Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

INTRA-OPERATIVE RADIATION (IORT) AT THE TIME OF PELVIC SALVAGE EXENTERATION IN PERSISTENT OR RECURRENT GYNECOLOGIC MALIGNANCIES: a series of 55 patients

S. Durante, R. Lazzari, G. Corrao, S. Vigorito, F. Cattani, A. Aloisi, V. Zanagnolo, A. Maggioni, N. Colombo, B.A. Jereczek-Fossa

UNIVERSITÀ DEGLI STUDI DI MILANO

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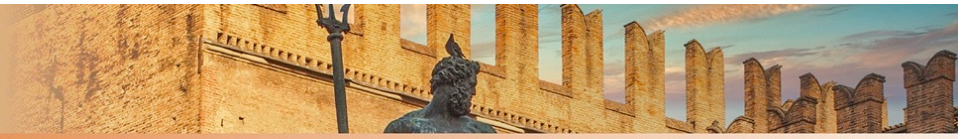
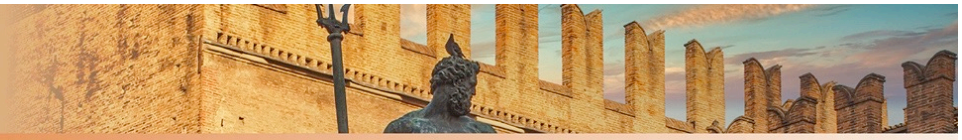


DICHIARAZIONE

Relatore: Stefano Durante

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro



- **BACKGROUND**
- AIM
- MATHERIALS AND METHODS
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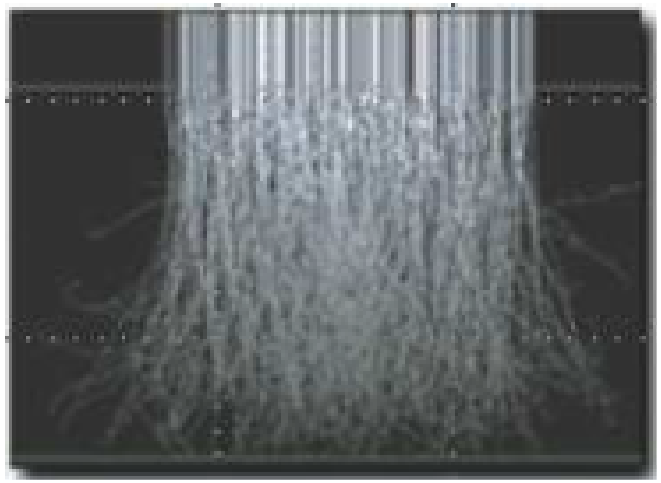
What is Intraoperative Electron Beam Radiation Therapy (IOERT)?

Intraoperative Electron Beam Radiation Therapy is the application of radiation directly to the residual tumor or tumor bed during cancer surgery



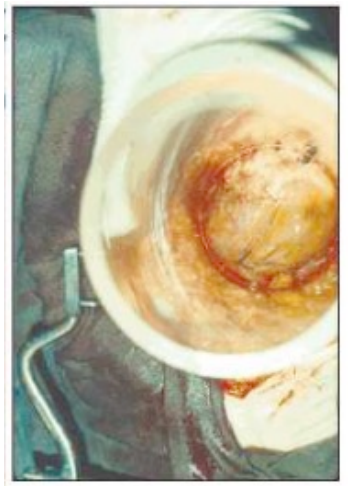
IORT Advantages and Benefits

- The treatment is performed at the time of surgery, when the target area (the tumor bed) is exposed and the applicator can be placed directly over the target
- Organs at risk may be retracted and shielded as necessary
- Residual tumor and tumor bed can be irradiated without irradiating sensitive skin.

Patients with advanced disease can safely receive a higher dose of radiation, Substantially increases the effective dose of radiation to the tumor bed

History

IORT is NOT a new approach to cancer management. As the result of pioneering work by Dr. Abe in Kyoto, Japan, IORT using linear accelerators has been used in the U.S.A., Europe and Japan for the treatment of malignancies in the abdomen (sarcomas, rectum, gynecologic and retroperitoneal tumors)



- *1909: Beck treated a patient with colon cancer using low-energy X-rays*
- *Early 1970, Dr. Abe in University of Kyoto, Japan*
- *1978, IORT pioneered in the U.S.A.:*

- Howard University/N.C.I., Washington, D.C.

- *Massachusetts General Hospital*
- Europe (Caen, 1983: Pamplona 1984, Innsbruck 1984, Lyon 1985, Milan 1985….)

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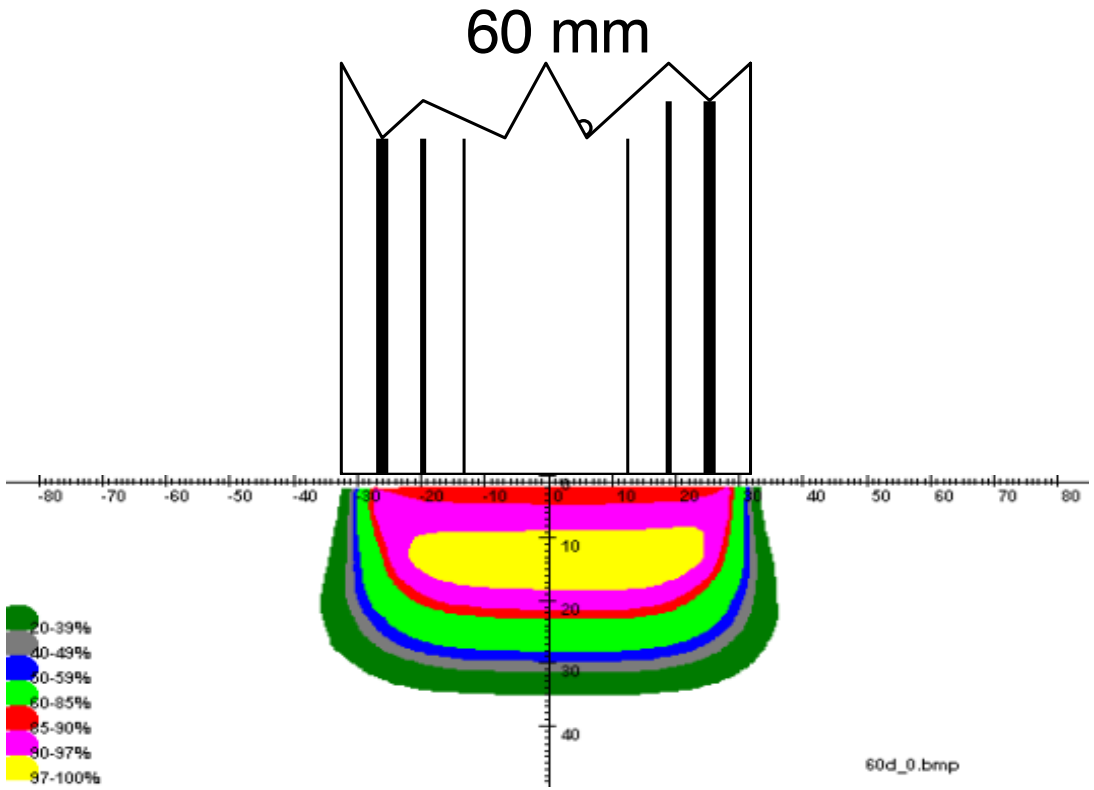
IORT with electrons



