The 4th MEMAGO Annual Congress In Associatlon wlth
the 1st Emlrates Gynecologlcal Oncology Conference

Université Saint-Joseph de Beyrouth
Faculté de médecine

HOTEL-DIEU DE FRANCE
Centre Hospitalier de l'Université Saint-Joseph de Beyrouth

Advanced cervical cancer: Management of residual disease after radio- chemotherapy

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Nothing to disclose

Learning objectives

- Describe RD as a prognostic factor
- Identify patients with RD
- Discuss current options to treat patients with RD

Introduction

- Recent progress in the treatment of cancer has not had a major impact on outcomes in advanced forms of cervical cancer.

- Increased emphasis on screening for HPV has led to diagnosis of most cases of the disease at an early, curable stage.

- Prognosis remains grim for women with recurrent or persistent cervical cancer, associated with a 5-year survival rate of only 5-15%.

Introduction

- What is the best modality to diagnose RD and when is the right time?

- What is the best therapeutic tool to manage this subset of patients?

Residual disease as a prognostic factor

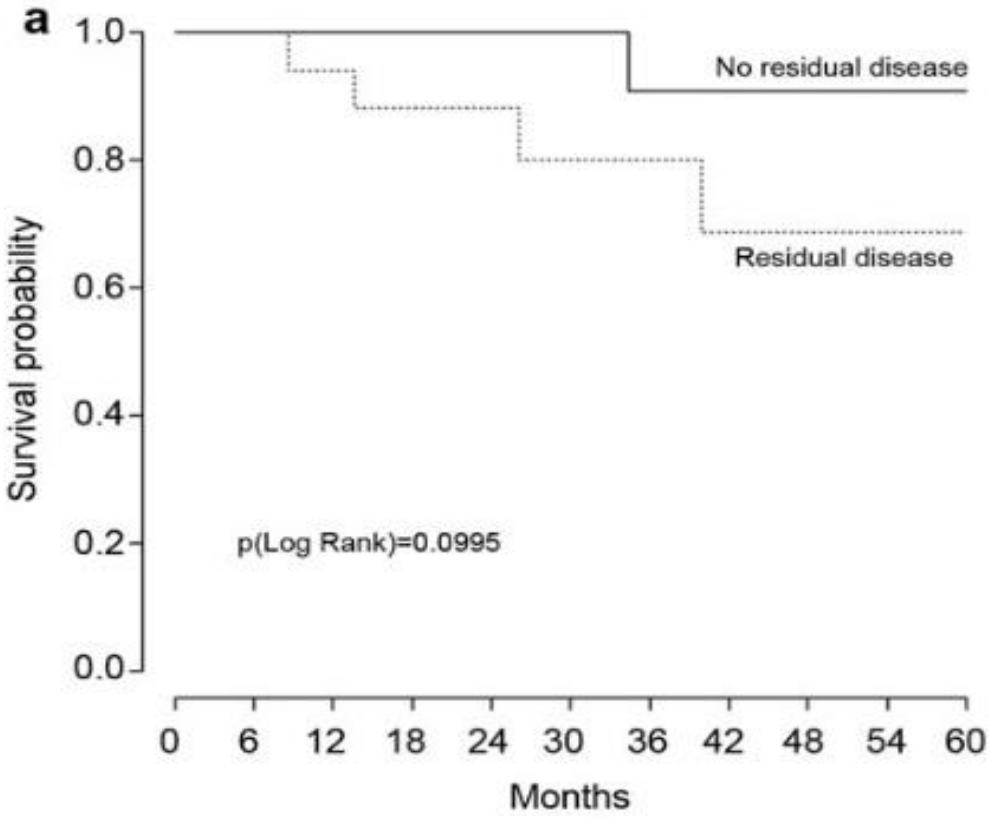


Figure 1. *Overall Survival according to residual disease on hysterectomy*

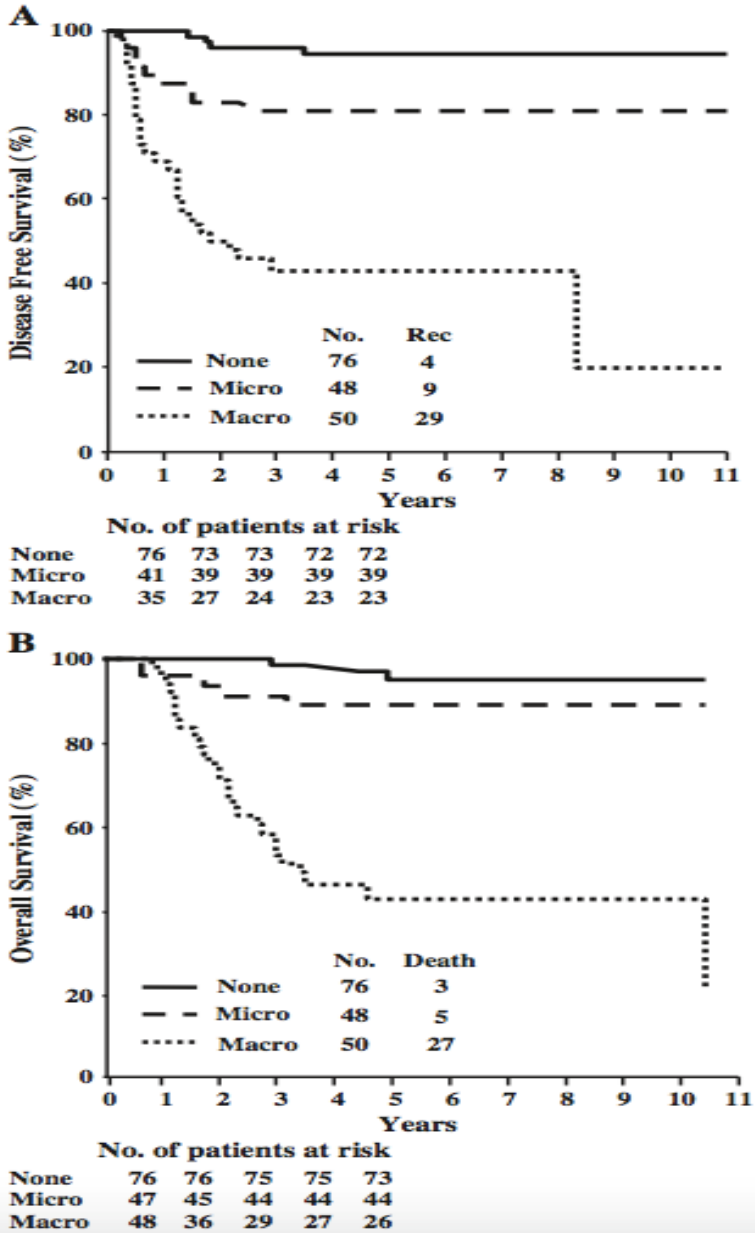
Overall survival seems to be **worse** in cases of residue

Chereau et al. The Role of Completion Surgery After CCRT in LACC Stages IB2-IIB. Anticancer Res. 2013;33(4):1661-6.

