PATTERN DI RICADUTA ED INTENSIFICAZIONE DEL TRATTAMENTO NEL CARCINOMA DELLA CERVICE LOCALMENTE AVANZATO

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NOTHING TO DECLARE

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Cervical Cancer

NCCN Guidelines Index
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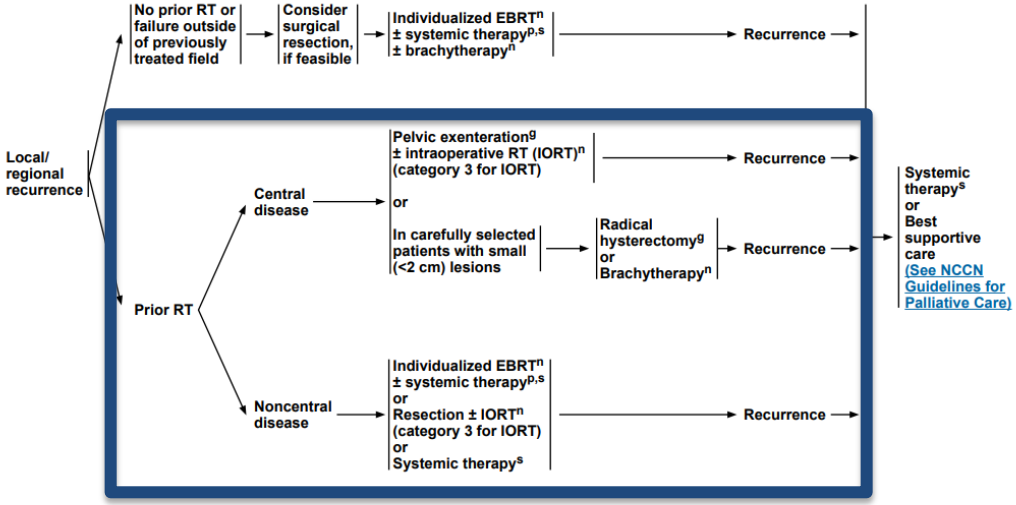
Discussion

THERAPY FOR RELAPSE



[g] See Principles of Evaluation and Surgical Staging (CERV-C).
[n] See Principles of Radiation Therapy (CERV-D).
[p] Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant).
[s] See Systemic Therapy for Cervical Cancer (CERV-F).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

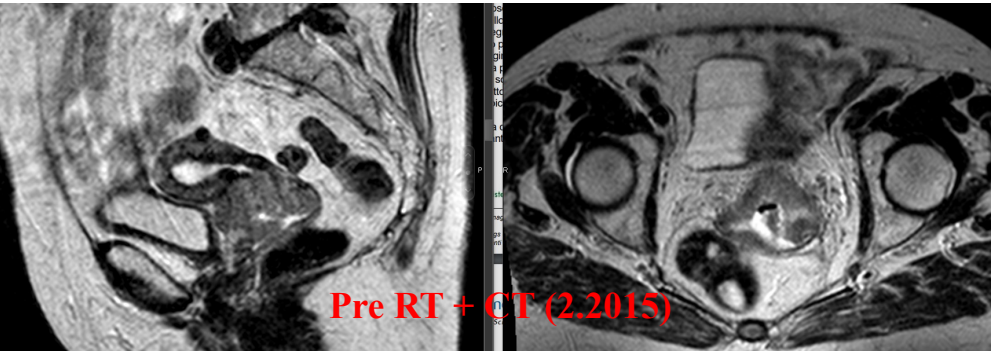
20-40% recurrence within 2 yrs
generally local
consider time from primary treatment
consider if correct doses of RT
consider general PS

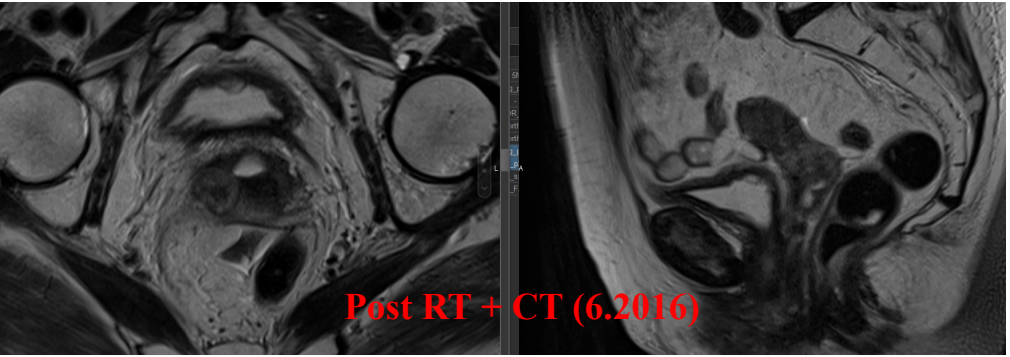
palliative surgery

Site of recurrence	Therapeutic options
Central	Surgery RH or PEx; Heavy Particles BRT
Pelvic lateral wall	Surgery + IORT Chemotherapy Re irradiation: Heavy Particles
Distant	Stereotaxis Chemotherapy

Site of recurrence	Therapeutic options
Central	Surgery RH or PEx Heavy Particles

RADICAL HYSTERECTOMY





SURGERY

ISTERECTOMIA RADICALE (CLASSEC1sec.QUERLEUMORROW)ANNESSIECTOMIA BILATERALE - CITOLOGIA PERITONEALE - POSIZIONAMENTO DI STENT URETERALI BILATERALI.