1960s

Megavoltage IORT (IOERT, 1965)

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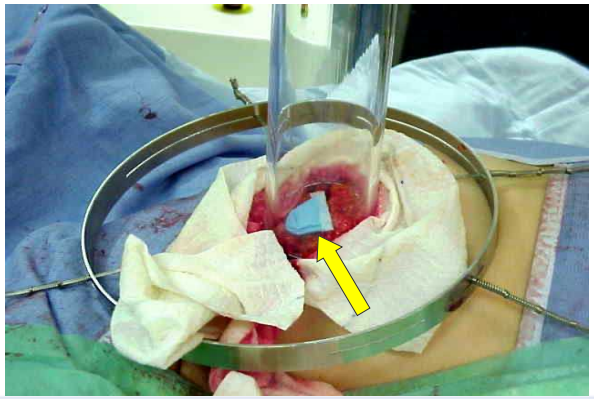
"Mobile"Linacs



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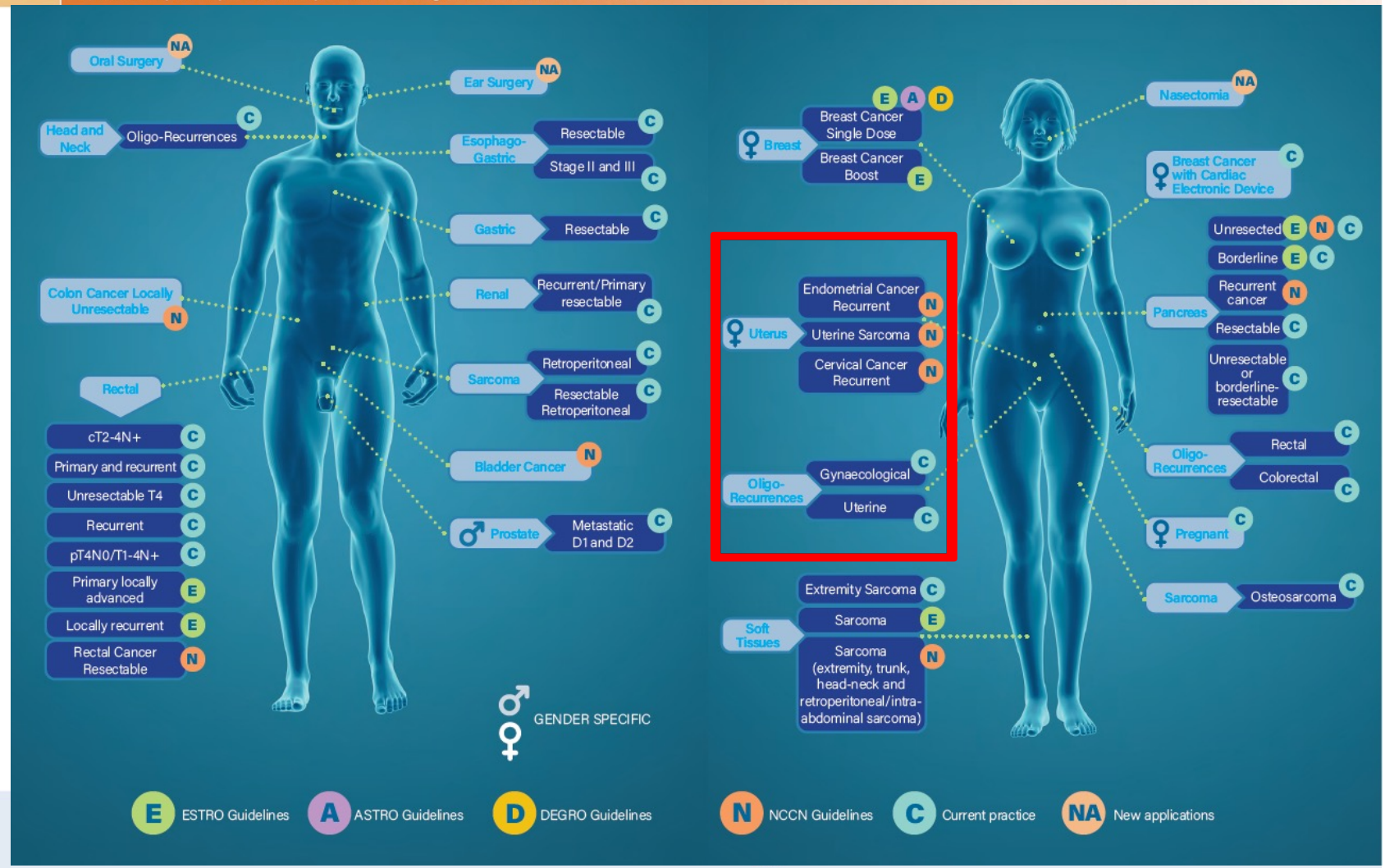
IORT Clinical Application