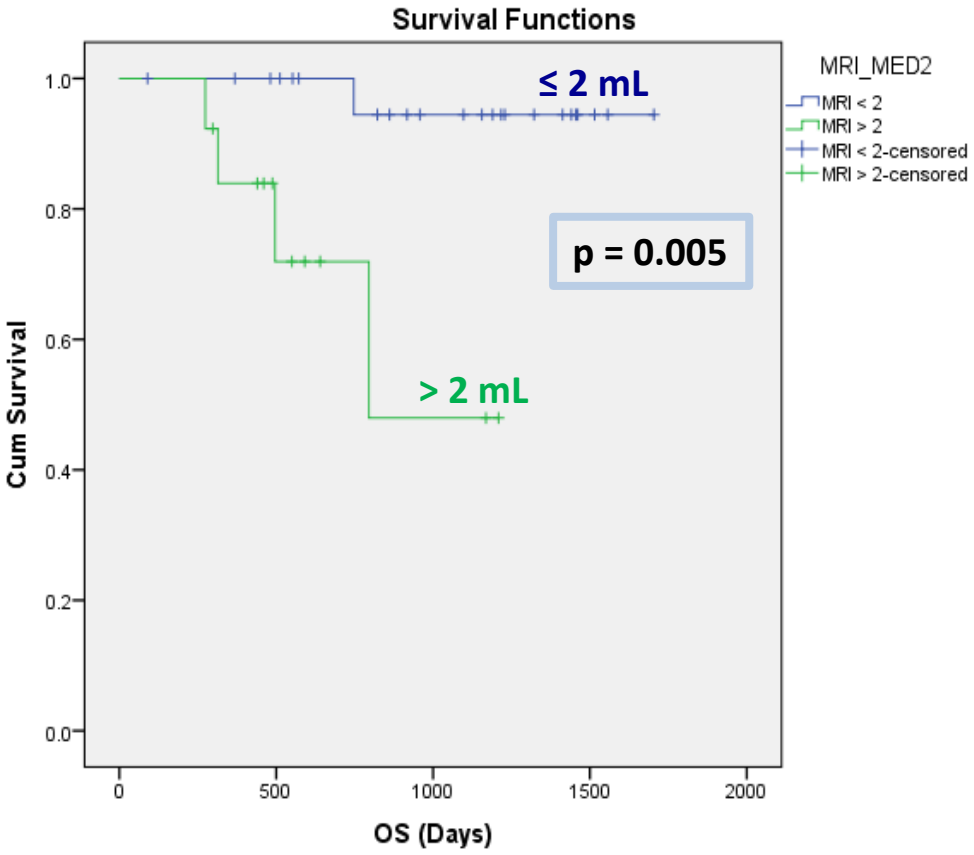
Residual disease as a prognostic factor

- Ferrandina et al. (2010) in their **prospective** study on **184 patients** with LACC demonstrated that:

- **Residual disease** is a relevant **prognostic factor for both DFS and OS** in univariate and multivariate analysis



Residual disease as a prognostic factor



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Pre-Brachy Residue	≤ 2mL	> 2mL
OS	95.8%	69.2%
p	0.005	

El Khoury et al. Pre-brachytherapy MRI-based 3D tumor volume evaluation for outcome prediction in cervical cancer patients treated with CCRT. IGCS 2019

How to evaluate residual disease?

- How can we identify good candidates for completion surgery ?
- Imaging in the assessment of response will usually begin with **MRI**
- Imaging is challenging in the first 6 months after CCRT to decipher **residual disease** from **post-treatment changes**
  - **Necrosis**
  - **Hyperemic changes**
  - **Scarring from active disease**
  - **Edema**
  - **Etc…**

MRI in the diagnosis of residual disease

- According to Hequet, **MRI** had a **poor sensitivity** (77.8%) and **specificity** (41.7%) in detecting residual disease after CCRT, with **high positive rates** (29.1 %)

(Hequet et al. 2013)

Residual disease at MRI (n = 144) and histopathological examination (n = 159).

	n or mean	% OR range
Residual disease at MRI*		
Residual cervical disease, n	98	68.1%
Size of cervical residual disease (mm)	15.2	[0–62]
Parametrial residual disease	27	18.8%
Residual lymphadenomegaly	17	11.8%
Residual disease at histopathological examination		
Residual cervical disease, n		
None	87	54.7%
<2 mm	2	1.3%
2 mm–10 mm	30	18.9%
≥10 mm	40	25.2%
Size of residual cervical disease (mm)	6.2	[0–55]
Lymph node involvement		
Pelvic[a]	11	13.8%
Para-aortic[b]	1	6.7%

45.4%

Hequet et al. Evaluation and impact of residual disease in LACC after CCRT: Results of a multicenter study. Eur J Surg Oncol. 2013 Dec;39(12):1428-3

MRI vs Histopathological Examination

Cervical cancer response to neoadjuvant chemoradiotherapy: MRI assessment compared with surgery

Acta Radiologica
2016, Vol. 57(9) 1123–1131

DOI: 10.1177/0284185115617346
acr.sagepub.com
SAGE

According to Gui (2016), 41 patients

T2W MRI vs. surgery in predicting residual disease post CCRT :

- **Sensitivity = 69 %**
- **Specificity = 71 %**
- Accuracy = 71 %
- Positive predictive value = 15 %
- **Negative predictive value = 96 %**

→ Tendency toward overestimation of residual mass with risk of FP results

→ Role of conventional MRI **+ functional techniques** should be evaluated

Gui et al. Cervical cancer response to neoadjuvant chemoradiotherapy: MRI assessment compared with surgery. Acta Radiol. 2016;57(9):1123-31.

Added value of DWI-MRI in detection of cervical cancer recurrence?

