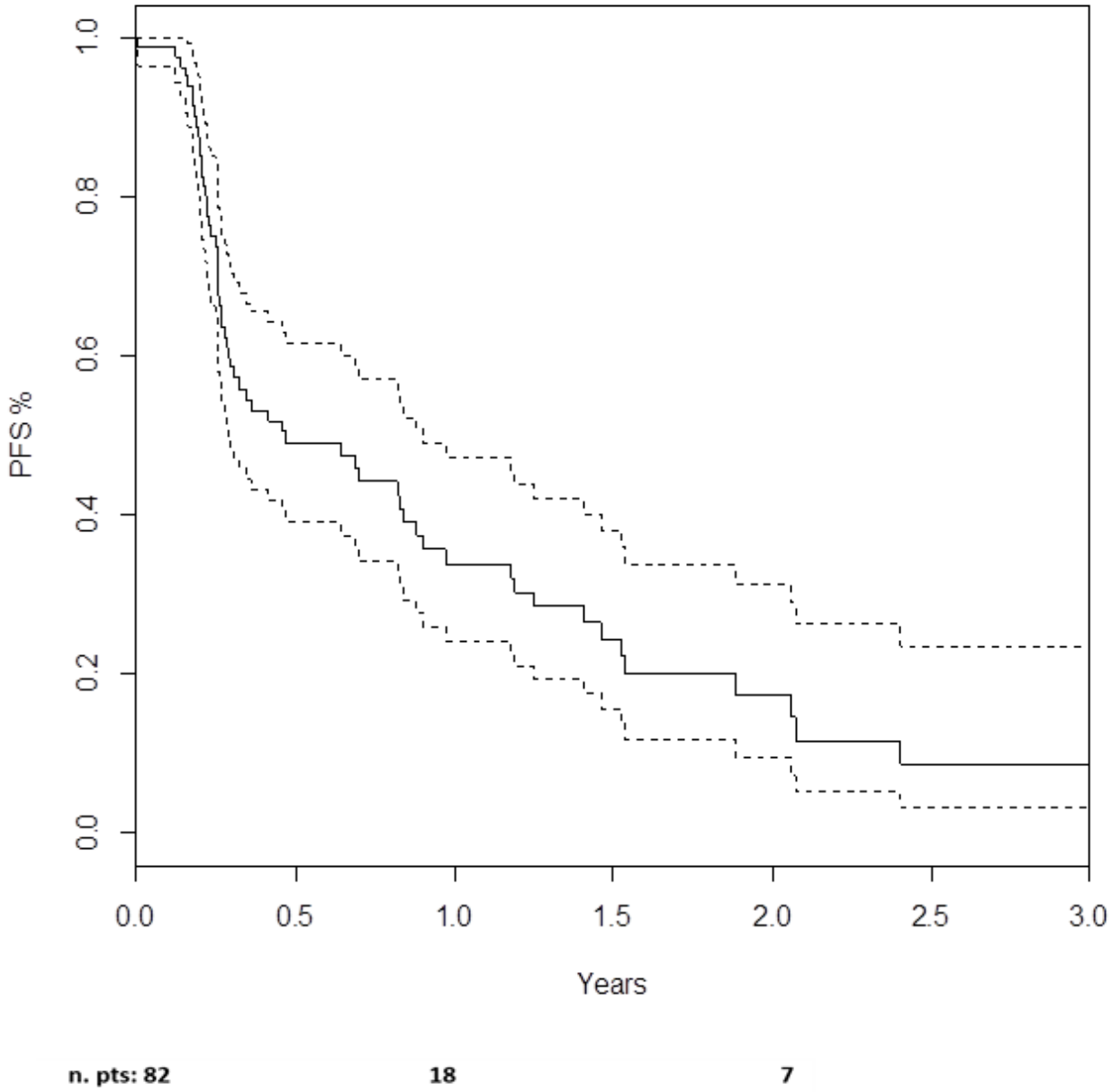

Fig. 2: Kaplan–Meier curve for local progression free survival (LPFS) of the 153 treated lesions over time (full line). Confidence interval (C.I.)= 95% (dashed line).

