Clinical and Translational Radiation Oncology 52 (2025) 100942

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Original Research Article

Correlation between radiation dose to bone marrow subregions and acute hematologic toxicity inendometrial cancer treated with external beam radiotherapy

R. Autorino [a], D. Cusumano [b], R.M. Rinaldi [a,*], R. Giannini [a], V. De Luca [a], M. Campitelli [a], V. Lancellotta [a], S. Di Franco [a], G. Macchia [c], G. Ferrandina [d], M.A. Gambacorta [a]

[a] UOC Radioterapia Oncologica, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Roma, Italy
[b] UO Fisica Medica e Radioprotezione, Mater Olbia Hospital, Olbia, Italy
[c] Unità Operativa di Radioterapia Oncologica, Responsible Research Hospital, 'Molise ART' Campobasso, Italy
[d] Woman, Child and Public Health Department, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Roma, Italy

ARTICLE INFO

Keywords:
Endometrial cancer
Bone marrow
Acute hematologic toxicity

ABSTRACT

Aim: To identify dosimetric parameters associated with acute hematologic toxicity (HT) in endometrial cancer treated with volumetric modulated arc therapy (VMAT-RT).

Methods: Patients with uterine adenocarcinoma treated in our Institution from March 2019 to November 2022 were retrospectively enrolled in this study. All patients underwent adjuvant external beam radiotherapy with Volumetric modulated arc therapy (VMAT) strategy plus a brachytherapy boost on vaginal cuff. When indicated, adjuvant platin-based chemotherapy was administered after surgery in upfront or sandwich setting. Pelvic bone marrow was contoured for each patient and divided into three subsites: lumbosacral spine (LSBM), ilium (IBM) and lower pelvis (LPBM). The volume of each region receiving 10,20,30 and 40 Gy (V10, V20, V30, V40, respectively) and mean dose (Dmean) was collected. Hematological toxicity during radiotherapy treatment was graded according to the CTCAE V 5.0. Linear logistic regression models were used to test associations between dosimetric parameters and HT.

Results: Data from 99 patients were retrospectively analyzed. Adjuvant external beam radiotherapy was delivered to the pelvis with Volumetric modulated arc therapy (VAMT) strategy for a total dose of 45 Gy, 1.8 Gy/fraction plus a brachytherapy boost on vaginal cuff for a total dose of 10 Gy in 2 fractions weekly. Thirty-one patients developed during radiotherapy treatment an HT $\geq$ grade 2.

With a sensitivity of 83.3 % and specificity of 61.5 %, V20 Gy LSBM $<$ 64 % is associated to a maximum 20 % risk of Grade 2 or worse HT in patients with $<$ 60 years old; for patients older than 70, the risk of toxicity is below 20 % independently by the percentage volume of V20Gy LSBM (95 % CI 0.60–0.87; p = 0.03).

No association between hematological toxicity and V10-20–30-40 or Dmean of IBM and LPBM were observed. Dosimetric parameters involving the lower pelvis had stronger association with hematological toxicity than those involving the ilium, even if not significant.

Conclusions: In this experience a dose constraint age-dependent was proposed, to reduce the risk of HT.

The volume of lombo-sacral pelvis receiving low-dose radiation (V20 LSBM $>$ 64 %) seems to be associated with HT in younger patients; instead in older than 70 patients the percentage of V20Gy LSBM seems not correlate with risk of toxicity. Future investigations should seek to confirm these findings through the inclusion of these parameters in the planning process.

Introduction

Nowadays external beam radiotherapy (EBRT) is often indicated to treat pelvic cancers and especially gynecological cancers. If we focus on endometrioid cancer, various international guidelines, as ESGO/ESTRO/ESP and NCCN, highlight how important the role of EBRT is to treat this pathology [1]. Surgery is the primary interventional treatment for endometrioid cancer and it is usually represented by a total

* Corresponding author.

https://doi.org/10.1016/j.ctro.2025.100942
Received 29 June 2024; Received in revised form 10 October 2024; Accepted 27 February 2025
Available online 28 February 2025

hysterectomy (TH), a bilateral salpingo-oophorectomy (BSO) and if needed a pelvic and/or *para*-aortic lymph node dissection. In this setting EBRT is mostly used in an adjuvant timing and mode and timing are modulated basing on clinical pathological, molecular risk factors. In certain circumstances EBRT can be associated with platinum-based chemotherapy which may represent the principal reason for myelosuppression [2]. To treat endometrioid cancers, the role of EBRT is principally curative and the most frequently used technique is the volumetric modulated arc therapy (VMAT). This technique permits to better define the dose distribution and reduces the risk of adverse events thanks to the dose modulation on the organ at risk (OAR).