Recurrent/persistent gynecological diseases

- Patients with poor prognosis without other curative options in persistent or recurrent gynecological malignancies
- Treatment Options: **AGGRESSIVE SALVAGE SURGERY**
  - Pelvic Exenteration (PE) : central disease, survival rate 47%
  - Laterally extended endopelvic resection (LEER): disease involves the lateral pelvic sidewall or sacrum

The surgical treatment of cancer of the cervix uteri; a radical operation for cancer of the cervix

A BRUNSCHWIG

PMID: 18883045 PMCID: PMC1871507
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Performance and outcome of pelvic exenteration for gynecologic malignancies: A population-based study

Koji Matsuo [1], Rachel S Mandelbaum [2], Crystal L Adams [2], Lynda D Roman [3], Jason D Wright [4]

Affiliations + expand
PMID: 30792003 PMCID: PMC7521603 DOI: 10.1016/j.ygyno.2019.02.002
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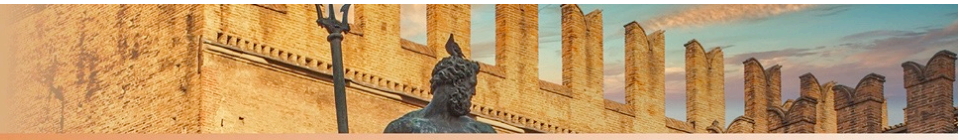

Toxicity

Intraoperative radiation therapy
Part 2. Clinical results

Felipe A. Calvo[a,*], Rosa M. Meirino[b], Roberto Orecchia[c]
[a] Hospital General Universitario Gregorio Marañon, Madrid, Spain
[b] Clínica La Luz, Madrid, Spain
[c] European Institute of Oncology and University of Milan, Milan, Italy

Accepted 13 April 2006

2.4. Gynaecologic cancers

In patients with locally recurrent gynaecologic cancer in the pelvic sidewalls and/or para-aortic or pelvic lymph nodes, the use of aggressive salvage surgery and IOERT, with or without EBRT, and the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) may be beneficial when compared with standard EBRT. The 5-year OS were 27 and 32% respectively in the separate series from Mayo Clinic [49] and the University of Washington [50]. Patients with only microscopic residual disease after maximal resection at the time of IOERT had significantly higher 5-year OS rate than those with gross residual disease (37% versus 10%, $p = 0.02$). The risk of distant metastases at 3 years was 42% (77% with gross residual and 31% with microscopic residual, $p = 0.001$). There was a trend towards fewer metastases (27% at 5 years) in patients who received MVAC chemotherapy ($p = 0.09$). Based on the higher response rate observed in patients receiving chemotherapy and the observed trend toward improved distant control and DFS, Mayo Clinic is using MVAC before surgery and IOERT as standard treatment.

Int J Radiat Oncol Biol Phys. 1997 Mar 1;37(4):839-43. doi: 10.1016/s0360-3016(96)00546-9.

Intraoperative radiation therapy in gynecologic cancer: update of the experience at a single institution

ve

G R Garton [1], L L Gunderson, M J Webb, T O Wilson, S S Cha, K C Podratz

Affiliations + expand

PMID: 9128960 DOI: 10.1016/s0360-3016(96)00546-9

Intraoperative radiotherapy in gynaecological and genito-urinary malignancies: focus on endometrial, cervical, renal, bladder and prostate cancers

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Marco Krengli [1 2], Carla Pisani [3 4], Letizia Deantonio [3 4], Daniela Surico [3 5], Alessandro Volpe [3 6], Nicola Surico [3 5], Carlo Terrone [3 6]

Affiliations + expand

PMID: 28100242 PMCID: PMC5244540 DOI: 10.1186/s13014-016-0748-x
Free PMC article

Gy

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NCCN Guidelines Version 1.2021
Endometrial Carcinoma

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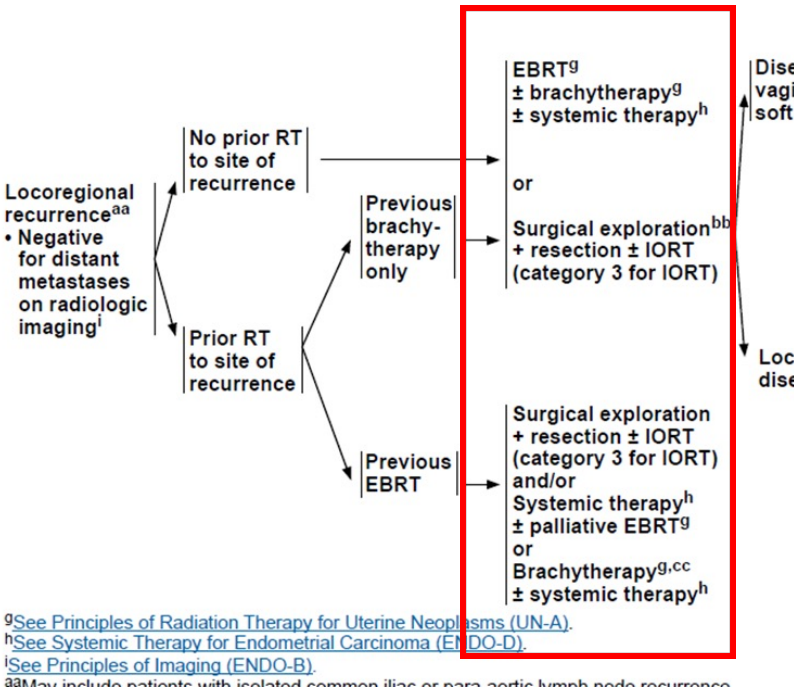
CLINICAL PRESENTATION

THERAPY FOR RELAPSE



[g] See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] See Systemic Therapy for Endometrial Carcinoma (ENDO-D).
[i] See Principles of Imaging (ENDO-B).
[aa] May include patients with isolated common iliac or para-aortic lymph node recurrence