Small diameter (3-5? cm)
N negative
Negative parametria
No distant mets

Low morbidity – Low mortality

SEVERAL PROGNOSTIC FACTORS SHOULD BE EVALUATED IN PTS WITH RECURRENT CERVICAL CANCER BEFORE CONSIDERING A PELVIC EXENTERATION

1) SIZE OF TUMOR RECURRENCE: lesions > 5 cm diameter have been shown to have almost no chance of remission despite complete removal of the tumor

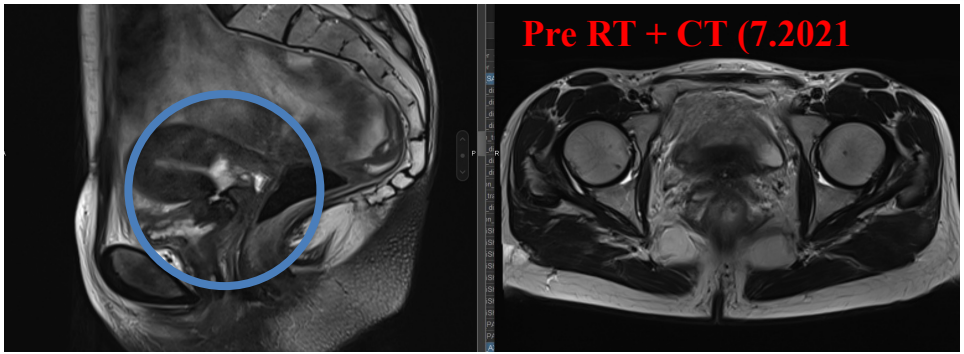
2) LENGTH OF TIME BETWEEN INITIAL TREATMENT AND RECURRENCE:
recurrence <2 yrs, between 2 and 5 yrs and >5 yrs after initial treatment is associated with a 5-year OS of 16.8%, 28.0% and 83.2% respectively

3) HISTOLOGY: squamous cell carcinomas are associated with a significantly worse prognosis than adenocarcinomas.

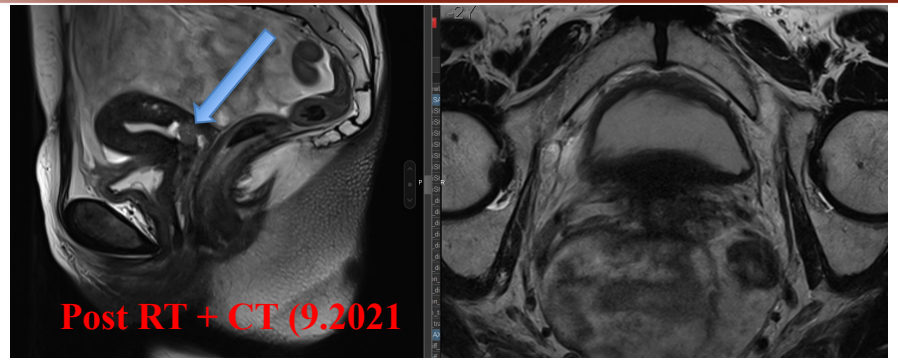
4) PRESENCE OF LYMPH NODE INVOLVEMENT AT INITIAL PRESENTATION: controversial

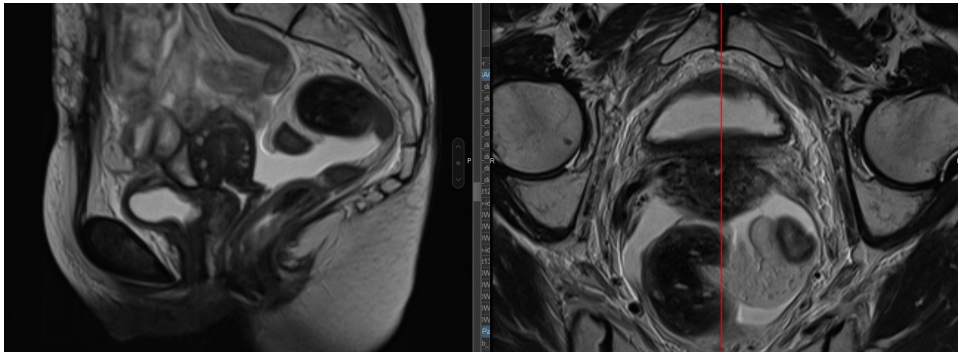
PELVIC EXENTARATION IS ALSO CONTROINDICATED IN CASE OF:

- DISEASE EXTENDED TO THE PELVIC SIDE WALLS
- EXTRAPELVIC SPREAD OF DISEASE



CT carboplatin + taxol VII cicles





Before surgery

SURGERY

EVISCERAZIONE PELVICA ANTERIORE SOVRADIAFRAMMATICA: ISTERECTOMIA RADICALE CON ANNESSIECTOMIA BILATERALE - COLPECTOMIA RADICALE -CISTECTOMIA RADICALE
Indicazione a follow up

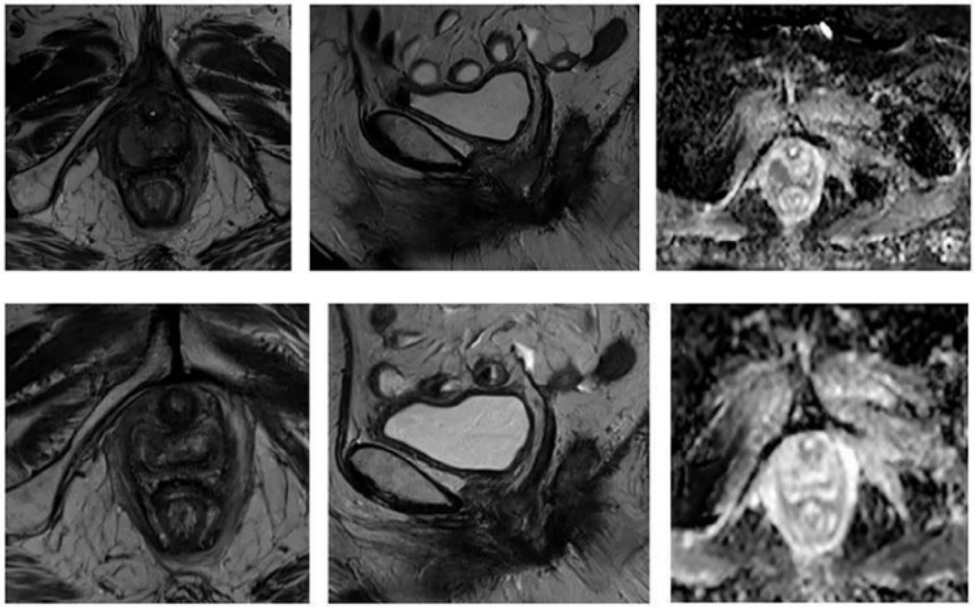
Tumori Journal
Volume 107, Issue 6, December 2021, Pages NP67-NP72

https://doi-org.bibliosan.idm.oclc.org/10.1177/03008916211007930

Case Reports

Is a tailored strategy using proton beam radiotherapy for reirradiation advantageous for elderly women? A case report