Table 2. Performance of each MRI technique separately and in combination

	T2W	DCE	T2W/DCE	T2W/DWI
n	38	35	35	38
TP/correctly identified	28 (73.7)	28 (80)	28 (80)	33 (86.8)
FP/incorrectly identified	2 (5.3)	2 (5.7)	2 (5.7)	0 (0)
TN/correctly rejected	0 (0)	0 (0)	0 (0)	2 (5.3)
FN/incorrectly rejected	8 (21.0)	5 (14.3)	5 (14.3)	3 (7.9)
Unable to perform	0	3	3	0
PPV, TP/(TP+FP)	93.3	93.3	93.3	100
Sensitivity, TP/(TP+FN)	77.8	84.8	84.8	91.7
Accuracy, (TP+TN)/total	73.6	80	80	92.1
P (comparison with T2W)	-	1.000	1.000	0.016

Data are presented as n (%).
T2W, T2-weighed; DCE, dynamic contrast-enhanced; DWI, diffusion-weighted imaging; n, number of patients; TP, true positive; FP, false positive; TN, true negative; FN, false negative; PPV, positive predictive value.

- 38 patients > 6 mths after CCRT
- MRI vs. Histology

→ Addition of DWI to T2W considerably improved the diagnostic ability of MRI

Lucas et al. Added value of diffusion-weighted MRI in detection of cervical cancer recurrence. Diagn Interv Radiol.2015;21(5):368-75.

Pet-CT in the diagnosis of residual disease

- Avoid surgery when negative?

- LACC treated with CCRT , BT and hysterectomy. Pet-CT 5 wks after BT

- In more than 50% of patients in which control FDG-PET did not show any lesion, there were positive histological findings (NPV = 52%). **The FN rate is too high!**

- It's more an important diagnostic test for residual lymph node involvement evaluation

Motton et al. 18 FDG PET and LACC. Int J Gynecol Cancer. 2009;19(1):8-12.

Pet-CT in the diagnosis of residual disease

INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER

The role of positron emission tomography in the selection of patients for salvage hysterectomy following chemoradiotherapy for locally advanced cervical cancer

Chrishanthi Rajasooriyar,[1,2] Ming-Yin Lin,[1] Rashi Kalra,[1,3] Andrew Lim,[1] Kailash Narayan[1]

- 612 patients evaluated after CCRT
- 49 candidates for salvage hysterectomy based on:
  - Clinical suspicion of RD
  - Suspicious FDG uptake on primary site
  - Biopsy
- 33% had disease on hysterectomy specimen
- 33% had grade 3-4 toxicity
- 23% died from pelvic, extra pelvic nodal and distant failure
- 13% long-term survivors

→ High rate of false positive on Pet 3-6 mths

→ 1st Pet should be done at 6 mths after the completion of RT

→ Confirmatory Pet after 3 mths if uptake on primary site

Rajasooriar et al. The role of Pet-CT in the selection of patients for salvage hysterectomy following CRT for LACC. **Int J Gynecol Cancer 2019;29:266–271.**

Gynecological Exam and Biopsy

Gynecological exam under anesthesia **8 to 10 wks** after CRT + cervical biopsies

