MANAGEMENT OF
LOCALLY ADVANCED CERVICAL CANCER
(LACC)

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Cervical Cancer

* Second most common cancer among women
* Second most common cause of Ca-related mortality

DEVELOPING COUNTRIES
234,000 deaths/year
- Poor screening
- Low resource settings

DEVELOPED COUNTRIES
40,000 deaths/year

Cervical Cancer

* 71% of new cases as early disease (FIGO Stages I-II_A)

High chance of cure with surgery or Rt alone

* Patients with more advanced lesions:
  - Greater risk of recurrence
  - Majority of cervical cancer deaths

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FIGO Stages $I_{B2} - II_{A} - II_{B}$ (Bulky > 4 cm disease)
- Disease confined to the pelvis
- Lack of “optimal management”
- Poor prognosis (since 1950)

5-year survival

80-90% - small tumors

50-60% - bulky disease

Horn LL, Gynecol Oncol 2007.
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Standard traditional treatment

Radiotherapy
(External Beam ± Brachytherapy)


NIH Consensus, J Natl Cancer Int Monogr 1996.
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Addition of Concomitant CHEMO to RT
* Cisplatin 40mg/m² IV weekly x 6 weeks

50% reduction of relative risk of death from CaCx
- By decreasing local / pelvic failure
- By decreasing distant metastases

Rose PG, Drugs 2000.
NCI Clin Announcement on CaCx 2005.
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STAGING

• It helps clinicians to plan patients’ treatment
• To estimate patient’s prognosis
• It helps researchers to exchange information
• It provides a common language for evaluating the results of clinical trials
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FIGO staging system: CLINICAL

≠

All other gynecological cancers: SURGICAL

• Palpation, inspection, colposcopy, ECC, hysteroscopy, cystoscopy, proctoscopy, IVP, X-ray lungs – skeleton
• Bx and histologic confirmation of bladder and rectal involvement
• Conisation – cervical amputation

* OPTIONAL EXAMS

Laparoscopy, U/S, CT scanning, MRI, PET scanning

( Depending on availability)
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TRADITIONAL STAGING WORK-UP
IVP, Barium enema, EUA, cystoscopy, Proctoscopy.

NEW TRENDS IN STAGING WORK-UP
CT scanning with IV contrast, Office exam, Biopsy (Necessary) EUA, cystoscopy and proctoscopy on higher risk of involvement.

• MRI superior to CT and clinical exam for evaluation the pelvic extent of disease.

Sensitive imaging instead of invasive procedures.

Russell AH, Gynecol Oncol 1996.
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**STAGING – PET SCANNING**

* Fluorodeoxyglucose-FDG PET vs structural imaging techniques
  - More accurate for diagnosis, staging and treatment decisions

* 15 studies evaluating the extent of disease

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<tr>
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<th>PET-SCAN</th>
<th>MRI</th>
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<tr>
<td><strong>Pooled sensitivity</strong></td>
<td>Paraaortic d. 0,84</td>
<td>- Pelvic d. 0,72</td>
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<td>- Pelvic d. 0,79</td>
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<td><strong>Pooled specificity</strong></td>
<td>Paraaortic d. 0,95</td>
<td>- Pelvic d. 0,96</td>
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<td>- Pelvic d. 0,99</td>
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* Havrilesky LJ, Gynecol Oncol 2008.*
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STAGING – PET SCANNING

PET superior of MRI in detecting lymphatic spread

Choi HJ, Cancer 2006 – Prospective trial.

USA Centres for Medicare & Medical Services:

National coverage determination paying for FDG-PET for the detection of pretreatment metastases (staging) for new CaCx cases with negative conventional imaging extrapelvic findings.
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SURGICAL STAGING (LN-dissection)

* The most accurate method of detecting lymphatic metastasis
  - Dependent on the extent of the resection
  - Grossly involved nodes reducing surgery might increase cure

*Moore DH, Obstet Gynecol 2006.*
*Kim PY, Gynecol Oncol 1998.*
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SURGICAL STAGING

Laparotomy
- Transperitoneal (↑ risk bowel obstruction)
- Retroperitoneal (↓ risk bowel obstruction)