Amelia Barcellini [1], Antonino Ditto [2], Alfredo Mirandola [3], Marianna Roccio [4], Sara Imparato [5], Francesco Raspagliesi [2], and Ester Orlandi [1]



HEAVY PARTICLES

PROTONS for re-RT central recurrence (39 GyE/ 11 fx)

Previous X-RT 45 Gy/25 fractions
BT 15 Gy/ 3 fractions

Baseline

CR at 1 year

Thanks to Drssa A. Barcellini

Site of recurrence	Therapeutic options
Pelvic lateral wall	Surgery + IORT Re irradiation: Heavy Particles Chemotherapy

SURGERY + IORT

Radical Extirpation With Intraoperative Radiotherapy for Locally Recurrent Gynecologic Cancer: An Institutional Review

MAYO CLINIC 2021

Ritchie Delara, MD; Jie Yang, MD, PhD; Elena Suárez-Salvador, MD; Sujay Vora, MD; Javier Magriña, MD; Kristina Butler, MD, MS; and Paul Magtibay, MD

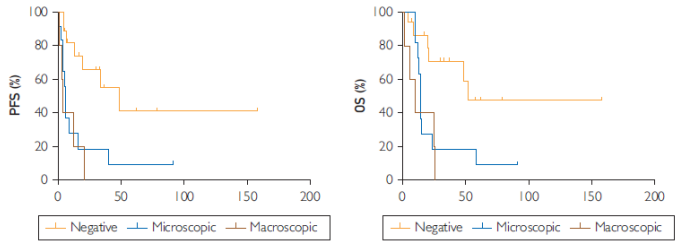
Recurrence		
RT		
Prior EBRT (at initial diagnosis)	50 (35-70)	25 (67.6)
Preoperative RT (prior to extirpation)	45 (19.8-57)	35 (94.6)
Both	95.4 (75.2-110)	23 (62.2)
Site of recurrence or disease progression prior to extirpation		
Central	NA	5 (13.5)
Pelvic wall		16 (43.2)
Lymph node		8 (21.6)
Multisite		8 (21.6)

TABLE 3. Treatments and Disease Status at Recurrence in the Cohort.

Variable	No. (%) of patients (N=7)
Tumor type	
Cervical	3 (42.9)
Ovarian	1 (14.3)
Uterine	1 (14.3)
PUO	2 (28.6)
Type of surgery	
LEER	4 (57.1)
PE	3 (42.9)
Residual tumor	
Negative	7 (100.0)
Microscopic	0 (0.0)
Macroscopic	0 (0.0)
Site of recurrence or disease progression after IORT	
Central	0 (0.0)
Locoregional	0 (0.0)
Distant	4 (57.1)

IORT, intraoperative radiotherapy; LEER, laterally extended endopelvic resection; PE, pelvic exenteration; PUO (pelvic of unknown origin).

Calvo FA, Sole CV, Lozano MA, et al. Gynecol Oncol. **2013**;130(3):537-544.
Garton GR, Gunderson LL, Webb MJ, Wilson TO, Cha SS, Podratz KC. Int JRadiat Oncol Biol Phys. **1997**
Del Carmen MG, Eisner B, Willet CG, Fuller AF. Surg Oncol Clin N Am. **2003**
Garton GR, Gunderson LL, Webb MJ, et al. Gynecol Oncol. **1993**



		Median PFS	3-year PFS (%)	*P*	Median OS	3-year OS (%)	*P*
No IORT	Negative	26	54.8	.69	61	70.8	.88
IORT	Negative	48	51.8	.006	52	62.9	.035
	Microscopic	6	20.5		14	20.0	
	Macroscopic	4	0		10	0	

FIGURE. Kaplan-Meier survival curves. A, Progression-free survival (PFS) of patients with negative, microscopic, or macroscopic residual tumor in the intraoperative radiotherapy (IORT) cohort. B, Overall survival (OS) of patients with negative, microscopic, or macroscopic residual tumor in the IORT cohort. C, Progression-free survival of patients with negative residual tumor with or without IORT. D, Overall survival of patients with negative residual tumor with or without IORT.

HEAVY PARTICLES

CYCLOPS Carbon ions

Study Design	Monocentric, prospective phase II study
Study Population	Patients affected by pelvic recurrence of gynecological neoplasia, already undergone to radiotherapy on pelvis, will be enrolled in the study.
Treatment	PTV will receive a total dose of 48-52.8 GyRBE in 12 fractions, 4 fractions per week. Treatment expected duration is 3 weeks, 4 fractions per week.
Statistical Considerations	Fleming one stage design
Aims	Primary endpoint: 1-year local control (LC) Secondary endpoints: • Overall survival (OS) • Toxicity according to Common Terminology Criteria for Adverse Events (CTCAE version 5.0) • Symptoms control, evaluating pain reduction (screened by NRS scale) and variation in the use of analgesic drugs (decrease or increase) • Subgroup success rate analysis with stratification according to: Histology (adenocarcinoma vs squamo-cellular)
Sample size	55 subjects

Thanks to Drssa A. Barcellini

Carbon ions

Inclusion Criteria

- Patients ≥ 18 years of age
- Karnofsky Index ≥ 70
- **Histological or radiological diagnosis** of pelvic recurrence
- **Contraindications for radical surgery**
- No other distant progression or stable disease (SD) of known secondarisms (≥6 months)
- Previous radiation therapy on pelvis
- Distance ≥ 10 mm between tumour and close intestinal tract (small intestine), radiologically evaluated
- **Possibility to perform a surgery to space the intestinal loops, in case of distance < 10mm**
- If needed, **spacer** in biocompatible material (silicon, goretex) or anatomical material (omentum, muscle patch), **non-absorbable.**
- DICOM images of the previous treatment plan availability