One of the main OAR in the pelvis is the Bone Marrow (BM), being the haematopoietically active mainly comprised in this district [2]. Bone marrow is composed by the vascular and the hematopoietic compartiment which is crucial for the hematopoietic function. Several studies, mostly concerning anal cancer and cervix cancer have demonstrated that the hematological toxicity is directly related to the dose taken by bone marrow during pelvic treatments [2]. Mell et al. [3] firstly defined how to contour pelvic bone marrow on planning CT and how to divide it in three different areas.

The Bone Marrow Sparing can improve the tolerance to chemotherapy, prevent hospitalizations, decrease the need for transfusions or growth factors therapy and reduce the chronic effects of RT on bone marrow suppression, improving chemotherapy tolerance in the recurrence setting.

In the current literature several studies have explored hematologic toxicity in other cancers, but there is limited data on endometrial cancer.

It could impact patient care and treatment protocols in a meaningful way. Nowadays, the optimization of radiotherapy planning can reduce toxicity by decreasing the dose of pelvic bone marrow.

The aim of this study is to identify dosimetric parameters associated with acute hematologic toxicity (HT) in endometrial cancer treated with volumetric modulated arc therapy (VMAT-RT).

Materials and Methods

Adults' patients treated at the Department of Radiation Oncology of Policlinico Gemelli in Rome from March 2019 to November 2022 were retrospectively analyzed. To be included in this study patients had to have a diagnosis of endometrial cancer and had to undergo radiotherapy. Each patient history was firstly discussed in the internal multidisciplinary tumor board of the Comprehensive Cancer Center in order to define the stage of the disease and the subsequent therapeutic process.

All the enrolled patients underwent total hysterectomy (TH) and bilateral salpingo-oophorectomy (BSO) with or without pelvic and/or *para*-aortic lymph node dissection. A subsequent adjuvant external beam radiotherapy (EBRT) with volumetric modulated arc therapy (VMAT) strategy plus a brachytherapy boost on vaginal cuff was proposed to all patients. When indicated, adjuvant platinum-based chemotherapy was administered after surgery in upfront to radiotherapy treatment or in a sandwich setting. The patients were treated consecutively. All patients signed a written informed consent prior undergoing the radiotherapy treatment, chemotherapy treatment and for clinical data utilization.

Exclusion criteria included: (1) Patients with a history of hematologic diseases or other malignancies; 2) Patients who have previously received treatments for endometrial cancer; (3) Patients who were pregnant or breastfeeding; (4) Patients concurrently enrolled in other clinical trials.

Radiotherapy treatment

All patients received external beam radiotherapy (EBRT) to the pelvis with volumetric modulated arc therapy (VMAT) technique. The clinical target volume (CTV) was composed by the intern iliac and extern iliac lymph nodes, the obturator nodes and the third superior of the vagina. If the cervix was involved at the initial staging, the pre-sacral nodes were involved in the CTV; if the common iliac nodes were involved at the initial staging, the lombo-aortic nodes were involved in the CTV; if the pelvic nodes were involved at the initial staging, the common iliac nodes were involved in the CTV. The planned target volume (PTV) was defined by the CTV + 0.8 cm.

VMAT plans were delivered using 6 or 15 MV photon beams. The total prescribed dose to the PTV was 45 Gy with a dose per fraction of 1.8 Gy.

Treatment plans were normalised setting the prescription dose to the 50 % of the PTV according to ICRU 83 and optimized ensuring the respect of the following dose objectives related to the target: V95% $>$ 95 % and V105% $<$5%.

An additional brachytherapy boost on vaginal cuff was administered around 1 weeks after the end of EBRT done with a high dose rate (HDR) technique and consisted of a total dose of 10 Gy in 2 fractions of 5 Gy weekly.