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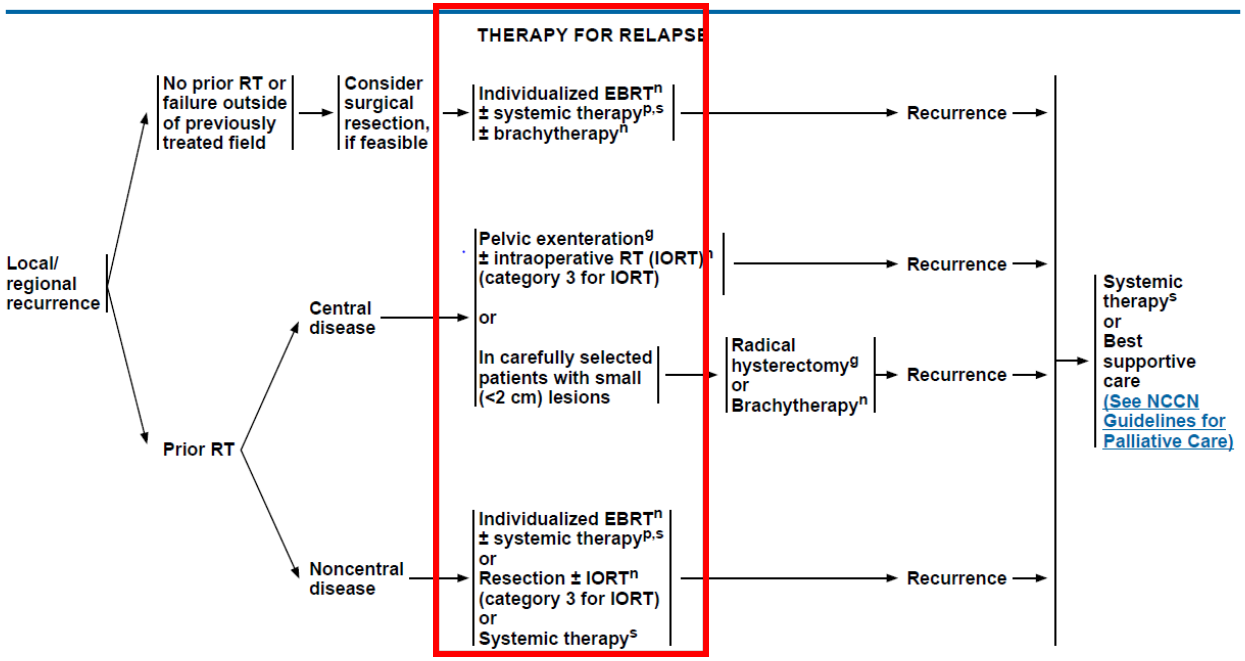

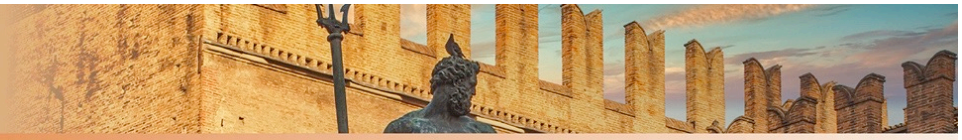

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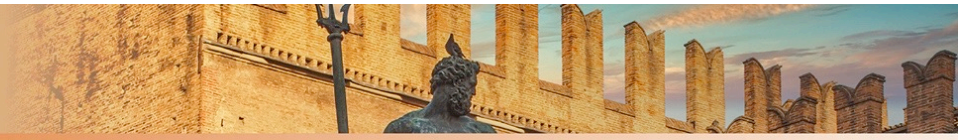
- To describe the experience at European Institute of Oncology with IORT at the time of PE or LEER in patients with locally recurrent gynecologic malignancies
- To determine the impact of IORT on recurrence of disease and survival
- Seconday endopoint: identify factors associated with recurrence



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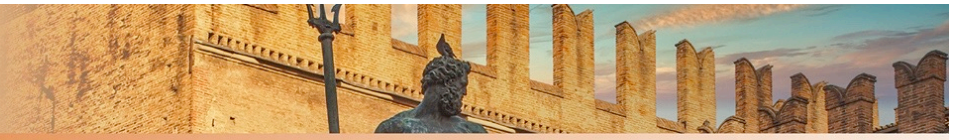
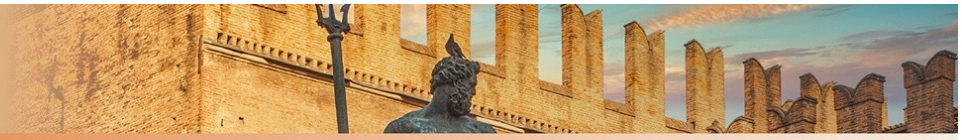


- Retrospective monocentric study
- Inclusion criteria:
  - Patients with Persistent / recurrent gynecologic malignancies who underwent PE/LEER with curative intent
  - IORT administered at the time of surgery (for not radical surgical margin, close margin (<1 mm) or positive lymph nodes)
  - All gynecologic cancers were considered
  - informed written consent acquired



- BACKGROUND
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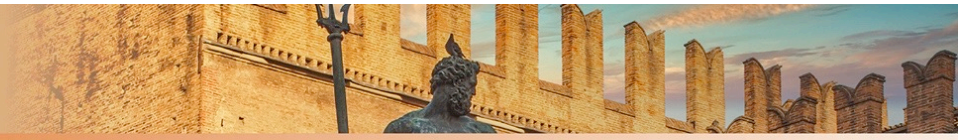


- From January 2001 to March 2019, we retrospectively identified 55 women

- Reason for surgery:
  - persistent disease 24 patients (43.6%)
  - recurrent disease 31 patients (56.4%)

- Previous oncologic treatments: 53 patients (96.4%)

