FERTILITY SPARING SURGERY
FOR GYNAECOLOGICAL CANCER PATIENTS

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GYNECOLOGIC MALIGNANCIES

* Most often diagnosed among postmenopausal women

DURING THE LAST 2 DECADES

- Increasing incidence in premenopausal age
- Delayed conception

Most frequent malignancies among women < 40 years old

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>INCIDENCE</th>
<th>5-year SURVIVAL</th>
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</thead>
<tbody>
<tr>
<td>Ca breast</td>
<td>0.48% (1/207)</td>
<td>88%</td>
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<tr>
<td>Leukemia</td>
<td>0.13% (1/799)</td>
<td>46%</td>
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<tr>
<td>Melanoma</td>
<td>0.21% (1/484)</td>
<td>91%</td>
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<tr>
<td>Lymphoma (Non-Hodgkin)</td>
<td>0.09% (1/1147)</td>
<td>59%</td>
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<tr>
<td>Ca Cervix</td>
<td>0.16% (1/636)</td>
<td>73%</td>
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<tr>
<td>Ca endometrium</td>
<td>0.06% (1/1632)</td>
<td>84%</td>
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- Removal of uterus and both adnexa
  permanent sterility

- Halsted principle of the en bloc removal of primary tumor with the target-organ has been revised for early disease
Better understanding of the natural history of the disease

Nulliparous women wishing to maintain fertility

Development of minimally invasive procedures
  - Adequate control of the disease
  - Fertility preservation
FERTILITY PRESERVATION SURGERIES

- Selection of patients
- Understanding of the “experimental” nature of the approach
- Acceptance of the “undefined risk of recurrence”
- Close surveillance is required
CERVICAL CANCER – EPIDEMIOLOGY

- Incidence: 1.5 – 14.9/100,000 women aged 20 – 49 years.
- 28% of new cases: Women aged 29-39 years.
- Increasing incidence of AdenoCa among young patients.
- Increased birthrate among women over the age of 35 years.

Einstein MH, Gynecol Oncol 2008.
CERVICAL CANCER
TRADITIONAL SURGICAL APPROACH

- Hysterectomy (radical – Simple extrafascial) and systematic pelvic lymphadenectomy

- Preservation and upper transposition of ovaries (when pelvic radiotherapy is required)
**CERVICAL CANCER**
**FERTILITY – SPARING PROCEDURES**

- Excisional conization
- Radical trachelectomy

50% of women < 40 years eligible for surgical management

Candidate for conservative management

Chi D, Oncologist 2005.
CERVICAL CANCER & FERTILITY PRESERVATION

CERVICAL CONIZATION

* Effective treatment for CaCx Stage IA1 (FIGO)
  - Depth of invasion ≤ 3 mm
  - Horizontal spread ≤ 7 mm
  - No vascular or lymphatic invasion
  - Same management for squamous and adeno-lesions
  - Small possibility of nodal metastases
    - Squamous Ca(MIC): 0.8%
    - Adeno Ca (MIAC): 1 – 1.5%

Schorge JO, Gynecol Oncol 2000.
Benedet JC, Obstet Gynecol 1996.
Rodolakis A,
CERVICAL CANCER & FERTILITY PRESERVATION
CERVICAL CONIZATION

- Residual microscopic disease up to 5% in clear - margins cones
- With no clear surgical margins

Up to 10% chance of having a lesion >3 mm
FURTHER MANAGEMENT & NODE EVALUATION

CERVICAL CANCER & FERTILITY PRESERVATION
CERVICAL CONIZATION

* Adequate local control for stage IA2 (FIGO)
  - Depth of invasion 3-5 mm
  - Horizontal spread ≤ 7 mm
  - Clear surgical margins

* Chance of pelvic nodal metastases: 5-8%

Pelvic lymph-node dissection mandatory

Dargent D, Gynecol Oncol 2000.
Benedet JC, Obstet Gynecol 1996.
CERVICAL CANCER & FERTILITY PRESERVATION

CaCx Stage IB1

• Traditional approach: Radical Hysterectomy (type II-III) and pelvic lymphadenectomy

• ALTERNATIVE FERTILITY – SPARING APPROACH

Radical trachelectomy

Vaginal (RVT)  Abdominal(RAT)
CERVICAL CANCER & FERTILITY PRESERVATION
RADICAL VAGINAL TRACHELECTOMY (RVT)