CTCAE V 5.0 was used.

According to our internal guidelines, for grade 1 and 2 Hematological Tocixity patients repeat blood exam after 2–3 days with a clinical close monitoring; for a grade 3 or 4 hematological toxicity we evaluated patients case by case with an interruption of radiotherapy and/or chemotherapy if it is necessary, blood transfusion or granulocyte colony-stimulating factor administration.

Chemotherapy treatment

The chemotherapy regimen consisted of Carboplatin to achieve an area under the concentration–time curve (AUC) 6 plus paclitaxel at a dose of 175 mg per square meter every 21 days for six cycles.

Chemotherapy induced-toxicity effects include myelosuppression (neutropenia, thrombocytopenia, anaemia), GI toxicities, alopecia, neuropathy, renal and hepatic toxicities. Women receiving chemotherapy were monitored closely. Routine prophylaxis with granulocyte colony-stimulating factor (GCSF) were not administered.

Bone marrow delineation

The pelvic BM was retrospectively delineated on the planning CT scan contouring all bones within the pelvis by an expert Radiation oncologist. We divided the pelvic BM into three different subsites:

- the lumbosacral spine BM (LSBM): from the highest vertebral body included in the planning target volume (usually L5) to the entire sacrum;
- the ilium BM (IBM): from the iliac crests extending to the superior border of the femoral heads;
- the lower pelvis BM (LPBM): consisting of the pubes, ischia, acetabula, and proximal femora extending from the superior border of the femoral heads to the inferior border of the ischial tuberosities.

For each of these three regions we collected the volume receiving 10, 20, 30 and 40 Gy (V10, V20, V30, V40, respectively) and the Dmean.

All patients undergoing radiotherapy in our center had weekly blood tests which included a complete blood count to identify an early hematological toxicity. Hematological toxicity during radiotherapy treatment was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0.

Statistical analysis

A comprehensive database including dosimetric data, clinical information and acute hematological toxicities was created.

The aforementioned clinical and dosimetric parameters were analyzed in relation to the presence or absence of grade 2 early hematological toxicity, treated as a dichotomous outcome.

Patients were randomly split in training and validation set: univariate analysis was conducted using either the Wilcoxon Mann Whitney (WMW) test or the *t*-test, depending on the normality of data distribution, which was previously evaluated using the Shapiro-Wilk test [4,5].

A linear logistic regression model combining the two most significant variables was then elaborated.

The predictive performance of the model elaborated was evaluated using the area under the Receiver Operating Characteristic (ROC) curve (AUC), with 95 % confidence intervals calculated via the bootstrap method with 2000 iterations [6]. The optimal cut-off threshold was determined by maximizing the Youden Index (J), and sensitivity and specificity values at the best threshold were accordingly computed [7].

Tailored dose constraints were then derived, considering three levels of toxicity occurrence probability (20 %, 30 % and 40 %), being 43 % the probability of occurrence observed in the training set. The performance of the predictive model was further evaluated on the validation set [8].

The entire statistical analysis was conducted using R software (version 3.6.1, Vienna, Austria) and dedicated packages [9].

Results

We retrospectively enrolled a total of 99 women patients: 66 were included in the training set and 33 in the validation set. Median age was 66 years with a range starting from 34 to 87 years old. 75 patients had a histological diagnosis of endometrial endometrioid cancer, 4 of endometrial non endometrioid cancer, other 4 of sarcoma and the remaining 16 had other type of histological. Even if most patients had a pathological stage ranging from IB to IIIC1, there were patients with different stages (from IA to IV) and 37 patients had a nodal involvement as IIIC1 stage (Table 1).

None of the enrolled patients had distant metastasis. A total of 52 patients out of 99 underwent adjuvant chemotherapy before starting radiotherapy or in a sandwich setting.

Table 1
Patient characteristics.