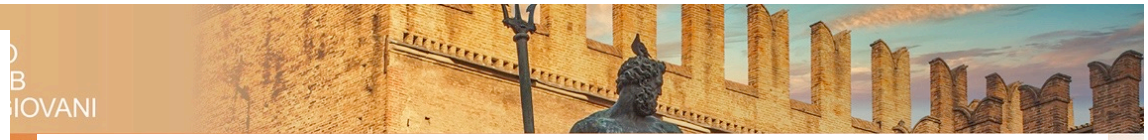


Table 1: Patients' Characteristics (N=55)

Variable	median	range
Age (years)	54	23-76
Body mass index (kg/m2)	24	18-39
	N	**%**
Type of tumor		
cervical	40	72.7
vulvar	3	5.5
vaginal	6	10.9
endometrial	6	10.9
Histotypes		
squamous	39	70.9
adenocarcinoma	7	12.7
adenosquamous	4	7.3
endometrioid	3	5.5
serous	1	1.8
clear cell	1	1.8
GRADE		
1	11	20
2	11	20
3	18	32.7
Not graded	15	27.3
Lymphovascular space invasion (LVI)	19	34.5
Previous oncologic treatment	53	96.4
Radiotherapy alone *	10	
Brachytherapy alone followed by chemotherapy	1	
Radiotherapy + brachytherapy¥	10	
Chemoradiation	12	
Chemoradiation + Brachytherapy	20	
Reason for surgery		
persistent disease	24	43.6
recurrent disease	31	56.4
Neoadjuvant chemotherapy (within 4 week from surgery)	12	21.8
Neoadjuvant radiotherapy (within 4 week from surgery)	1	1.8

* in 7 cases followed by chemotherapy.

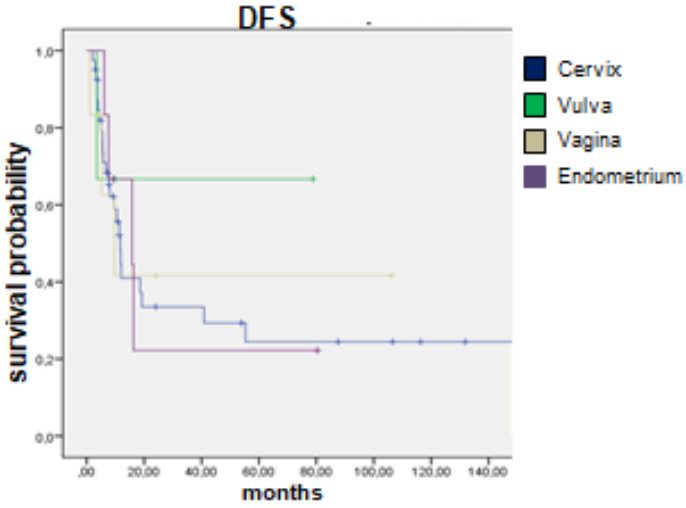
¥ in 6 cases followed by chemotherapy

Table 2: Perioperative characteristics (N=55)

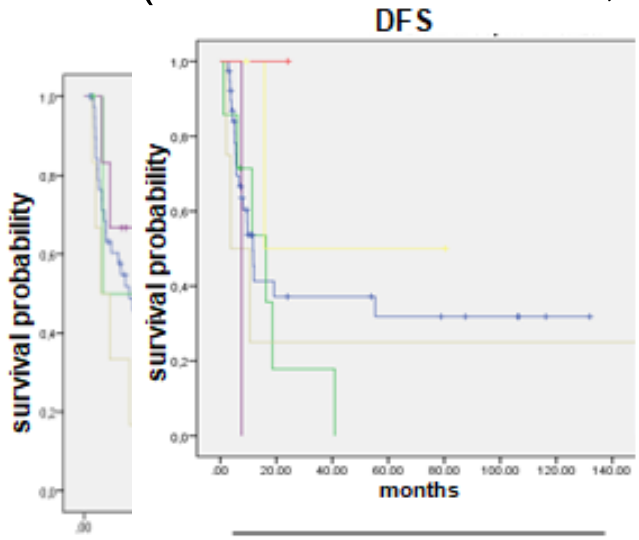
Variable	N	%
Type of exenteration		
total	35	63.6
anterior	18	32.7
posterior	2	3.6
Tumor size (mean ± DS)	41.1 ± 18.7	
Margins		
positive	19	34.5
negative	36	65.5
Pelvic lymph nodes (surgically assessed)	37	67.3
positive	12	32.4
negative	25	67.6
IORT		
monolateral	46	83.6
bilateral	9	16.4
Hospital stay (median, mean), days	18 (10-63)	
Field of irradiation*		
right pelvic wall	25	39.1
left pelvic wall	34	53.1
sinfisis or pubis	4	6.2
sacrum	1	1.6
IORT dose (median, range), Gy	15 (10-20)	
IORT energy (median range), Mev	6 (3-9)	
Dimension of the applicator (median, range), cm	5 (4-8)	
Angle of the applicator (median, range),	30 (0-45)	
Depth of irradiation (median, range), cm	0.5 (0-3)	
Adjuvant treatments	23	41.8
chemotherapy	18	
radiotherapy followed by chemotherapy	4	
chemoradiation	1	

3-year **DFS** was 34.7% (median 11.8 months, 95% CI 6.1-17.6)

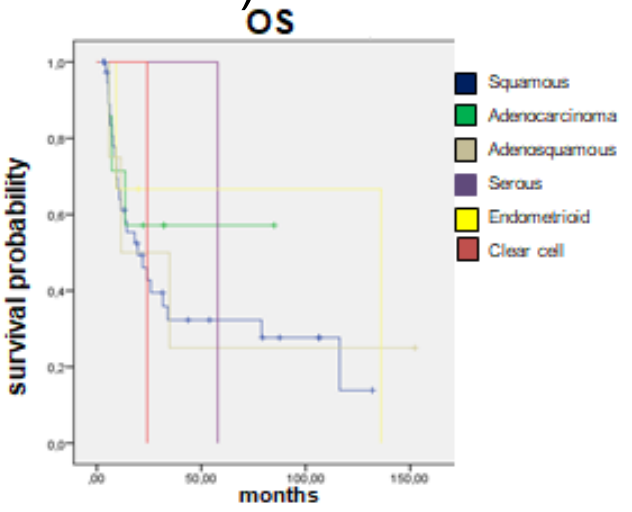
3-year **OS** was 41.8% (median 24 months, 95% CI 14.5-33.5)