Exclusion criteria

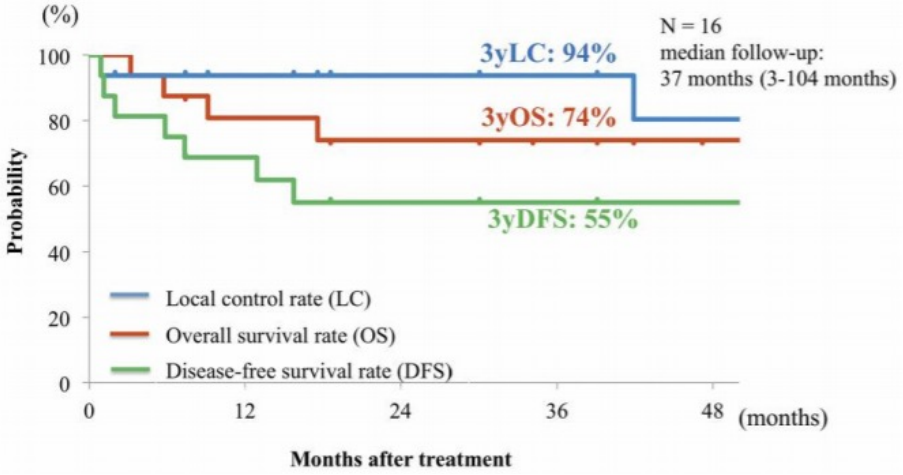
- prosthesis, metal prostheses or any other condition that prevents adequate imaging to identify the target volume and calculate the dose in the treatment plan
- **Intestinal infiltration**
- **Bladder infiltration**
- **Vessel infiltration**
- Previous therapy with **anti-angiogenesis drugs**
- Psychic or other disorders that may prevent informed consent
- Previous invasive tumor, with the exception of skin cancer (excluding melanoma) unless disease-free for at least 3 years
- **Spacer in absorbable material (i.e. vycril)**
- Distance < 10 mm between tumour and close intestinal tract (small intestine), radiologically evaluated
- Impossibility to assess MRI

Thanks to Drssa A. Barcellini

Carbon ions

Clinical Impact of Re-irradiation with Carbon-ion Radiotherapy for Lymph Node Recurrence of Gynecological Cancers

SHINTARO SHIBA[1,2], NORIYUKI OKONOGI[1], SHINGO KATO[3], MASARU WAKATSUKI[1,4], DAIJIRO KOBAYASHI[2,5], HIROKI KIYOHARA[6], TATSUYA OHNO[2], KUMIKO KARASAWA[7], TAKASHI NAKANO[2] and TADASHI KAMADA[1]



- Retrospective series of **16 cases**
- **Unresectable** recurrence at the edge of the previously irradiated field
- Median age 57 years (range=35-79 years)
- Median **tumor size was 27 mm** (range=14-80 mm)
- Total dose range: **48-57.6 GyE**

Organs involved	G0	G1	G2	G3	G4
Gastrointestinal tract	14	2	0	0	0
Urinary tract	15	1	0	0	0
Leg edema	15	0	1	0	0
Lower extremity nerve	14	2	0	0	0

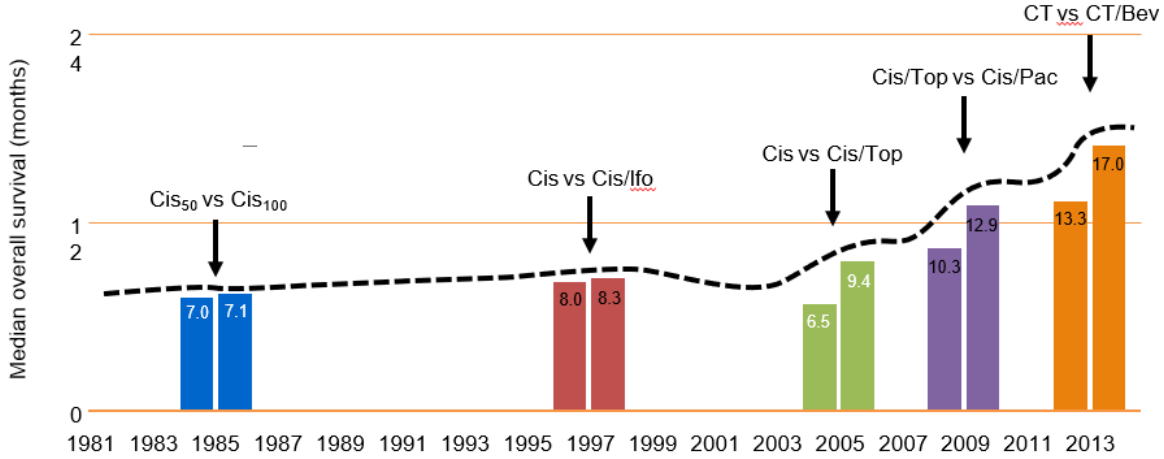
RTOG/EORTC, Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer.

Thanks to Drssa A. Barcellini

CHEMOTHERAPY

Progress in current treatment approaches for advanced cervical cancer made by GOG-0240

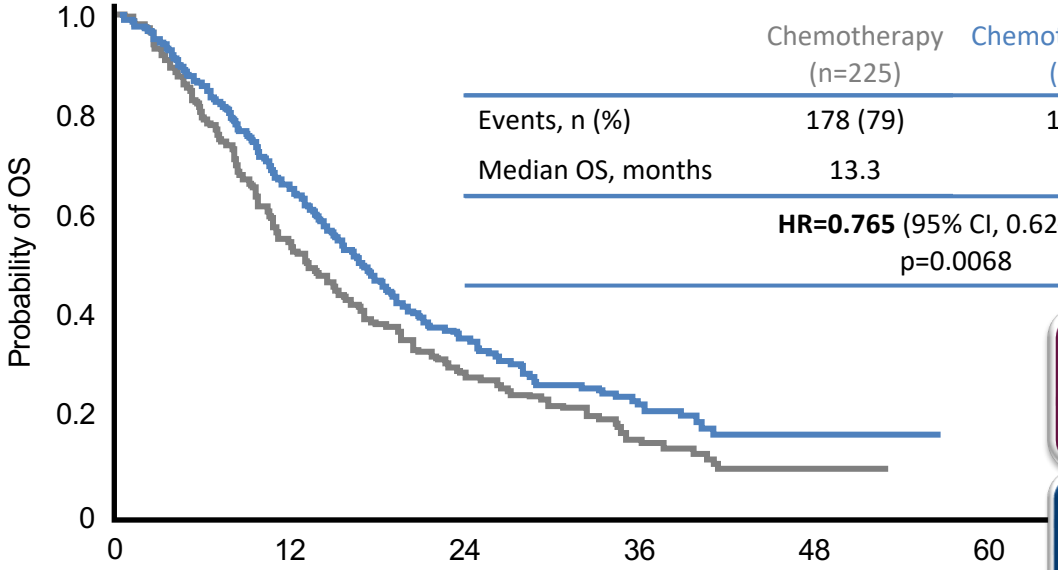
Phase III studies of chemotherapy in advanced cervical cancer