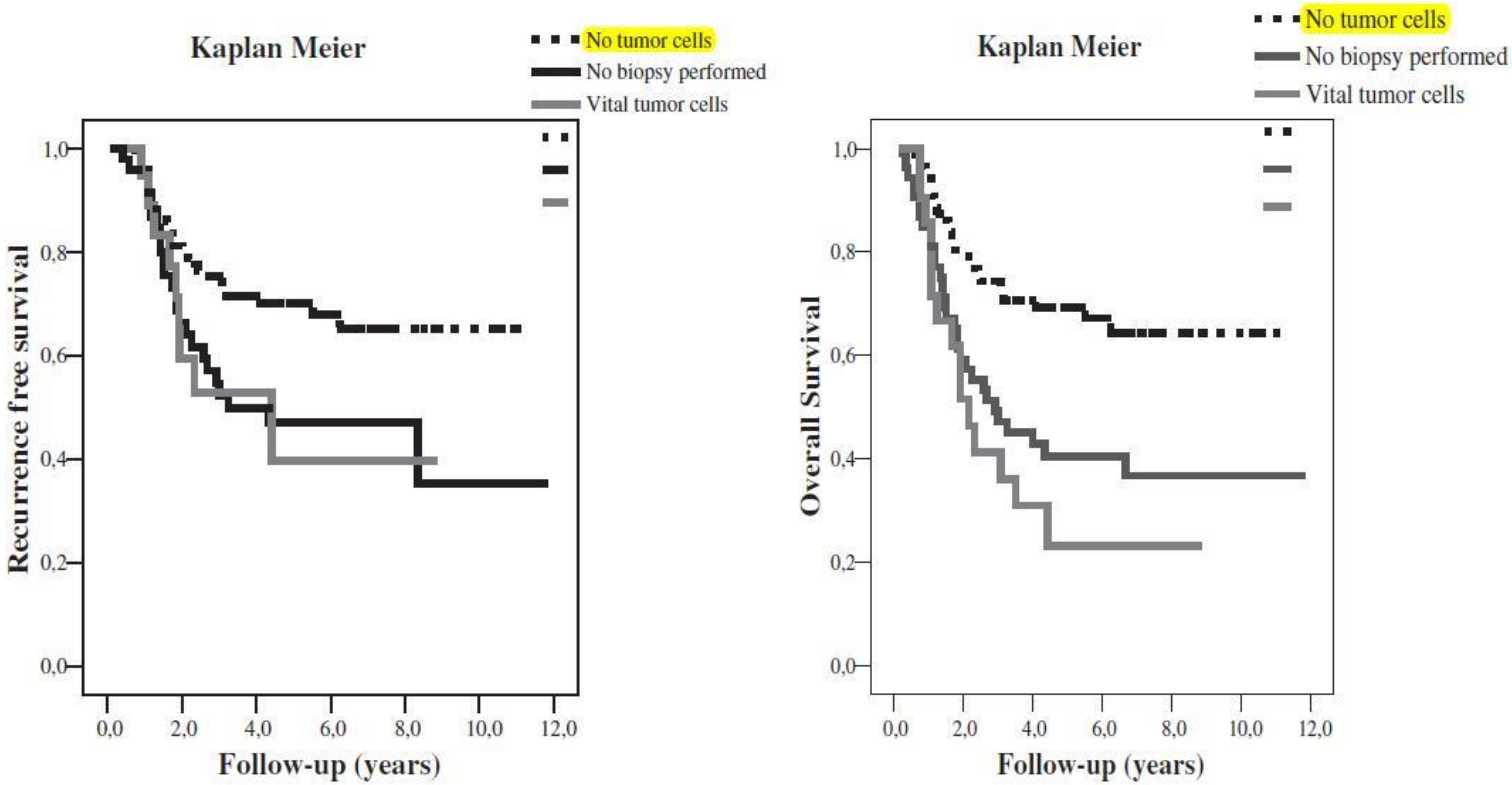


Fig. 1. Kaplan-Meier survival curves in 165 patients treated primarily with (chemo) radiation for cervical cancer show a significant benefit for recurrence-free and overall survival for patients with no vital tumor cells in their biopsy samples compared with patients with vital tumor cells or patients in whom no biopsies were performed. (a) Recurrence-free survival: log-rank test, 6.86, $p = 0.0324$. (b) Overall survival: log–rank test, 17.46, $p = 0.0002$.

Nijhuis et al. Gynecologic examination and cervical biopsies after CRT for cervical cancer to