* Radical removal of the cervix, paracervical tissue and upper vagina
  - Schauta F – Radical Vaginal Hysterectomy (1902)
  - Wertheim E – Radical Abdominal Hysterectomy (1900)

* Same philosophy of radicality

* Differences in the approach of lymphadenectomy

Schauta F, GynaRol 1902.
Wertheim E, Arch GynaRol 1900.
RADICAL VAGINAL TRACHELECTOMY (RVT)

1) Laparoscopic lymph-node dissection
   - Systematic (20-30 nodes from common iliac, external iliac, and obturator areas)
   - Frozen section for all suspicious nodes

2) Vaginal radical amputation of the cervix
   - Along with a rim of 1-2 cm of vagina
   - Dissection of paravesical, vesicouterine and pararectal spaces to obtain parametrial tissue
   - Ligation of descending division of uterine vessels

RADICAL VAGINAL TRACHELECTOMY (RVT)

- Endocervical canal tumour free margin ≥ 8 mm necessary
  (If not reexcision of 5 mm)
- Complete removal of endocervical canal for adenoCa
- Upper cervical or isthmic cerclage to prevent cervical incompetence
- Isthmic – vaginal reanastomosis

RADICAL VAGINAL TRACHELECTOMY (RVT)
ABORTED ATTEMPT

• Inability to obtain a negative cervical margin

• Positive lymph-nodes
  - Up to 11-12%
  - Turn to Radical Vaginal Hysterectomy (Schauta op)

Coveng A, Cancer 1999.
RADICAL VAGINAL TRACHELECTOMY (RVT)
PREOPERATIVE ASSESSMENT

MRI evaluation of:
-Tumour size
- Exact location
- Tumour distance from the isthmus
- Tumour free tissue of 1 cm
- Length of the endocervical canal
- Length of the endometrial cavity

RADICAL VAGINAL TRACHELECTOMY (RVT)  
GENERAL ELIGIBILITY CRITERIA

- Lesion size < 2 cm or < 3 cm if exophytic
- Histologically proven squamous, Adeno- or Adenosquamous carcinoma
- FIGO stages IA – IB1 disease
- Patient < 40 years of age
- Strong desire to preserve fertility
- No clinical evidence of impaired fertility
- No evidence of upper endocervical canal involvement
- No evidence of lymph node metastasis

Maltaris Th, Gynecol Oncol 2006.
RADICAL VAGINAL TRACHELECTOMY (RVT)

OBSTETRICAL OUTCOME

• Encouraging conception and pregnancy rates
• Among women tried to conceive 52% success
• Pregnancy outcome as of general population
• ↑ pregnancy losses (>14 weeks)
• ↑ prematurity rate (29%)
  - Loss of natural cervical barrier for infection
  - Loss cervical stroma – incompetence
  - Subclinical infections (cerclage)
• Delivery by Cesarean section

Burnett AF, Gynecol Oncol 2003.
RADICAL ABDOMINAL TRACHELECTOMY (RAT)

- Methodology same as Radical Hysterectomy (Type III)
- Removal of the cervix with a rim 1 - 2 cm of vagina and parametrium and paracolpium
- Uterine vessels ligated or preserved
- Bilateral systematic pelvic lymphadenectomy
- Permanent cerclage

Abu – Rustum NR, Gynecol Oncol 2006.
SIMILARITIES OF RADICAL VAGINAL & ABDOMINAL TRACHELECTOMY

- Same criteria of patients’ selection
- Same criteria of abandoning the procedure
- Same methodology of surgical approach
  (Lymphadenectomy -> trachelectomy)
- Same complications
- Same efficacy

DIFFERENCES BETWEEN RADICAL VAGINAL AND ABDOMINAL TRACHELECTOMY

- RAT may result in wider parametrial resection (> 50%)
- RAT for bigger (2 – 4 cm) tumours
- RVT requires a high expertise in radical vaginal surgery
- Expertise in Laparoscopic lymphadenectomy not necessary for RAT
- Increased blood losses for RAT

Covens A, Cancer 1999.
Abu – Rustum NR, Gynecol Oncol 2006.
Einstein MH, Gynecol Oncol 2009.
RADICAL TRACHELECTOMY – FOLLOW-UP