Thanks to Prof.ssa N Colombo

GOG-0240: final OS analysis
Addition of Bevacizumab to chemotherapy

At data cut-off of 7 March 2014, updated OS analysis demonstrated the sustained clinically meaningful survival benefit of bevacizumab-based therapy (maximum follow-up 50 months)



	Chemotherapy (n=225)	Chemotherapy + Bev (n=227)
Events, n (%)	178 (79)	170 (75)
Median OS, months	13.3	16.8

HR=0.765 (95% CI, 0.62–0.95)
p=0.0068

Regulatory approvals
FDA (August 2014)
EMA (April 2015)

Treatment guidelines
Category 1 recommendation in NCCN 2015 guidelines[2]

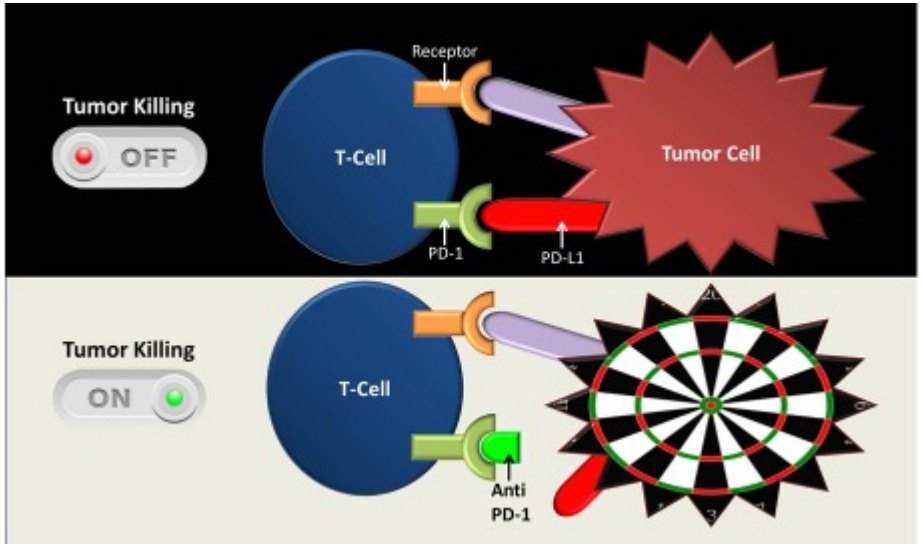
- CI, confidence interval; HR, hazard ratio; OS, overall survival

Lancet. 2017 Oct 7;390(10103):1654-1663.

Immunotherapy: The Next Frontier

Rationale: Anti-programmed death (PD)-1 therapy for cervical cancer

- Human papillomavirus (HPV) infection is the cause of more than 90% of cervical cancers
- HPV+ Tumor Microenvironment is enriched for PD-1+ CD8+ T Cells
- PD-L1 is significantly up-regulated in cervical cancer and detectable by immunohistochemistry in tumor cells:
  - **Squamous Cervical cancer between 54%- 80**% according to different series
  - **Adenocarcinoma: 14%**
- PD-L1 expression reduces the immune response since it is able to bind to PD1 on T lymphocytes, thereby inhibiting their function.
- These findings suggest **that targeting the PD-1/PD-L1 pathway may be therapeutically effective and should be considered in the treatment of cervical cancer patients**.



Liu C, et al. *Mol Med Rep* 2017;15:1063–1070; Mezache L, et al. *Mod Pathol* 2015;28:1594–1602; Heeren AM et al. *Mod Pathol.* 2016;29:753–763.

Single-agent anti PD-(L)1 activity, 2L+

Agent	N	ORR (95% CI)	ORR PD-L1+ (95% CI)	ORR PD-L1- (95% CI)
Pembrolizumab[1]	98	14.3% (8.0-22.8)	17.1% (9.7-27.0)	0% (0-21.8)
Cemiplimab[2]	304	16.4% (12.5-21.1)	18.3% (10.6-28.4)	11.4% (3.8-24.6)
Balstilimab[3]	140	15% (10.0-21.8)	20.0% (12.9-29.7)	7.9% (NR)

1. Chung et al. JCO2019, Virtual SGO 2021; 2. Tewari KS et al. NEJM 2022; 3. O'Malley DM, et al. Gynecol Oncol. 2021 Aug 24:S0090-8258(21)01316-0.

EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 Study Design* (NCT03257267)

Recurrent and metastatic cervical cancer **resistant to platinum-based chemotherapy ≥2nd line**
ECOG PS ≤1

N=604: 477 SCC, 131 AC
Randomized 1:1
Stratified by:
- Histology (SCC/AC)
- Geographic region
- Prior bevacizumab (Y/N)
- ECOG PS (0 vs 1)

Cemiplimab 350 mg Q3W IV

IC chemotherapy

Options:
- Pemetrexed 500 mg/m^2 Q3W IV
- Gemcitabine 1000 mg/m^2 IV on Days 1 and 8 and every 21 days
- Topotecan 1 mg/m^2 daily IV for 5 days, every 21 days
- Irinotecan 100 mg/m2 IV weekly x 4, followed by 10–14 days rest
- Vinorelbine 30 mg/m2 IV on Days 1 and 8 and every 21 days

Treat up to 96 weeks with option for re-treatment

Tumour imaging conducted on Day 42 (±7 days) of cycles† 1–4, 6, 8, 10, 12, 14, and 16

Primary endpoint: OS

Secondary endpoints:
PFS, ORR, Safety, QoL

Exploratory endpoints:
PK, Immunogenicity, Biomarkers, PD

- Two interim analyses were prespecified per protocol
- At first interim analysis, IDMC recommended trial to continue
- **At second interim analysis, IDMC recommended trial be stopped for efficacy; presented here**

- Patients were enrolled regardless of PD-L1 expression

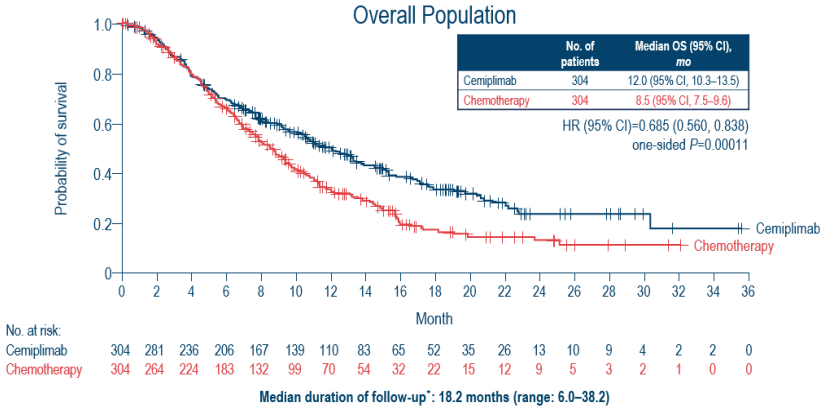
*Performed according to ENGOT Model C.[1] †To account for differences in drug administration schedules, one cycle is defined as 6 weeks.

AC, adenocarcinoma or adenosquamous carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, investigator's choice; IDMC, Independent Data Monitoring Committee; IV, intravenously; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; QoL, quality of life; SCC, squamous cell carcinoma.

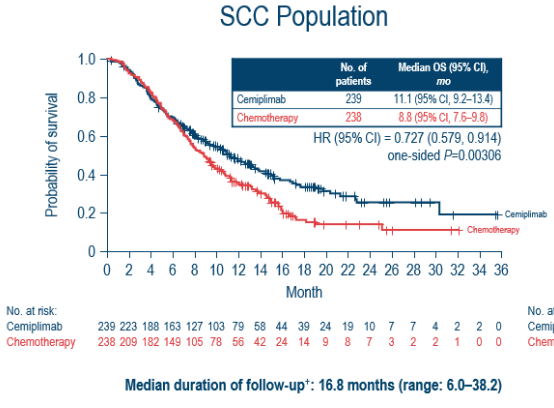
1. Vergote I et al. *Int J Gynecol Cancer.* 2019;0:1–4.

Krishnansu S Tewari et al. NEJM 2022

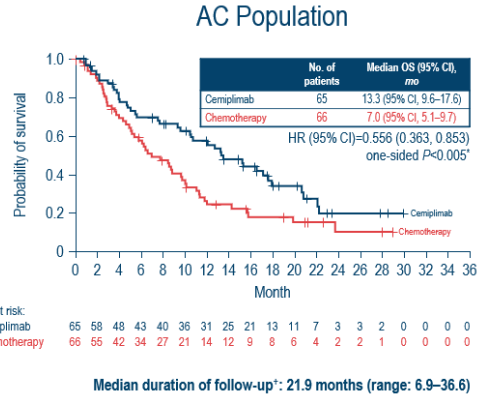
Overall survival



Median duration of follow-up*: 18.2 months (range: 6.0–38.2)



Median duration of follow-up*: 16.8 months (range: 6.0–38.2)



Median duration of follow-up*: 21.9 months (range: 6.9–36.6)

- PD1 inhibitors as monotherapy have modest activity.
- **Combination therapies** will likely be required to enhance and broaden the anti-tumor activity of immune checkpoint inhibition in cervical cancer

KEYNOTE-826: Randomized, Double-Blind, Phase 3 Study

Key Eligibility Criteria

- Persistent, recurrent, or metastatic cervical cancer not amenable to curative treatment
- No prior systemic chemotherapy (prior radiotherapy and chemoradiotherapy permitted)
- ECOG PS 0 or 1

Stratification Factors

- Metastatic disease at diagnosis (yes vs no)
- PD-L1 CPS (<1 vs 1 to <10 vs ≥10)
- Planned bevacizumab use (yes vs no)

R
1:1

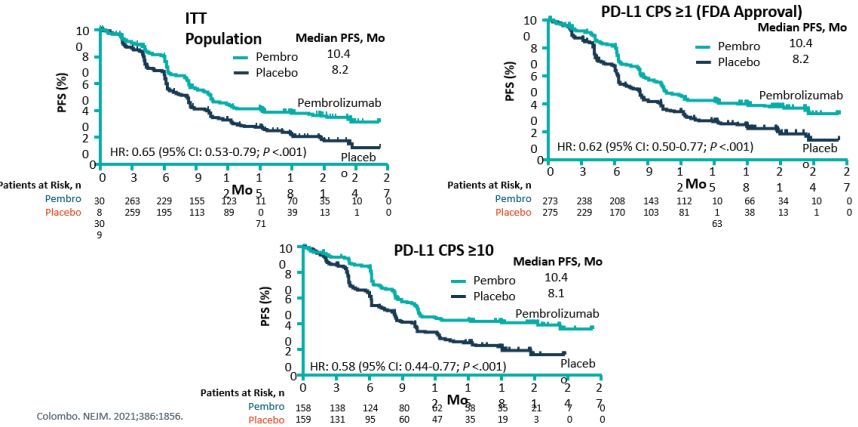
Pembrolizumab 200 mg IV Q3W
for up to 35 cycles
+
Paclitaxel + Cisplatin or Carboplatin IV Q3W
for up to 6 cycles[a]
±
Bevacizumab 15 mg/kg IV Q3W