Patients, n	99
Age, years (s.d.)	66 (34-87)
Pathology, n (%)	
Endometrial Endometrioid Adenocarcinoma	75 (75%)
Endometrial Non endometroid AdenoCarcinoma	4 (4%)
Sarcoma	4 (4%)
Other	16 (16%)
Clinical stage FIGO 2018, n (%)	
IA	3 (3%)
IB	27 (27%)
II	13 (13%)
IIA	1 (1%)
IIB	1 (1%)
IIIA	4 (4%)
IIIB	4 (4%)
IIIC1	37 (37%)
IIIC2	2 (2%)
IV	1 (1%)
IVA	2 (2%)
IVB	4 (4%)
Grading	
1	2 (2%)
2	48 (48%)
3	27 (27%)
NA	22 (22%)
CT	
No	21 (21%)
Yes	52 (52%)
NA	26 (26%)

There is not correlation between chemotherapy administration and outcomes.

Forty-three patients developed during radiotherapy treatment an HT > grade 2 defined as Hb < 10 g/dL, or Neutrophils < 1,500/mm^3, or platelets count < 75.000/mm^3.

At the univariate analysis, the most significant features correlated to hematological toxicity were age ($p = 0.03$) and V20 Gy of LSBM ($p = 0.04$). The two variables showed no mutual correlation ($R^2 = 0.03$ using the Pearson Correlation Coefficient).

Combining the two features, a logistic regression model with an AUC of 0.73 (0.60–0.87 as 95 % confidence interval) was obtained, with a sensitivity of 83.3 % and a specificity of 61.5 % at the best threshold (29 %) obtained maximising the Youden Index ($J = 0.45$).

Such results were confirmed in the validation set, were an AUC of 0.72 (0.60–0.87 as 95 % confidence interval) was observed. Fig. 1 reports the ROC curves in training and validation set.

Considering the two variables object of the predictive model, Table 2 containing the dose constraints related to V20Gy LSBM was calculated at varying of age and risk probability.

Based on the patients age, so it is possible to obtain a tailored dose constraint that correlate hematological toxicity to a dose constraint according to patient age.

Instead, from our analysis, for patients older than 70, the risk of toxicity is below 20 % independently by the percentage volume of V20Gy LSBM.

Discussion

To date, the standard treatment for intermediate-high or high risk endometrial cancer includes pelvic radiotherapy with non-pelvic bone marrow sparing with or without previous chemotherapy.

Often the combination of therapies can cause a severe hematological toxicity with a treatment interruption, and eventually decrease the patients' survival time.

Acute hematological toxicity was associated with the dose and volume of pelvic bone marrow irradiated in some studies moreover in cervical cancer.

So if we identify pelvic bone marrow by imaging and apply a dose constraints during the plan optimization, it could be possible to minimize the incidence of acute hematological toxicity.

Many controversies in the field remain with varied practice in target delineation, technical delivery approaches, and hematologic end points.

Some studies consider the entire bone whole pelvis as avoidance structure instead others delineated subsites of the pelvis, as in our study.

Different dosimetric parameters are considered as potential constraints such as V10-V20-V30-V40 and Dmean.

Recently, metanalyses are published demonstrating that integration pelvic (active) bone marrow into the radiotherapy treatment plan optimization could reduce the dose of pelvic (active) bone marrow exposed to radiation.

Probably, it is due to a different red marrow activity and distribution in younger age [10].

Different studies [11] demonstrated that in older patients the enhancement of marrow decrease as fat content increase. Bone and red marrow structure and function seems to decline by age. It could justify as the risk of toxicity is low for patients older than 70, independently by the irradiated and volume of percentage of bone marrow. It is not correlated with chemotherapy administration.

Marrow composition also changes throughout life with a decrease in the amount of unsaturated marrow fats. Marrow fat content inversely reflects the red marrow content of bone. The more metabolically active red marrow drives bone blood flow which is critical to bone healing.

There are no standard criteria for optimal BM dose-limitation regimens, and further exploration is necessary. Our study is similar to different studies [12–16] that support a rationale for bone marrow-sparing treatment planning to reduce the risk of hematologic toxicity.