-Cytologic (vaginal – isthmic) smear and colposcopy
  - Every 3-4 months X 2 years
  - Every 6 months thereafter
  - 6 month post-op contraception
  - MRI evaluation at 6 months – yearly thereafter

Einstein MH, Gynecol Oncol 2009.
RADICAL TRACHELECTOMY FOR CERVICAL CANCER
OBSTETRICAL OUTCOMES

- 43% tried to conceive
- 70% of those tried had a successful pregnancy
- 49% term – pregnancies
- 8% second trimester losses
- 16% first trimester losses
- 20% premature deliveries (< 36 weeks)

Boss EA, Gynecol Oncol 2005.
Plante M, Gynecol Oncol 2005.
Abu-Rustum NR, Gynecol Oncol 2006.
RADICAL TRACHELECTOMY FOR CERVICAL CANCER
SAFETY & EFFICACY

• Isthmic stenosis (DUB, subfertility, difficult follow-up)
• Recurrence rate similar to that of Radical Hysterectomy (3-4%)
  - Careful selection of patients
  - Tumors < 2 cm
• Recurrences usually among tumors > 3 cm

Bader AA, Gynecol Oncol 2005.
Einstein MH, Gynecol Oncol 2002.
OVARIAN CANCER – EPIDEMIOLOGY

- Leading cause of death from gynecological malignancies (Western countries)
- 90% of cases are of epithelial origin
- Majority of patients are postmenopausal
- Incidence among women 20-49 y: 1.6 – 16/ 100.000 women
- Incidence among women < 20 y: 0.7 – 1.4/ 100.000 women
  (germ cell of sex cord – stromal)

OVARIAN CANCER – TRADITIONAL TREATMENT

1. Primary surgical approach
   TAH BS + Surgical Staging

2. CHEMOTHERAPY
OVARIAN CANCER
RATIONALE FOR CONSERVATIVE MANAGEMENT

- Excellent prognosis for most of tumors of women < 20 y
  (malignant germ – cell tumors, sex cord of early epithelial)
- Many premenopausal with epithelial carcinomas
  - Borderline tumours
  - Early stage invasive tumors
- Strong wish to preserve fertility
OVARIAN CANCER – CONSERVATIVE MANAGEMENT

• Limited to those cases with carcinoma limited to one ovary
  - Malignant germ-cell tumors
  - Malignant sex – cord tumors
  - Selected cases of epithelial ovarian tumors

COMPREHENSIVE SURGICAL STAGING IS MANDATORY
OVARIAN CANCER – CONSERVATIVE MANAGEMENT
SURGICAL STAGING

- Removal of involved adnexa
- Preservation of uterus and normal appearing contralateral ovary
- Complete evaluation of upper and lower abdomen
  - Washings
  - Omentectomy
  - Multiple biopsies
- Evaluation of retroperitoneal space
  - Systematic pelvic lymphadenectomy
  - Paraaortic lymphadenectomy
EPITHELIAL OVARIAN CANCER – CONSERVATIVE MANAGEMENT

• 7 – 8% of epithelial ovarian Ca among women < 35 years

LOW RISK PATIENTS

CANDIDATES FOR CONSERVATIVE MANAGEMENT

• Evaluation based on:
  - FIGO stage
  - Histology
  - Grade
  - Ca 125

Maltharis Th, Gynecol Oncol 2006.
EPITHELIAL OVARIAN CANCER – CONSERVATIVE MANAGEMENT
ENTRANCE CRITERIA

- FIGO Stage IA
  (negative cytology, no rupture of the capsule)

- Histology
  (Mucinous and endometrioid of better prognosis than clear-cell)

- Grade 1 disease
  (Better prognosis than grade 2-3)

- Ca 125 values
  (High values -> increased tumor volume)
EPITHELIAL OVARIAN CANCER – CONSERVATIVE MANAGEMENT

- 5-year survival of stage IA patients: 98%
- Low recurrence rates in the contralateral ovary: 3-5%
- Bilaterality for stage I serous tumors up to 33%

Bx OF CONTRALATERAL OVARY
ONLY IN MACROSCOPIC FINDINGS

EPITHELIAL OVARIAN CANCER – CONSERVATIVE MANAGEMENT
CHEMOTHERAPY

- When is really indicated
- Premature ovarian failure (up to 68%)
- Amenorrhea for older patients (Cyclophosphamide)
- Current scheme (Carboplatin + Paclitaxel)

with ↓ possibility of ovarian failure

When it offered to carefully selected patients, recurrence and survival rates appear to be comparable with those patients who undergo radical surgery.