identify patients eligible for salvage surgery. Int J Radiat Oncol Biol Phys. 2006;66(3):699-705.

Performing **completion surgery after CCRT** remains the only method to obtain the most important prognostic information, i.e. **the real pathologically assessed extent of residual disease after treatment** …

To operate or No ?!!

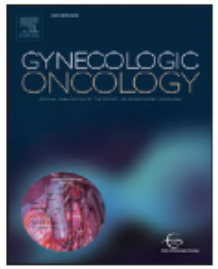
Observation?

Gynecologic Oncology 144 (2017) 34–39

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno



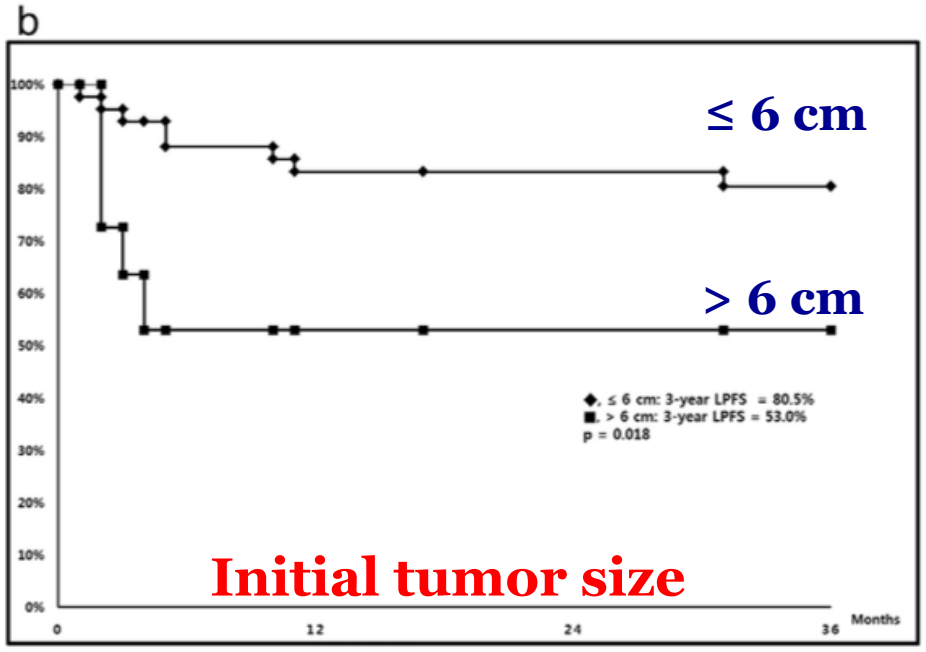
53/545 patients with residual cervical disease based on post-treatment MRI