Laparoscopy
- Transperitoneal
- Retroperitoneal

Reduced morbidity questionable number of lymph nodes removed

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SURGICAL STAGING (last decade trend)

- Less surgical staging
- More accurate imaging modalities (MRI-PET)

*No more mandating (-) surgical staging of PAALN as entry criteria to clinical trials of CHEMO and RT for LACC

- GOG protocol 120 -

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OPTIMAL MANAGEMENT – A CONTROVERSIAL ISSUE

• Primary Radiotherapy (External beam +/- Brachytherapy)
• Radiotherapy and TAH + BSO
• Radiotherapy, TAH + BSO and Chemotherapy
• Neoadjuvant Brachytherapy and Radical Hysterectomy
• Neoadjuvant Chemotherapy and Radical Hysterectomy
• Radical hysterectomy and individualized postoperative Radiotherapy
• Concurrent Chemoradiation
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PRIMARY RADIOTHERAPY
(External Beam + Intracavitary Brachytherapy)
* Requirement for High doses of Brachytherapy for local control of the disease

* Increased possibility of complications

(≈ 28% : vesicovaginal fistulas, rectal and ureter stenosis, rectovaginal fistulas, pelvic infections, vaginal vault necrosis, vaginal stenosis)

Peper CA, Gynecol Oncol 1987.
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PRIMARY RADIOTHERAPY
(External Beam + Intracavitary Brachytherapy)

* Controversial use of Brachy to treat LACC
-MRI based dosimetry not widely available (to be tested prospectively)
-Interstitial Brachytherapy need to be tested
-HDR for outpatient Brachytherapy (no anaesthesia)
-LDR for large bulky tumours

HDR and LDR overall equivalent local control, survival and complication rates

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PRIMARY RADIOTHERAPY ALONE FOR LACC

Fails to control the progression of CaCx in 35-90% of LACC.

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RADIOThERAPY & EXTRAfASCIAL TAH

(To reduce central pelvic failures)

* Better local control.

-Central failure rate from 15% to 2.6%.
  * Durrance FY, Am J Roentgend 1996.

-Central pelvic failure rate from 19% to 2%.
-Extrapelvic failure rate from 16% to 7%.

Increase morbidity with no improvement of local control.
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**RADIOTHERAPY ± CHEMO & EXTRAFASCIAL TAH**

- Radiotherapy → Adj. TAH
  (Ext. B. + Brachy)

- Radiotherapy + CHEMO → Adj. TAH
  (Ext. B + Brachy) + Cisplatin 40mg/m² weeks x 6 weeks

374 pts with Bulky (LACC)

The addition of concomitant CHEMO + Rt
- S.S. ↓ residual disease (47% vs 57%)
- S.S. ↑ survival (89% vs 79%)
- S.S. ↑ DFS (81% vs 69%)

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**PREOPERATIVE BRACHYTHERAPY**

Patients IB2 – IIb + Preop. Radium

+ Radical Hysterectomy + PLND

- Adequate local control
- Adjuvant External Beam Rt in LN (+) pts
  (↑ urologic morbidity)

_Timmer PR, Gynecol Oncol 1984._
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PRIMARY RADICAL SURGERY + ADJUVANT RADIOTHERAPY

- Posterolateral and not anterior disease
- Precise surgical staging
- Individualized adjuvant treatment
- Removal of bulky nodes (survival benefit)
- Removal of central tumor (↓ residual disease)
- Ovarian preservation in young women

Lawton FG, Gynecol Oncol 1990.
Mitchell PA, Gynecol Oncol 1998.
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**PRIMARY RADICAL SURGERY + ADJUVANT RADIOTHERAPY**

- Increased perioperative morbidity in large tumors
- Increased possibility of (+) pelvic and aortic nodes in large tumors
- 50% of patients with + nodes ≈ bulky nodes

- Removal of bulky nodes + Adj. Radiotherapy
  (same prognosis with that of micrometastatic disease)

Rodolakis A, Gynecol Oncol 2002.
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CONCURRENT CHEMOTHERAPY + RADIOTHERAPY