Schilder, JM, Gynecol Oncol 2002.
Maltharis Th, Gynecol Oncol 2006.
BORDERLINE TUMORS (LMP – BOT)

- Frequently among young women (median age: 39 years)
- Low recurrence rates
- Excellent prognosis even for advanced stages
  (5-year survival 80-96%)

RATIONALE FOR CONSERVATIVE APPROACH FOR YOUNG WOMEN WISHING TO PRESERVE FERTILITY

BORDERLINE TUMORS & CONSERVATIVE MANAGEMENT

- Unilateral salpingoophorectomy or even cystectomy
- Increased recurrence rates in cystectomy (≈36%)
  (vs ≈ 20% of S.O.)
- Increasing rates of intraoperative capsule rupture or recurrence in cystectomy

CYSTECTOMY SHOULD BE RESERVED FOR THOSE PATIENTS WITH PREVIOUS S.O. AND RECURRENT BOT

BORDERLINE TUMORS & CONSERVATIVE MANAGEMENT

THE ROLE OF SURGICAL STAGING

- Does not seem to offer a better prognosis
- Justified only if intraoperatively Frozen section analysis is compatible with BOT
  (Final histology upgrading to invasive d. of up to 53%)

BORDERLINE TUMORS & CONSERVATIVE MANAGEMENT

- Obstetrical outcome very good
- Relapsing rate acceptable
- Disease related death rate minimal (0.18%)
MALIGNANT GERM-CELL TUMORS
CONSERVATIVE MANAGEMENT

- Conservative approach for young women and children
- Unilateral salpingoophorectomy & complete surgical staging
- Preservation of uterus and nontralateral ovary
- Chemotherapy when indicated (BEP – VAC)
  (Excellent 5 –y survival : 25% for early stage d.)
- Reproductive outcome very good

ENDOMETRIAL CANCER – EPIDEMIOLOGY

- The most common gynecological malignancy
- Median age of diagnosis in postmenopausal years
- Rarely found among women < 45 of age (7.9%)
- Incidence: 1.2 – 24/100,000 women aged 25-49 years

ACS Data 2004.  
ENDOMETRIAL CANCER – RISK FACTORS

- Past medical history of infertility
- Unopposed of conjugated estrogen
- Obesity
- Increased endogenous estrogen (Stein – Leventhal S)

Trope CG, Curr Opin Oncol 1999.
Maltharis Th, Gynecol Oncol 2006.
**ENDOMETRIAL CANCER**

**CURRENT STANDARD MANAGEMENT**

**TAH & BSO**

Pelvic ± paraaortic lymphadenectomy

- Permanent loss of reproductive potential
- Prognosis of young women excellent (95% 5y – survival)
  - Better differentiated tumors
  - Less myometrial invasion

Chiva L, Gynecol Oncol 2008.
ENDOMETRIAL CANCER
CONSERVATIVE MANAGEMENT

- Local excision of endometrial disease by hysteroscopy or curettage (1-2 X)

- Adjuvant use of progesterone based on the tumor’s hormonal sensitivity
ENDOMETRIAL CANCER
RATIONALE FOR HORMONAL INTERVENTION

Progesterone compounds:
- Inhibit estrogen receptor function
- Inhibit endometrial cell mitosis
- Promote apoptosis
- Partial anti – angiogenetic effect
- Used for metastatic endometrial Cancer

ENDOMETRIAL CANCER
HORMONAL INTERVENTION

Most common:
- Megestrol Acetate 40-160 mg/ daily
- Medroxyprogesterone Acetate (MPA) 200-800 mg/ daily

Alternatively:
- GnRH analogs
- Antiestrogens
- Aromatase inhibitors
- Tamoxifen

Chiva L, Gynecol Oncol 2008.
CONSERVATIVE MANAGEMENT
OF ENDOMETRIAL CANCER
PATIENTS’ SELECTION

PATIENT’S CRITERIA
- Not having a major contraindication for medical treatment
- Patient < 40 years, strongly wishing to preserve fertility
- Reliable patient wishing to have a close follow-up
- Careful counseling and acceptance of the undefined risk of recurrence
- Recognition of the “experimental” nature of the management

Chiva L, Gynecol Oncol 2008.
CONSERVATIVE MANAGEMENT OF ENDOMETRIAL CANCER PATIENTS’ SELECTION

DISEASE CRITERIA

- Well differentiated tumors (Grade I)
- Endometrioid histology
- Disease confined to the endometrium (Stage IA) or minimal stromal invasion (MRI) (Stage early IB)
- No evidence of LVSI
- Absence of suspicious pelvic or paraaortic nodes
- Absence of synchronous ovarian tumors (laparoscopy?)