DIAGNOSIS	DFS Rate (+/- SE)	Median (95% CI) in months
CERVIX	33.5 % (+/-8.7%)	11.7 (9.7–13.6)
VULVA	66.7 % (+/-27.2%)	NOT REACHED
VAGINA	41.7 % (+/-22.2%)	9.7 (0.2–19.2)
ENDOMETRIUM	22.2 % (+/-19.2%)	15.8 (6.1–17.6)



HISTOTYPE	DFS Rate (+/- SE)
SQUAMOUS	37.2 % (+/-9.1%)
ADENOCARCINOMA	17.9 % (+/-16%)
ADENOSQUAMOUS	25 % (+/-21.7%)
SEROUS	NA
ENDOMETRIOID	50 % (+/-35.4%)
CLEAR CELL	NA



HISTOTYPE	OS Rate (+/- SE)
SQUAMOUS	39.5% (+/-8.5%)
ADENOCARCINOMA	57.1% (+/-18.7%)
ADENOSQUAMOUS	25% (+/-21.7%)
SEROUS	NA
ENDOMETRIOID	66.7 % (+/-27.2%)
CLEAR CELL	NA

RELAPSE

Relapse	33	60
local	15	45.5
distant	7	21.2
multisite	11	33.3
local+distant	5	
local multisite	5	
distant multisite	1	
RELAPSE IN FIELD OF IRRADIATION	18	32.7

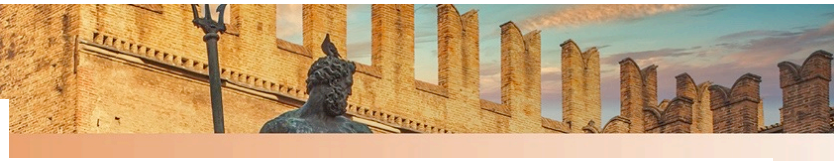


Table 3: Univariable and multivariable analysis of factors related to relapse

Variable	Univariate		Adjusted I
	HR (95% CI)	P value	
Diagnosis			
cervical	1.5 (0.4-4.8)	0.5	
others	Reference		
Histology			
squamous	0.4 (0.1-1.4)	0.1	0.4 (
others	Reference		Ref
Grade	1.1 (0.7-1.9)	0.6	
Tumor size			
≤ 5 cm	Reference		
> 5 cm	1.2 (0.3-3.8)		
Indications for surgery			
persistent	Reference		
relapse	0.9 (0.3-2.6)	0.8	
L VI			
no	Reference		Ref
yes	2.5 (0.7-8.4)	0.1	2.4 (
Lymph nodes			
negative	Reference		
positive	2.9 (0.7-12.3)	0.1	
Margins			
Negative	Reference		
positive	1.1 (0.3-3.1)	0.9	
Reason for IORT			
Positive margin	2.2 (0.5-9.8)		1.5 (
Positive lymph node	4.7 (0.8-26.2)		2.6 ((
Negative margin	Reference		Ref
Dosage	0.9 (0.8-1.2)	0.7	
Diameter of applicator	1 (0.5-1.9)	0.9	
Angle of applicator	1 (0.9-1.1)	0.8	

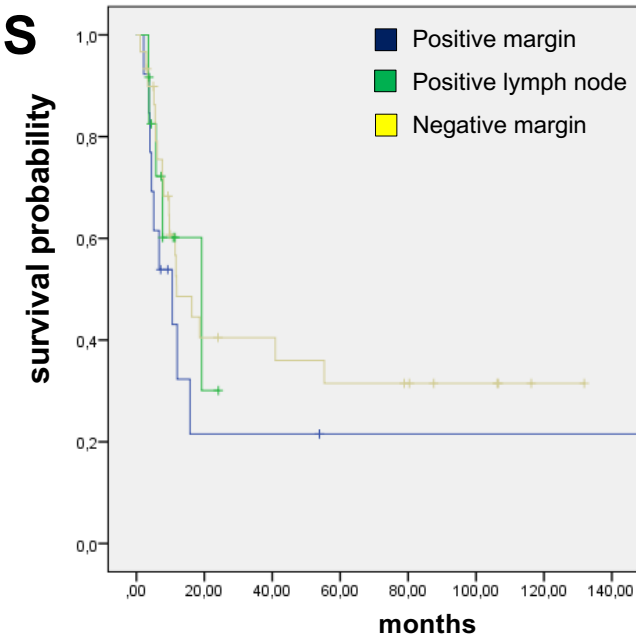
All variables were tested for multicollinearity. Clinically significant variables and variat
were included in the multivariable analysis.

Univariable and multivariable analysis of factors related to relapse in field

Variable	Univariate		Multivariable	
	HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Diagnosis				
cervical	10.3 (1.2-86.5)	0.03	7.8 (0.9-71.4)	0.06
others	Reference		Reference	
Histology				
squamous	0.9 (0.3-3.2)	0.9		
others	Reference			
Grade				
G1	Reference		Reference	
G2	3.7 (0.3-43.3)	0.3	3.7 (0.3-47.5)	0.3
G3	10 (1.1-95.2)	0.04	5.9 (0.6-61.4)	0.1
Gx	5 (0.5-50.8)	0.2	2.9 (0.3-32.5)	0.4
Tumor size				
≤ 5 cm	Reference			
> 5 cm	1.9 (0.6-6.6)	0.3		
Indications for surgery				
persistent	Reference			
relapse	0.7 (0.2-2.1)	0.5		
L VI				
no	Reference			
yes	1.9 (0.6-6.1)	0.3		
Lymph nodes				
negative	Reference			
positive	1.4 (0.3-6.7)	0.7		
Margins				
Negative	Reference			
positive	1.7 (0.5-5.3)	0.4		
Reason for IORT				
Positive margin	2 (0.5-7.7)	0.3		
Positive lymph node	0.8 (0.2-3.7)	0.7		
Negative margin	Reference			
Dosage	1.1 (0.8-1.3)	0.6		
Diameter of applicator	1 (0.5-2)	0.9		
Angle of applicator	0.9 (0.9-1.03)	0.3		