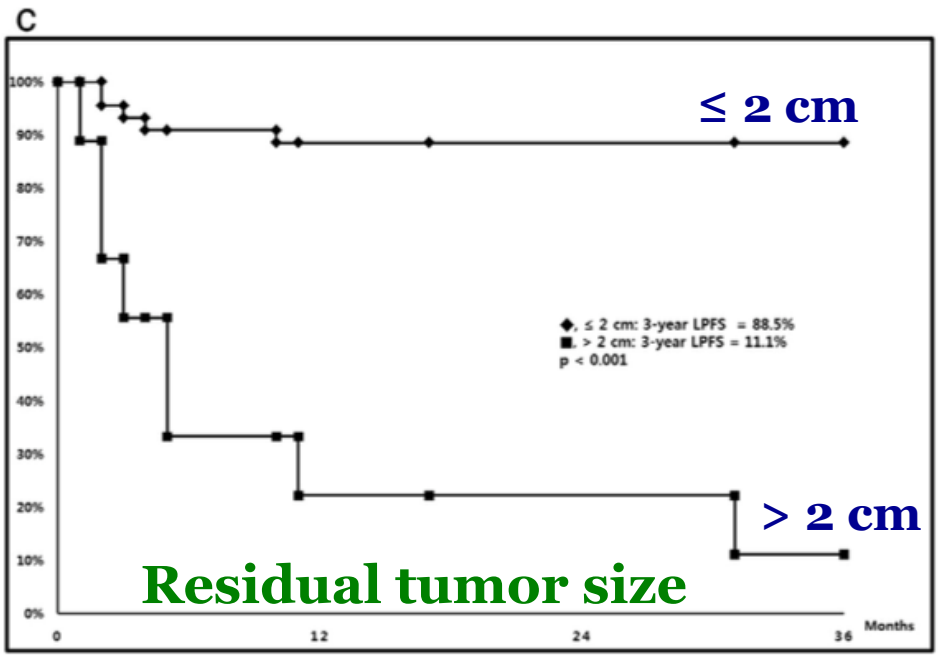
- 32 patients were disease-free at the last follow-up
- Of them, 31 had a **residual tumor size of ≤2 cm**
- 30 showed **spontaneous regression** of residual tumor during follow-up **without salvage treatments**
- the remaining two were alive with no evidence of disease after salvage surgery and chemotherapy

Kim et al. Disease courses in patients with residual tumor following CCRT for LACC. Gynecol Oncol.2017;144(1):34-39.

Observation?

- Local progression-free survival according to **initial** and **residual tumor size**