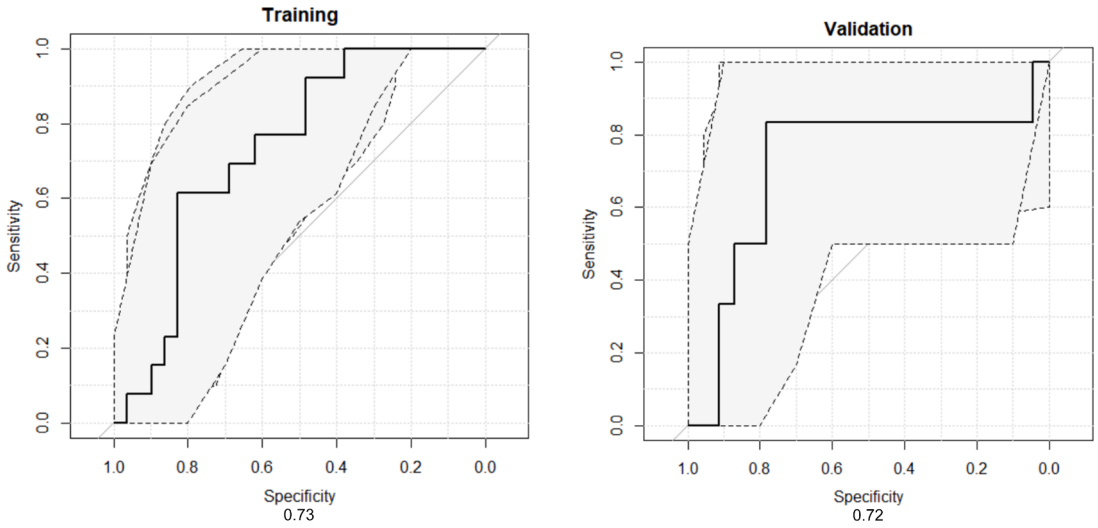

Fig. 1. ROC curves in the training and validation set.

Table 2
V20Gy of LSBM to varying of age and risk probability.

V20Gy LSBM [%] G2-G3 risk	Age <40	40–50	50–60	60–70	>70
20 %	28 %	46 %	64 %	82 %	99 %
30 %	38 %	56 %	74 %	93 %	99 %
40 %	46 %	65 %	83 %	99 %	99 %

Bone marrow is located near radiation volume, and in particular LSBM, when we irradiated primary tumor and pelvic nodes. So there could be a strongly correlation with hematological toxicity and concurrent radiochemotherapy treatment.

Nevertheless, some doubts remain in the current study: no consensus on dose limits for pelvic bone marrow, the clinical benefit of pelvic bone marrow protection planning is uncertain, and whether pelvic ABM protection planning are better than pelvic bone marrow protection planning.

There were many other limitations in our study. First, it is a retrospective study, so we cannot determine the clinical impact or outcomes and we need of a prospective study.

Secondly, the small number of patients included in the study may be another limitation, moreover about statistical interpretation and interval uncertainty.

We included also oligometastatic patients to the diagnosis treated with surgery and chemiotherapy followed by radiotherapy treatment to increase local control.

Conclusions

In this experience a dose constraint age-dependent was proposed, to reduce the risk of HT.