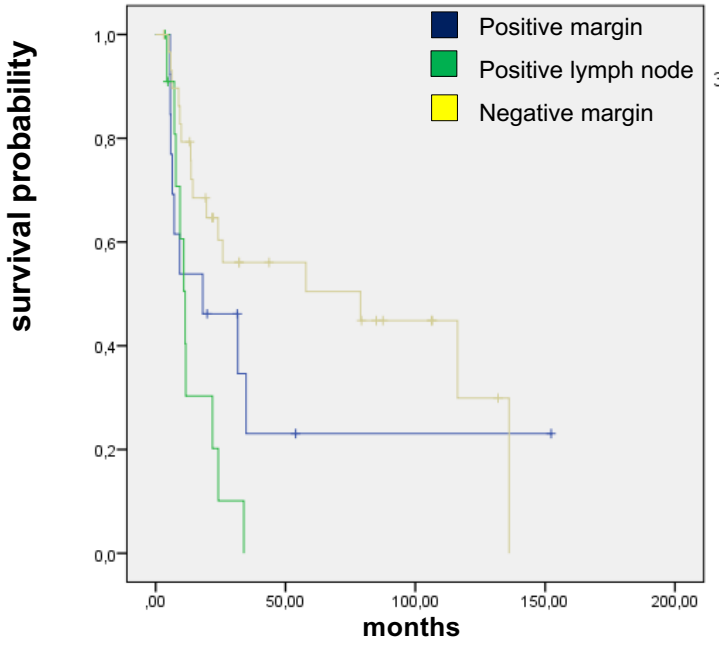
All variables were tested for multicollinearity. Clinically significant variables and variables with p <0.2 on univariate analysis were included in the multivariable analysis.

DFS



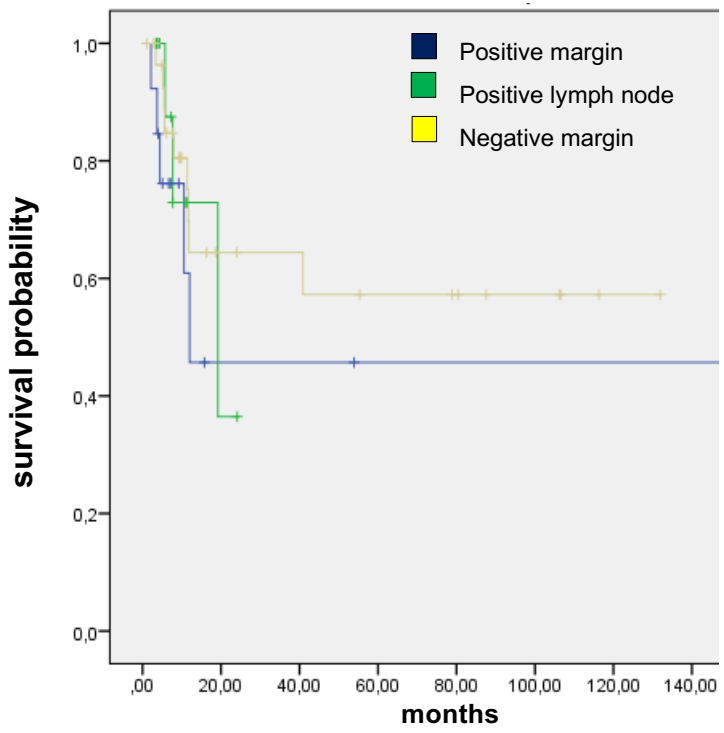
REASON FOR IORT	DFS Rate (+/- SE)	Median (95% CI) in months	P Value
Positive margin	21.5 (+/-13%)	10.6 (2.1 –19.1)	P=0.5
Positive lymph node	30.1% (+/- 22.7%)	19.2(2.2– 36.2)	
Negative margin	40.5% (+/-9.6%)	11.8 (4.1– 19.7)	

OS



REASON FOR IORT	OS Rate (+/- SE)	Median (95% CI) in months	P Value
Positive margin	34.6% (+/-14.4%)	18.1 (1 –42.7)	P=0.007
Positive lymph node	30.3% (+/-14.6%)	11.4 (8.3– 14.4)	
Negative margin	56.1% (+/-9.7%)	78.9 (1– 176.1)	

DFS- relapse in field of IORT



REASON FOR IORT	DFS Rate (+/- SE)	P Value
Positive margin	45.7 (+/-18.2%)	P=0.6
Positive lymph node	36.5% (+/-27.1%)	
Negative margin	64.4% (+/-10.4%)	

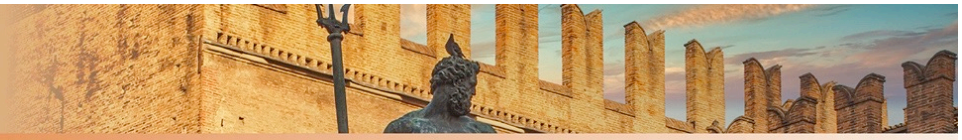


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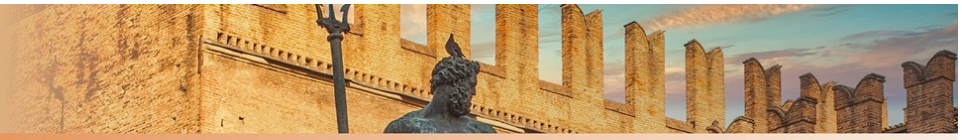
Table 1 IORT studies for endometrial and cervical cancer

