Update on Cervix and Vulva

Anuja Jhingran
Vulva
Vulvar Cancer

- ~3500 cases per year in US (4% of all Gyn malignancies)
- RF: Age (>70), HPV+ (50%), smoking, VIN, Paget’s disease, Bowen’s disease, lichen sclerosis
- Presentation: pruritus, spotting/bleeding, discharge, mass
- Histology: SCC (~85%), melanoma, basaloid, adenocarcinoma
- 5 yr OS for LN+ 20% lower (vs. cervix/anal)
Anatomy- Vulva Subsites

- Labia (2/3 cases)
- Perineal body
- Mons
- Clitoris
- Vaginal vestibule
- Bartholin’s glands
- Posterior forchette
Workup

- H&P; PAP smear; EUA and biopsy of primary
- MRI/CT ± PET
- CXR
- Lymph node biopsies
- Cysto/Sigmoidoscopy
Pretreatment Evaluation

- Treatment selection
  - Sites of possible regional involvement
    - Guide operative procedure
    - Guide external beam planning
  - Extent of primary disease
    - Selection of local treatment
- Assign FIGO stage
- Predict prognosis
Pre-treatment evaluation of distal vaginal and vulvar cancers

Tomographic scanning of the pelvis

- Will detect large nodes that are not palpable
- Guides RT planning
  - Dose
  - Need for LND
  - Field arrangement
  - Electron energy

![CT scan showing a tumor with 5.5 cm annotation](image)
Patterns of Spread

- Direct extension: vagina, urethra, anus, pelvic bones
- Superficial and Deep Inguinal Nodes:
  - Depth of Invasion:
    - <1 mm = <5%
    - 1-3 mm = 5-15%
    - >3 mm = 25%
    - >5 mm = 40%
    - Tumors >2 cm in size have a >20% inguinal metastasis rate
- Pelvic Nodes

Gunderson and Tepper, 2007
LN drainage from vulva

Lymphatics:

1<sup>st</sup> echelon:
• Superficial inguino-femoral

2<sup>nd</sup> echelon:
• Deep inguino-femoral
• Femoral

3<sup>rd</sup> echelon:
• External iliac/pelvic nodes
# FIGO Staging

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</tr>
<tr>
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</tr>
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<tr>
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<td>3+ LN &lt;5 mm, or 2+ LN ≥5 mm</td>
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<tr>
<td>IIIC</td>
<td>LN with ECE</td>
</tr>
<tr>
<td>IVA</td>
<td>Fixed/ulcerated LN, extension to upper 2/3 urethra/vagina, bladder/rectal mucosa or fixed to pelvic bone</td>
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## Pelvic lymph node status vs. survival

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## Survival by stage

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<th>FIGO stage</th>
<th>Survival, 1 year</th>
<th>Survival, 2 years</th>
<th>Survival, 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (n=286)</td>
<td>96%</td>
<td>90%</td>
<td>78%</td>
</tr>
<tr>
<td>II (n=266)</td>
<td>88%</td>
<td>73%</td>
<td>59%</td>
</tr>
<tr>
<td>III (n=216)</td>
<td>75%</td>
<td>54%</td>
<td>43%</td>
</tr>
<tr>
<td>IV (n=71)</td>
<td>35%</td>
<td>17%</td>
<td>13%</td>
</tr>
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Why are pelvic LNs considered M1?
Homesley trial (GOG 36)

- 114 pts tx’d with radical vulvectomy and bilateral inguinal LND
- If positive inguinal nodes, pts randomized to:
  - Pelvic LN dissection vs.
  - Post-op RT to pelvic and inguinal nodes
- Outcomes:
  - Groin Recurrence: RT 5% vs. surgery 24% (SS)
  - OS: RT 68% vs. surgery 54%
Radiation therapy vs pelvic node resection for carcinoma of the vulva with positive groin nodes


$P = 0.004$
Pelvic lymph node status vs. survival

- Poor prognosis of pelvic N+ led to M1 designation
- Graph shows arms from the surgery alone arm
  - 23% OS at 2 yrs. for + pelvic nodes

Pelvic lymph node status vs. survival

- Poor prognosis of pelvic N+ led to M1 designation
- From losing control arm of Homesley et al.
  - No groin or pelvic RT
- Today:
  - Pelvis rarely dissected
  - Postop RT standard for inguinal N+
  - Prognosis of pelvic N+ after RT unknown

Should pelvic N+ be M1?