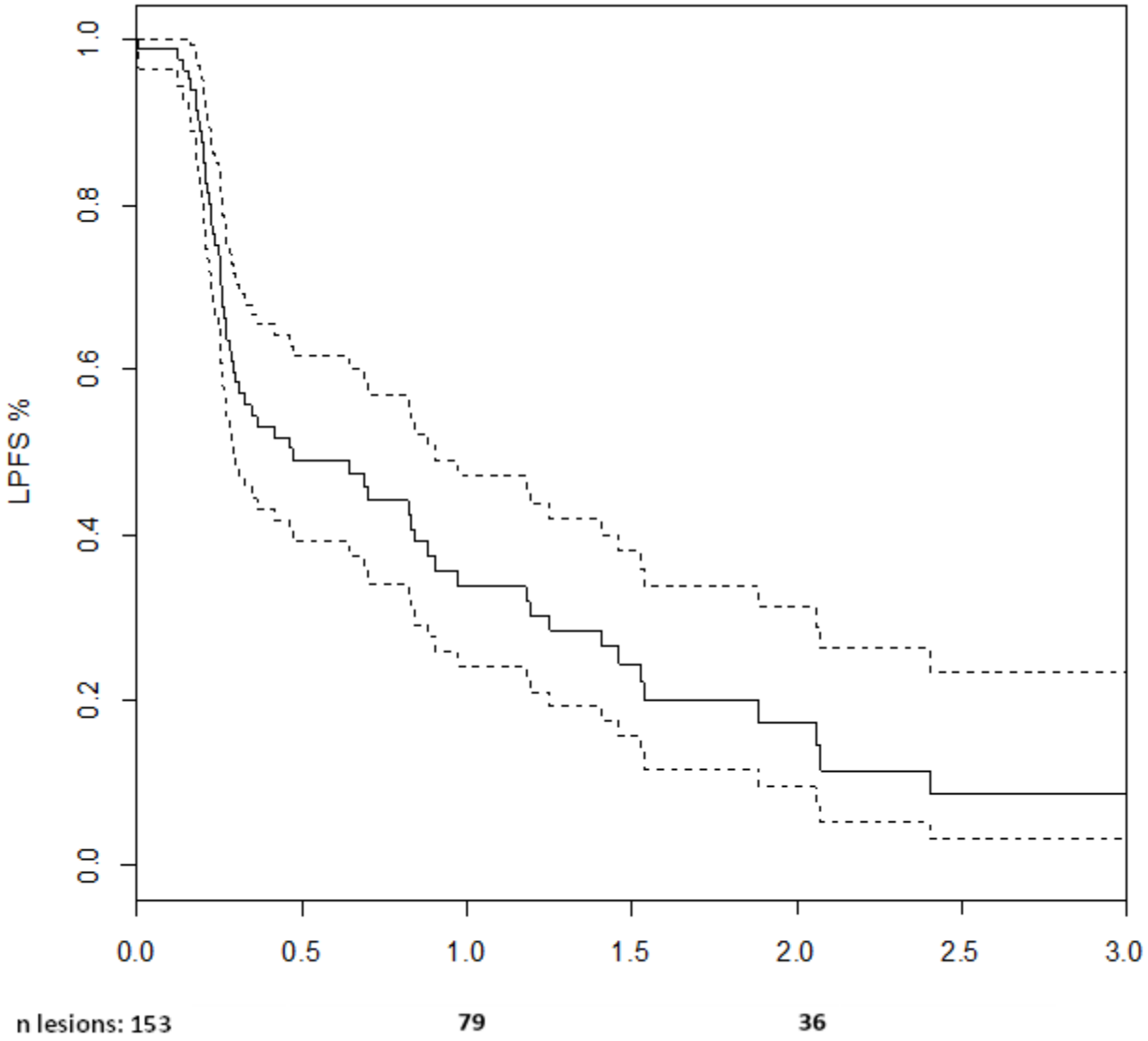

Fig. 3: Kaplan–Meier curve for overall survival (OS) of the 82 patients over time (full line). Confidence interval (C.I.)= 95% (dashed line).