Placebo IV Q3W
for up to 35 cycles
+
Paclitaxel + Cisplatin or Carboplatin IV Q3W
for up to 6 cycles[a]
±
Bevacizumab 15 mg/kg IV Q3W

End Points

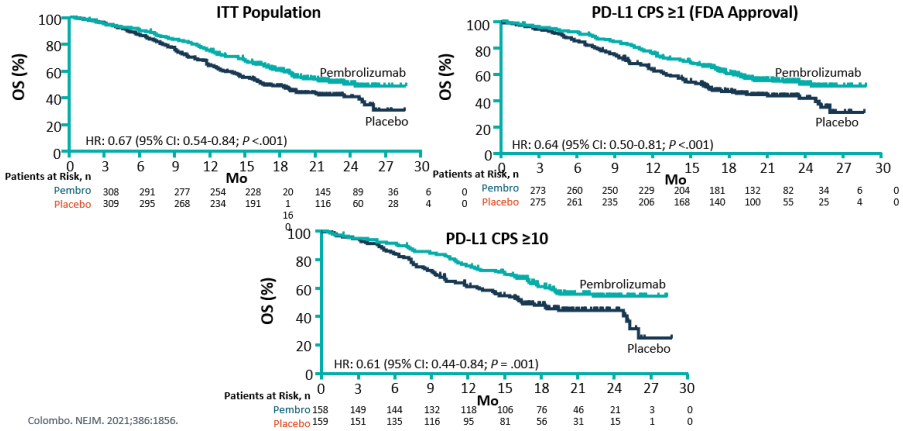
- **Dual primary: OS and PFS per RECIST v1.1 by investigator**
- **Secondary: ORR, DOR, 12-mo PFS, and safety**
- **Exploratory: PROs assessed per EuroQol EQ-5D-5L VAS**

KEYNOTE-826: PFS



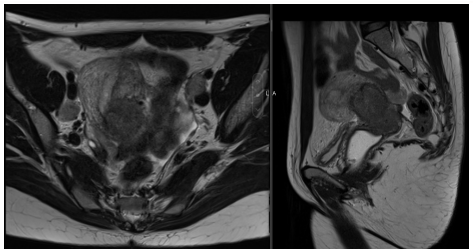
Colombo. NEJM. 2021;386:1856.

KEYNOTE-826: OS

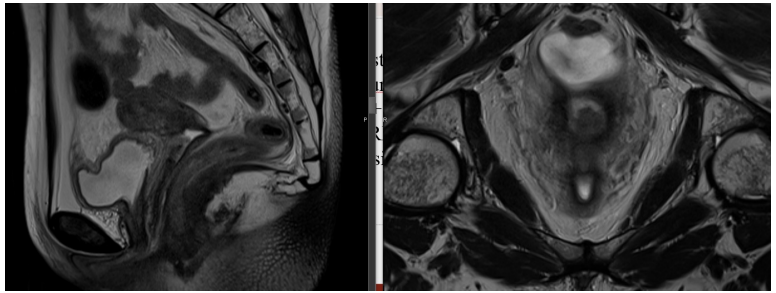


Colombo. NEJM. 2021;386:1856.

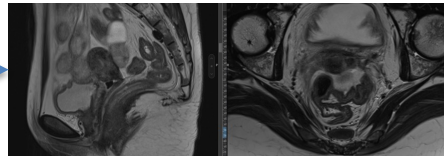
	Locally advanced	Front line metast/recur	II line
Standard	None (chemo-radiation)	Pembro+Chemo+/-bev	Pembrolizumab Cemiplimab Tisotumab Vedotin Bal/Zal (fast Track designation)
Concluded/ Ongoing	**CT/RT+ Durvalumab Pembrolizumab**	**Atezolizumab+chemo+bev Prolgolimab +chemo+/-bev Cadolinimab+chemo+/-Bev**	**Geptanolimab- Zimberelimab Dual Chekpoint blockade Camrelizumab+famitinib Tiragolumab/Atezolizumab Adoptive cell therapy (LN-145)**



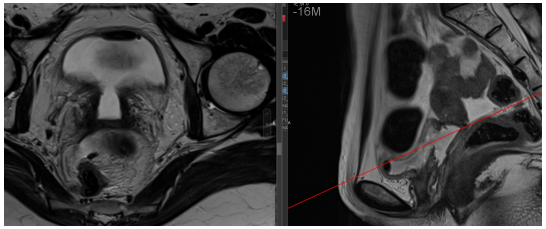
Anni nata 1985
Carcinoma squamoso portio stadio IIIC1 (IIB N+)
Rifiuta protocollo pembrolizumab vs placebo
RTE 45 Gy pelvi, 53.4 Gy N+ SIB; BRT 7 Gyx4 stop 4.2021
8.2021 biopsia: persistenza; RMN e PET +
4 cicli carbo + taxolo + bevacizumab
Persistenza 10x12x7 mm, eco TV e visita negative
Consulto IEO
Ulteriori 3 cicli (stop 1.2022)



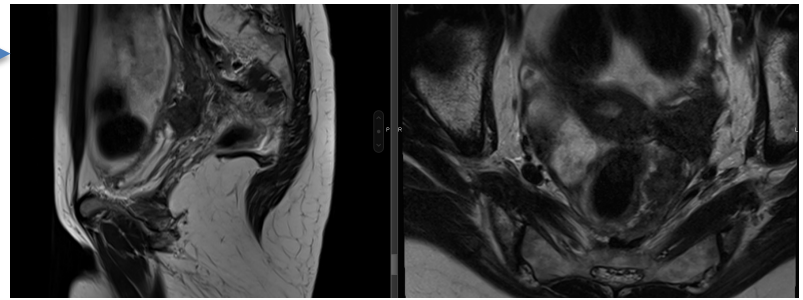
2.2022 RMN esiti, sottile tessuto residuo 4x15 mm



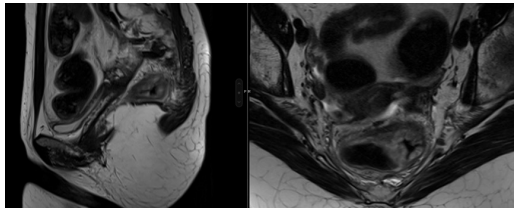
PET negativa
2.2022 visita narcosi e biopsie: atrofia, fibrosi
Prosegue bevacizumab mantenimento
5.2022 fistola vescico vaginale, nefrostomie