Reference	N.pts	Type of cancer	Primary/recurrent	EBRT N. pts Dose (Gy)	IORT dose (Gy)	Technique	Median follow-up months(range)	Local Control	Overall Survival	Toxicity
Sole [7]	61	Uterus 18 Cervix 32 Other 11	Pelvic recurrent 35 (57%) Paraortic recurrent 26 (43%)	Mean 31 Gy (29–45)	R0: 10–12.5 Gy R1: 15 Gy	IOERT	42 (2–169)	5-years 65%	5-years 42%	RTOG acute ≥ G3: 23 RTOG late ≥ G3: GI 6 GU 3 Neuropathy 1
Foley [8]	32	Cervix 21 Uterus 6 Other 5	Pelvic recurrent 26 (81%) Primary 6 (19%)	NA	Mean 13.5 Gy (10–22.5)	IOERT	Median 26 (3–196)	5-years R1 73% 5 years R2 71%	5-years 70% R1 77% R2 55%	≥G3 47% 5 IORT-related GU 2 Bone 1 Lymphedema 2
Backes [9]	32 21 IORT	Cervix 21 Other 11	Recurrent 32 (100%)	6 pts, mean 26 Gy (10–40)	Median 17.5 Gy (10–20 Gy)	IOERT HDR IORT	NA	Median PE + IORT 10 months LEER + IORT 9 months PE 33 months	Median PE + IORT 10 months LEER + IORT 17 months PE 41 months	NA
Barney [10]	86	Cervix	Pelvic recurrent 73 (85%) Primary 13 (15%)	61 pts (71%) No prior RT: median 45 Gy Prior RT: median 39.6 Gy	median 15 Gy (6–25 Gy)	IOERT	32 (1–306)	3-years 62%: 70% primary 61% recurrent	3-years 25%	≥G3 GI 4 GU 1 Neuropathy 1 Other 4
Calvo [11]	35	Uterus 7 Cervix 20 Other 8	Pelvic recurrent 35 (100%)	16 pts: 45 Gy no previous RT 30.6 Gy previous RT	R0: 10–12.5 Gy R1: 15 Gy	IOERT	46 (3–169)	5-years 58%	5-years 42%	acute ≥3: 14 late ≥3: GI 5 GU 2 Neuropathy 1
Giorda [12]	35	Cervix	Primary 35 (100%)	neoadj 50.4 Gy	Mean 11 Gy (10–15)	IOERT	NA	2-years 89%	5-years 49%	Peri/post-surgery GU 10
Tran [13]	36	Cervix 17 Uterus 11 Other 8	Recurrent 32 (88%)	18 pts (50%) mean 44 Gy	Median 11.5 Gy (6–17.5)	Orthovoltage-IOERT	Mean 50 (2–198)	5-years 44% Cervix 45% Uterus 58%	5-years 42%	≥G3 10 pts 28%
Dowdy [14]	25	Uterus	Recurrent 25 (100%)	21 pts 45 Gy	Median 15 Gy (10–25 Gy)	IOERT	Median 34	84%	5-years: 71% R0 47% R1 0% R2	Neuropathy 8 GU 5 Fistulas 5 Bone fractures 2
Awtrey [15]	27	Uterus	Pelvic Recurrent 27 (100%)	12 pts	NA	IOERT 9 pts	Median 24 (5–84)	NA	2-years 78%	NA
Martinez-Monge [16]	67	Cervix	Pelvic Recurrent 36 (54%) Primary 31 (46%)	36 pts : 45 Gy	Primary: 12 Gy median (10–25) Recurrent: 15 Gy (10–20)	IOERT	Primary: 58 (8–144) Recurrent 19 (1–138)	10-year 69%: 93% primary 47% recurrent	10-year 35%; 58% primary 14% recurrent	5% IORT related
Gemignani [17]	17	Cervix 9 Uterus 7 Other 1	Recurrent 17 (100%)	2 pts dose NA	Mean 14Gy (12-15Gy)	HDR-IORT	20 (3–65)	67	54	NA
DelCarmen [18]	15	Cervix 5 Uterus 3 Other 7	Pelvic Recurrent 14 (93%) Primary 1 (7%)	-	10-22.5 Gy	IOERT	(3–36)	54%	74%	Neuropathy 4 GU 3 Lymphedema 2



Intraoperative radiation therapy
Part 2. Clinical results

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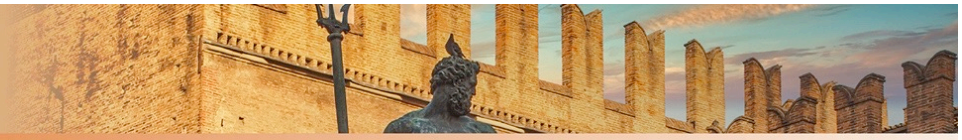
…However,
when available and in the absence of effectiveness of other treatments, a specialist could prescribe IORT where potential benefits could be expected,
as in case of dose escalation studies, notwithstanding a lack of consensus in the literature



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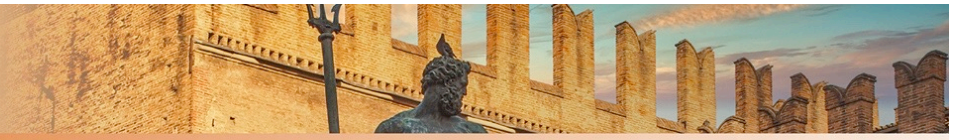

- IORT may improve disease control and survival outcomes if optimal surgical resection is achieved
- IORT is beneficial for its ability to deliver high-dose radiation therapy to the site of recurrence, decreasing risk of radiation to surrounding critical structures
- Our reults in line with the litterature
- Limitations of the Study: retrospective nature, small sample size of patients, no cohort of patients not treated with IORT
- BUT: negative selected patients, treatments in pre-advanced RT-era

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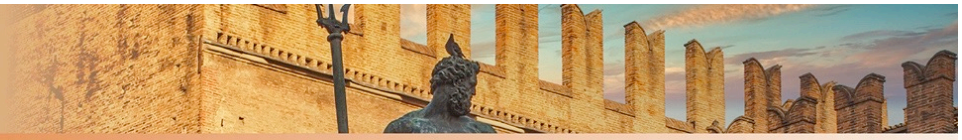

Radioterapia di precisione per un'oncologia innovativa e sostenibile

Associazione Italiana Radioterapia e Oncologia clinica

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BOLOGNA, 25-27 NOVEMBRE
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