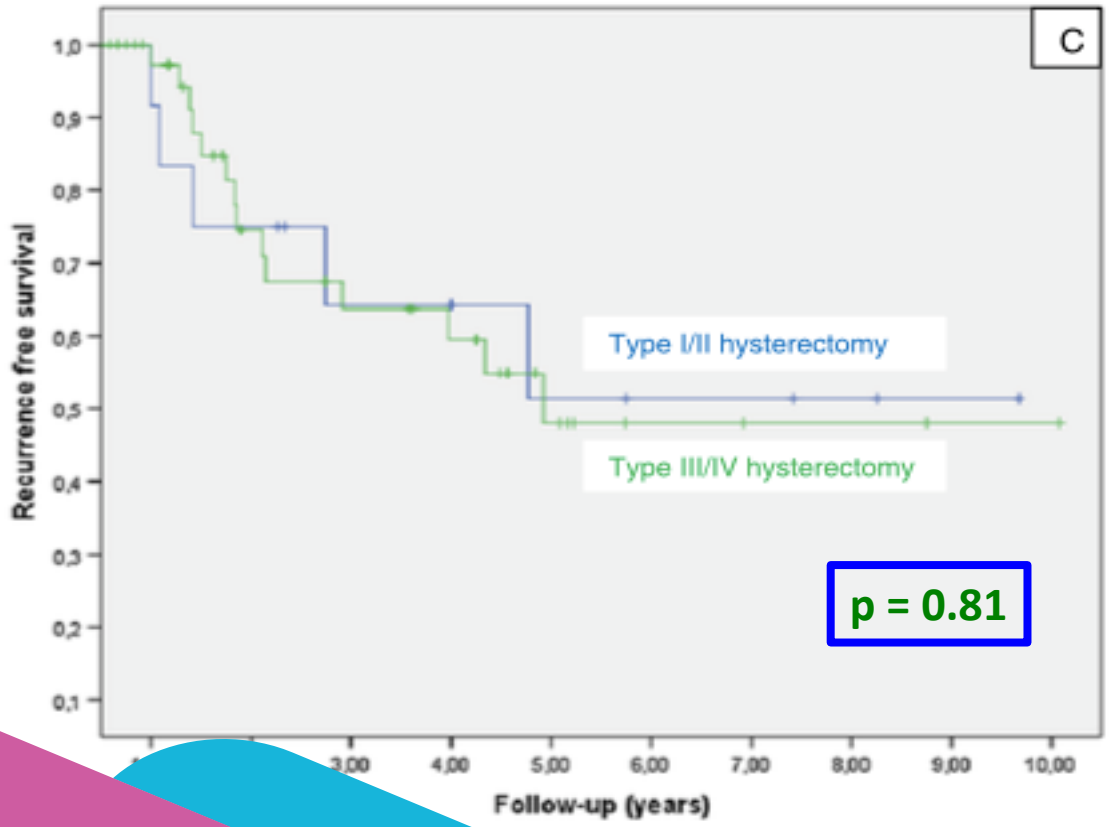




Kim et al. Disease courses in patients with residual tumor following CCRT for LACC. Gynecol Oncol.2017;144(1):34-39.

Completion Surgery or Not? More is better?

- Gynecologic examination with biopsies 8 to 10 weeks after treatment
- Surgery was performed for central residual disease



- More radical surgery was **not** associated with improved disease-specific survival

Boers et al. Radical Surgery in Patients With Residual Disease After CRT for Cervical Cancer. Int J Gynecol Cancer. 2014;24(7):1276-85.

What about incomplete responders >1cm?

Cancer/Radiothérapie 19 (2015) 710–717

ELSEVIER MASSON

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Original article

What to expect from immediate salvage hysterectomy following concomitant chemoradiation and image-guided adaptive brachytherapy in locally advanced cervical cancer

CrossMark

- Immediate salvage hysterectomy in **incomplete responders (≥1 cm)** provided a **4-year disease-free survival of 51%**, its impact on late morbidity is significant

- **Overall treatment time** (> 55 days) and **histological subtype** (adenocarcinomas or adenosquamous carcinomas) significant predictive factors for macroscopic remnant after treatment completion (p=0.021 and p=0.017, respectively)

Castelnaud et al. What to expect from immediate salvage hysterectomy following CCRT and iIGBT in lLACC. Cancer Radiother. 2015;19(8):710-7

What about bulky residual disease?

ELSEVIER

Available online at www.sciencedirect.com
ScienceDirect

EJSO 33 (2007) 498–503

EJSO
the Journal of Cancer Surgery
www.ejso.com

Contribution of surgery in patients with bulky residual disease after chemoradiation for advanced cervical carcinoma

30 patients: surgery after CCRT for LACC with residual disease **≥2 cm**

- Adjuvant surgery to CCRT could improve the **local control, the disease-free survival and even the overall survival** in case of **residual disease ≥ 2 cm**

- 5-year OS of 55.6% after curative intervention

Houvenaeghel et al. Contribution of surgery in patients with bulky residual disease after CRT for LACC. Eur J Surg Oncol. 2007;33(4):498-503

Chemotherapy

- Disease recurring after CRT
- Patients are not surgical candidates
- Disease-free interval of more than 16 months
  - tumor is platinum-sensitive: The standard of care in these cases is chemotherapy with a platinum-based doublet of paclitaxel and cisplatin
- Treatment with bevacizumab + cisplatin and paclitaxel or topotecan and paclitaxel was approved by the FDA in August 2014 for persistent, recurrent, or metastatic cervical cancer GOG-240 trial

Tewari et al. Improved survival with Bevacizumab in advanced cervical cancer. N Engl J Med. 2014;370:734-743.