Biopsie negative Discussione: sospende beva, eviscerazione anteriore vs. osservazione
7.2022 visita noto tramite fistoloso con ispessimento cervicale (paracolpo) di circa 1 cm di consistenza dura e poco mobile
7.2022 visita in narcosi con biopsie negative per RMN: lungo il margine infero-anteriore della portio, al versante laterale sinistro, persiste riconoscibile tessuto solido sospetto esteso per circa 9x14 mm.
9.2022 SCC= 23
9.2022 PET accumulo a livello di neoformazioni (almeno quattro) rilevabili in sede pre-sacrale e iliaco-otturatoria sinistra, piccole alterazioni non solide polmonari periferiche lievemente ipermetaboliche, reperti in prima ipotesi di significato flogistico
Avvia cemiplimab
12.2022 RMN : tessuto patologico lungo il peritoneo pelvico sin



8 cicli carboplatino + taxolo



Buona risposta
PET dubbia

ISTERECTOMIA RADICALE - ANNESSIECTOMIA BIALTERALE - COLPECTOMIA 2/3 SUPERIORI CON TRAMITE FISTOLOSO VESCICO-VAGINALE - CISTECTOMIA RADICALE - RESEZIONE RETTO-SIGMA E ANATOMOSI T-T BASSA CON CONFEZIONAMENTO DI J POUCH COLICA) - LINFADENECTOMIA PELVICA BILATERALE - RADICALIZZAZIONE PARETE PELVICA DI SINISTRA - CONFEZIONAMENTO DI COLOSTOMIA DERIVATIVA SU COLON DISCENDENTE - ALLESTIMENTO DI URETEROILEOCUTANEOSTOMIA SEC. BRICKER - ANASTOMOSI ILEALE MECCANICA L-L - POSIZIONAMENTO DI J -FLAP OOMENTALE IN SEDE PELVICA

Carcinoma spinocellulare non cheratinizzante (hPV correlato) della cervice, dopo chemio e radioterapia, infiltrante la parete vaginale craniale e del possibile residuo cervicale (dopo pregressa conizzazione) anteriore, la tonaca muscolare vescicale (con risparmio della mucosa vescicale) e il parametrio di sinistra (uretere di sinistra indenne) fino in stretta prossimità del margine di resezione laterale. La neoplasia misura 15 mm di diametro maggiore e presenta invasione perineurale. In vagina è presente anche lesione intraepiteliale squamosa di alto grado (CIN 3), assente nella parte inferiore. Margini di resezione vaginali e sui parametri bilaterali esenti da neoplasia, con tuttavia invasione perineurale in stretta prossimità del margine di resezione sul parametrio di sinistra

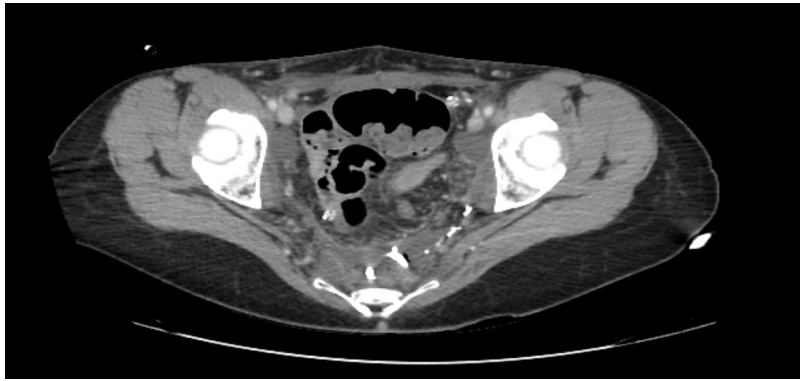
NB dal verbale operatorio: EI estemporaneo sui margini pelvici di sinistra (positivo per malattia microscopica)
Confezionamento di flap omentale infragastro-colico con duplicatura (spessore di circa 1 cm a livello pelvico sinistro sede delle **clips lasciate come repere**) del flap omentale posizionato (mediante punti staccati in vicryl 3/0) a protezione della porzione mediana in prossimità dei monconi vaginale e anastomosi anale. Ancoramento del flap omentale a livello delle pareti pelviche bilaterali.

Complicanze post operatorie:
deiscenza anastomosi retto sigma ultrabassa--→ endosponge
raccolta fluida pre scarale--→ drenaggio poi rimosso

Complicanze post dimissione: comparsa di feci in vagina, rettoscopia documenta piccolo tramite fistoloso 3 mm
10.23 RMN: a circa 2cm dall'orifizio anale esterno si riconosce tramite fistoloso a livello della parte anteriore dell'ano di circa 5mm con la parete posteriore del moncone vaginale residuo (se 31 im17), meritevole di valutazione endoscopica e valutazione in ambito specialistico. Sostanzialmente stabile in dimensioni la raccolta pre-sacrale di circa 5x2,5cm con contenuto disomogeneo come per fenomeni organizzativi e che presenta pareti ispessite e caratterizzate da enhancement non nodulare.

Programma terapeutico:
Terminalizzazione della colostomia
Re irradiazione della parete pelvica postero laterale sinistra
sede di clips chirurgiche.

Simulazione per fotoni e proton terapia



Conclusioni

- La recidiva è sempre challenging ma le armi a disposizione ci sono
- Grande varietà di presentazione clinica:
  recidiva precoce vs tardiva
  locale vs a distanza
- Le pazienti sono spesso pluritrattate: valutare storia e dosi di RT
- Nella scelta terapeutica molto dipende dal team con cui lavori:
  che chirurghi hai?
  che oncologi hai?

Conclusioni

- Le nuove tecnologie ma anche i nuovi farmaci aprono continui nuovi scenari

- Ogni anatomia pelvica è diversa dall'altra per questo merita un approccio personalizzato (ed è per questo che non ci si annoia mai!)

GRAZIE PER L'ATTENZIONE!

TEAM WORK!