* To improve control of the local and distant metastatic disease

Cisplatin 6-CHEMO + Radiotherapy

Standard of care of patients with LACC

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CONCURRENT CHEMORADIATION

- Addition of Concomitant weekly Cisplatin (40mg/m²) to External Beam Radiotherapy

  * 50% reduction of the relative risk of death from the disease by:
    - Decreasing local / pelvic failure
    - Decreasing distant metastases

Rose PG, Drugs 2000.
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CONCURRENT CHEMORADIATION AS ADJUVANT TREATMENT TO RADICAL HYSTERECTOMY

• Survival benefit.
• Decrease of local / pelvic failure.
• Decrease of distant metastases.

Monk BJ, Gynecol Oncol 2005.
Yessaian A, Gynecol Oncol 2005.
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CONCURRENT CHEMORADIOOTHERAPY

- Once / week Single – agent Cisplatin (40mg/m\(^2\))
  (the standard radiosensitizer in LACC)
- Combination of Cisplatin + 5-Fu
  (Added toxicity)

* Weekly CHEMO along with External Beam Pelvic RT
* Avoiding CHEMO during Brachytherapy (esp. HDR)

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NEOADJUVANT CHEMOTHERAPY + RADICAL HYSTERECTOMY

Metanalysis 5 randomized trials – 872 patients (NACT + Surgery (±RT) VS Radiotherapy)
- Improvement of 2-year S 8%-14%
- Improvement of 5-year S 12%-16%

Ideal CHEMO regimen to be specified
- TIP (Paclitaxel, Ilosfamide, Cisplatin)
- IP (Ilosfamide, Cisplatin)

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NEOADJUVANT CHEMOTHERAPY + RADICAL HYSTERECTOMY

* Trials designed and planned before the use of CHEMORADIOTHERAPY as standard treatment

* Lack of randomized trials (Phase III)

NACT + Radical surgery

vs

CONCURRENT CHEMORADIOTHERAPY

(EORTC Protocol 55994 still ongoing)
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NEOADJUVANT CHEMOTHERAPY + RADICAL HYSTERECTOMY

- Cisplatin based CHEMO
  (3-5 courses / 20 days)
- Tumor shrinkage, control of micrometastatic disease, increased operability

Sardi JE, Gynecol Oncol 1997.
Park DC, Gynecol Oncol 2004.
Chei Hum C, Gynecol Oncol 2007.

- Optimal response of LACC : 73-95%

Parc DC, Gynecol Oncol 2004.
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NEoadjuvant Chemotherapy + Radical Hysterectomy

Advantages

• Better potential activity against micrometastatic disease.
• Debulking effect → improvement surgical outcome.
• Less toxic scheme.
• Easier management of salvage therapy.

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NEOADJUVANT CHEMOTHERAPY + RADICAL HYSTERECTOMY

CONTROVERSIES

• Lack of survival benefit and local control of the disease.
• Survival benefit only for those patients who will have an operation.
• Non-responders to NACT will delay treatment and will have a worst prognosis.
• Development of radioresistant cell clones.
• Cross-reaction with radiotherapy.

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PREOPERATIVE CONCOMITANT CHEMORADIOOTHERAPY + RADICAL SURGERY

THEORETICAL ADVANTAGES

- Removal of potential chemoresistant foci.
- Assessment of the pathological response.
- Psychological impact of “feeling free of disease”.

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PREOPERATIVE CHEMORADIOOTHERAPY + RADICAL SURGERY

- 15 studies (1000 pts with LACC).
  - Pelvic Radiotherapy (40-80 Gy).
  - Cisplatin based chemotherapy.
  - Major differences on the use of brachytherapy and/or second drug (5-Fu).
  - DFS from 57% to 85%.
  - Overall survival from 64% to 90%.

- INCREASED MORBIDITY
  - Overall surgical complications 32,9%.
  - Severe toxicities (Grade 3) in 9,9% (urinary tract complications).

- Individualized surgery to reduce complication rate.

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CONCOMITANT CHEMORADIOTHERAPY

Gold standard in the treatment of LACC