Chiva L, Gynecol Oncol 2008.
CONSERVATIVE MANAGEMENT OF ENDOMETRIAL CANCER
EVALUATION OF MYOMETRIAL INVASION

Imaging techniques
- CTScan
- MRI
- TVS

MRI (contrast – enhanced): the most reliable method

POSSIBILITY OF UNDERESTIMATION OF THE DISEASE SPREAD BY ALL METHODS

CONSERVATIVE MANAGEMENT
OF ENDOMETRIAL CANCER
HISTOLOGICAL ASSESSMENT

- Hysteroscopy and Endometrial sampling (Pipelle) –for disease confirmation (95% sensitivity)
- Better agreement with final grade and detection of occult disease by D & C
- Post hysterectomy upgrading (26% for office Bx vs 10% for D & C)
- Post hysterectomy absence of residual disease (2% for office Bx vs 11% for D & C)

D & C: necessary before initiation of treatment

LIMITED DATA

MPA 200-600 mg / daily x6 / months
- 76% complete response
- 24% no response
- 30% recurrence rate → 2\textsuperscript{nd} line treatment (High-80% response rate)

Chiva L, Gynecol Oncol 2008.
Ramirez RT, Gynecol Oncol 2004.
CONSERVATIVE MANAGEMENT OF ENDOMETRIAL CANCER
EFFICACY & SAFETY

133 pts (mean age 31y)

Persistent complete response (68/133) → 51%

Temporary response (35/133) → 25%

No response (68/133) → 24%

Chiva L, Gynecol Oncol 2008.
CONSERVATIVE MANAGEMENT OF ENDOMETRIAL CANCER
POST TREATMENT FOLLOW-UP

- Routine periodical sampling (Hysteroscopy/ Pipelle)
- Evaluation of treatment response at 12 weeks
- D & C for evaluation of ambiguous findings
- Evaluation of stromal invasion (MRI, TVS)
- Consolidation treatment for 6 months even with negative findings at 12 weeks

Chi D, Oncologist 2005.
Chiva L, Gynecol Oncol 2008.
CONSERVATIVE MANAGEMENT OF ENDOMETRIAL CANCER DISEASE PROGRESSION

- Reports of stages I – III (FIGO)
- Reports for peritoneal carcinomatosis

CONSERVATIVE MANAGEMENT OF ENDOMETRIAL CANCER
DISCONTINUATION OF TREATMENT

- Histological or imaging findings of recurrence or disease progression
- Patient’s poor compliance
- Contraindication for continuing systematic therapy
- Inadequate follow-up
- Completion of childbearing

Chiva L, Gynecol Oncol 2008.
Maltharis Th, Gynecol Oncol 2006.
CONSERVATIVE MANAGEMENT OF ENDOMETRIAL CANCER
REPRODUCTIVE OUTCOMES

- Timing of pregnancy for good responders now well defined
- Consultation for the “earlier possible” after a documented disease remission
- Use of Assisted Reproductive Techniques (ART)
- No evidence that IVF increases the risk of recurrence

Chiva L, Gynecol Oncol 2008.
Maltharis Th, Gynecol Oncol 2006.
CONSERVATIVE MANAGEMENT OF ENDOMETRIAL CANCER
OPEN ISSUES

- Ideal treatment
- Optimal dose and duration of treatment
- Follow up – methodology
- Consolidation treatment
- Indication for hysterectomy
- Removal of normal appearing ovaries (Double primaries)
GYNECOLOGICAL CANCERS
CONSERVATIVE MANAGEMENT

FEASIBLE
- Better understanding of the natural history of the disease
- Improvement of surgical techniques
- Increased awareness of young women for proper consultation
- Strong desire for fertility preservation

NECESSARY
- Promote the knowledge of new conservative procedures
- Establish highly specialized centers where a multidisciplinary approach could be accomplished
- Recognition of “the undefined risk of recurrence” and the experimental nature of the approach