Such constraint was focused on the optimization of the 20 Gy isodose on lombo-sacral pelvis: in particular, the volume of lombo-sacral pelvis receiving low-dose radiation (V20 LSBM > 64 %) seems to be associated with HT in younger patients; instead, in patients older than 70 years, the percentage of V20Gy LSBM seems not correlate with risk of toxicity. Future investigations should seek to confirm these findings through the inclusion of these parameters in the planning process.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Concin N, Matias-Guiu X, Vergote I, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer 2021 Jan;31(1):12–39. https://doi.org/10.1136/ijgc-2020-002230. Epub 2020 Dec 18 PMID: 33397713.
[2] Franco P, Ragona R, Arcadipane F, et al. Lumbar-sacral bone marrow dose modeling for acute hematological toxicity in anal cancer patients treated with concurrent chemo-radiation. Med Oncol 2016;33:137. https://doi.org/10.1007/s12032-016-0852-7.
[3] Mell LK. Trials and tribulations of bone marrow sparing radiotherapy for cervical cancer. Re: Zhou et al. Radiother Oncol. 2021;165:103-118. Radiother Oncol. 2022;167:78-80. doi: 10.1016/j.radonc.2021.11.025.
[4] Sanfratello A, Cusumano D, Piras A, Boldrini L, D'Aviero A, Fricano P, et al. New dosimetric parameters to predict ano-rectal toxicity during radiotherapy treatment. Phys Med 2022;99:55–60. https://doi.org/10.1016/j.ejmp.2022.05.007.
[5] Taylor J. Introduction to Error Analysis, the Study of Uncertainties in Physical Measurements, 2nd Edition. 1997.
[6] International Commissioning on Radiation Units and Measurements. Receiver Operating Characteristic (ROC) Analysis in Medical Imaging. ICRU Report 79. 2008.
[7] Ruopp MD, Perkins NJ, Whitcomb BW, Schisterman EF. Youden Index and Optimal Cut-Point Estimated from Observations Affected by a Lower Limit of Detection. Biometrical Journal Biometrische Zeitschrift 2008;50:419. https://doi.org/10.1002/bimj.200710415.
[8] Cusumano D, Meijer G, Lenkowicz J, Chiloiro G, Boldrini L, Masciocchi C, et al. A field strength independent MR radiomics model to predict pathological complete response in locally advanced rectal cancer. Radiol Med 2021;126:421–9. https://doi.org/10.1007/s11547-020-01266-z.
[9] Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez J-C, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinf 2011;12:77. https://doi.org/10.1186/1471-2105-12-77.
[10] Blebea JS, Houseni M, Torigian DA, Fan C, Mavi A, Zhuge Y, et al. Structural and functional imaging of normal bone marrow and evaluation of its age-related changes. Semin Nucl Med 2007 May;37(3):185–94. https://doi.org/10.1053/j.semnuclmed.2007.01.002. PMID: 17418151.
[11] Bani Hassan E, Ghasem-Zadeh A, Imani M, Kutaiba N, Wright DK, Sepehrizadeh T, et al. Bone Marrow Adipose Tissue Quantification by Imaging. Curr Osteoporos Rep 2019 Dec;17(6):416–28. https://doi.org/10.1007/s11914-019-00539-5. PMID: 31713178.
[12] Ruben Carmona, MD, MAS, Jakub Pritz, PhD, Mark Bydder, PhD,y Sachin Gulaya, BS, He Zhu, MD, PhD, Casey W. Williamson, BA, Christian S. Welch, MD, Florin Vaida, PhD, Graeme Bydder, MD, and Loren K. Mell, MD Fat Composition Changes in Bone Marrow During Chemotherapy and Radiation Therapy. International Journal of Radiation Oncology*Biology*Physics Volume 90, Issue 1 , 1 September 2014, Pages 155-163.
[13] Miszczyk M, Wu T, Kuna K, Stankiewicz M, Staniewska E, Nowicka Z, et al. ZhouClinical outcomes of pelvic bone marrow sparing radiotherapy for cervical cancer: A systematic review and meta-analysis of randomised controlled trials; Clin Transl. Radiat Oncol 2024 Jul;47:100801.
[14] Williamson CW, Sirák I, Xu R, Portelance L, Wei L, Tarnawski R, Mahantshetty U, Heide ES, Yashar CM, McHale MT, Bosch W, Lowenstein J, Saenz CC, Plaxe S, Eskander R, Einck J, Mundt AJ, Mayadev J, Mell LK. Positron Emission Tomography- Guided Bone Marrow-Sparing Radiation Therapy for Locoregionally Advanced Cervix Cancer: Final Results From the INTERTECC Phase II/III Trial. Int

J Radiat Oncol Biol Phys. 2022 Jan 1;112(1):169- 178. doi: 10.1016/j.ijrobp.2021.08.019.

[15] Arcadipane F, Silvetti P, Olivero F, Gastino A, De Luca V, Mistrangelo M, Cassoni P, Racca P, Gallio E, Lesca A, Fiandra C, Ricardi U, Franco P. Bone Marrow-Sparing IMRT in Anal Cancer Patients Undergoing Concurrent Chemo-Radiation: Results of the First Phase of a Prospective Phase II Trial; Cancers (Basel). 2020 Nov 9;12(11):3306. doi: 10.3390/cancers12113306).

[16] Arcadipane F, Silvetti P, Olivero F, Gastino A, Carlevato R, Chiovatero I, et al. Concurrent Chemoradiation in Anal Cancer Patients Delivered with Bone Marrow-Sparing IMRT: Final Results of a Prospective Phase II Trial. J Pers Med 2021 May 18;11(5):427. https://doi.org/10.3390/jpm11050427).