Immunotherapy

- June 2018: FDA approval of Pembrolizumab for treatment of recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS 1 or greater)

- Safety and Efficacy of Nivolumab Monotherapy in Recurrent or Metastatic Cervical, Vaginal, or Vulvar Carcinoma: Phase I/II CheckMate 358 Trial.

HPV-Targeted drugs

- AXAL (axalimogene filolisbac) = (HPV)-targeting immunotherapy
- Highest-ever 12-month survival of 38% in patients with recurrent, metastatic cervical cancer
- Of 50 evaluable patients, 19 survived to 12 months, translating into a 12-month overall survival (OS) of 38% for treatment with (AXAL). None of more than 20 Gynecologic Oncology Group (GOG) trials conducted since 1995 produced a 12-month survival exceeding 30% for patients with advanced cervical cancer.

Shim et al. Risk assessment model for OS in patients with LACC treated with definitive CCRT. Gynecol Oncol. 2013;128(1):54-59.

HPV-Targeted drugs

- FDA placed a partial hold on Axal due to unexplained patient death.

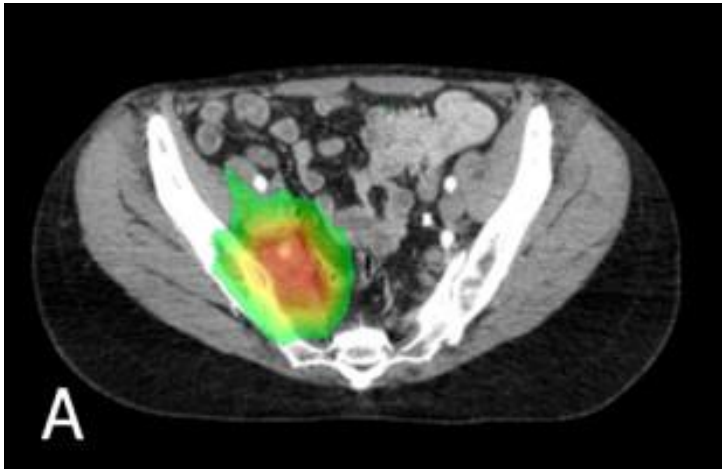
- Treatment-related adverse events: fatigue (52%), chills (52%), anemia (48%), nausea (32%), and fever (30%).

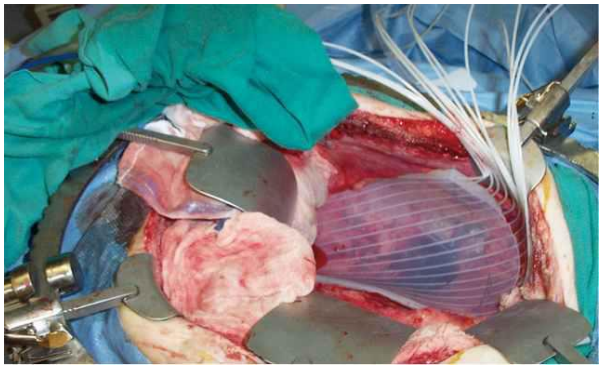
Reirradiation

- Not feasible -> Risk of complications!

- Nowadays: Recent advances in radiotherapy

  - SBRT
  - IORT
  - IGBT





Llewelyn et al. Re-irradiation of cervical and endometrial cancer. Curr Opin Oncol. 2017;29:343-350.

Take Home Messages

- No study in the literature gives a clear answer to the completion surgery after CCRT in LACC
- **Residual disease** is a relevant **prognostic factor for both DFS and OS**
- Residual disease after CRT is not effectively detected by MRI
- Completion surgery after CCRT remains the **only method** to enable a **pathologic evaluation of residual tumor tissue**
- While benefit in terms of survival is always controversial, **completion surgery aids the local control of the disease and decrease recurrences**

Take Home Messages

- For central pelvic recurrence after radiation therapy, modified radical hysterectomy (if the recurrence is smaller than 2 cm) or pelvic exenteration should be undertaken

- Disease-free interval > 16 months: Beva + chemo

- Disease-free interval < 16 months: Immunotherapy

- Reirradiation: investigational

THANK YOU!