• 20/516 patients from 1980 – 2010 had evidence of gross PLN involvement

• Criteria:
  • ≥ 1.5 cm on CT/MRI
  • FDG PET-avid
  • Biopsy-proven
  • CI/PA LNs not excluded
Overall Survival

5-yr OS 43%
Overall Survival

5-yr OS 50%  Excluding the 3 pts with CI/PA LN disease
Survival

- 8/20 pts NED at 3.9 y (range, 1.9 to 11.4)
- 1 pt NED until 18.6 yrs after treatment
- Of the 12 pts who died
  - 9 from progressive disease
  - 1 from cardiac cause
Changing the FIGO 2009 Staging

Disease-specific survival

Years after surgery

Adapted from Tabbaa et al. Gynecol Oncol. 2012.
Changing the FIGO 2009 Staging

Disease-specific survival

Years after surgery

Adapted from Tabbaa et al. Gynecol Oncol. 2012.
Conclusion

• Positive pelvic nodes should be treated with curative intent
• Consideration should be made with next FIGO staging meeting to remove pelvic nodes from stage IVB
Selecting treatment for vulvar cancer

- List possible treatments for primary disease
  - WLE ± RT
  - Pre-op RT
  - RT alone (± CT)

- Treatments for regional disease
  - Lymph node dissection ± RT (± CT)
  - Sentinel Nodes
  - RT alone (± CT)
Do the Groins Need Dissection?
GOG 88

- T1-T3 with clinical negative inguinal nodes
  - Arm 1) Bilateral inguinal/femoral LND
  - Arm 2) bilateral groin irradiation.

- Outcome:
  - 20% of Pts had LN+ in the surgery arm
  - Groin recurrence: RT 18% vs surgery 0% (SS)

**Radiation cannot control inguinal DZ**
Overall Survival GOG 88

Groin Dissection

Groin RT

Months on Study

Percent Surviving

Rx | Alive | Dead | Total
---|-------|------|------
Groin Dissection | 22 | 3 | 25
Groin RT | 17 | 10 | 27

P = 0.035
Criticisms of GOG 88

- Pts tx’d with RT alone only had tx of inguinal nodes vs. tx of inguinal + pelvic nodes in LND arm pts with LN+
- Evaluation of cN0 status determined clinically, not based on CT scans
- Analysis of 5 RT failures showed that inguinal nodes were underdosed by at least 30%
Criticisms of GOG 88

- Inguinal Radiation was prescribed to 3 cm
- Of the 5 pts who failed, 3 were underdosed by 30%
Criticisms of GOG 88

- 20% of surgery arm received PORT for LN+

Fig. 1. Radiation treatment fields.

Pelvis not treated
Treatment of Groins

- Superficial groin dissection is recommended
- Sentinel nodes may be done – however data from GROINS V – if < 2 mm invasion in node – groin dissection is recommended
- Post-op RT recommended - > 1 node +, ECE
Management of Vulvar SCC

Resectable?

Yes

Surgery per stage

Stage 1A

WLE only

Stage > 1A

WLE + Inguinal LN dissection

No

RT +/- chemo

Preop ChemoRT

Definitive

Post-op radiation as indicated
General Management Principles

- Radiation for vulvar cancer
  - Initial Preop/Definitive RT
    - Unresectable
    - High complete response rates with CRT, but no randomized trials comparing RT alone with CRT
  - Post-op indications:
    - Vulva (Heaps criteria): (+) margins, margin < 8 mm pathologically or < 1 cm clinically, LVSI, lesions > 5 mm deep
    - Inguinal/pelvic nodes (Homesley GOG371986): clinically + groin LN, >1 groin LN+, nodal ECE
Pre-operative Radiation Therapy
A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: a gynecologic oncology group study.
Moore, et al Gyn Onc 2012

- T3 or T4 vulvar lesions
- Treatment:
  - Radiation – 1.8 Gy x 32 fx = 57.6 Gy
  - Weekly cisplatin – 40 mg/m2
  - 4-6 wks. later – biopsy or surgical resection
- Results:
  - 58 evaluable patients
  - 37 (63.8%) clinical CR
  - 29 (50%) pathological CR

- 1996-2007 – 28 patients
- Treatment:
  - Split course RT – 40 Gy – 2 wks. Split 20 Gy
  - Chemo: 5FU x 4 days and Mitomyocin C day 1
  - Surgery
- Results
  - 20 pts. (72%) CR
  - 4 pts. (14%) PR
  - LRC, PFS & OS at 4 yrs. – 75%, 71% & 65%
How effective is definitive RT?

Koay et al ASTRO 2013

- SCC of the vulva from 1980 to 2011 at MDACC:
  - 88 patients treated with RT +/- chemo alone
  - Median age 67 years (37-91)
  - Median follow up 40 months (1-298)

- Main reasons for non-surgical management:
  - Marginally resectable or unresectable disease
  - Comorbid illness
Locally advanced presentations

50% had lesions larger than 5 cm
Locally advanced presentations

Percentage of patients

Node involvement

Inguinal

Pelvic
Despite advanced presentations, long-term survival achieved.
Survival influenced by same factors as local and distant failure

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Significant factor(s)</th>
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<tbody>
<tr>
<td>Vulva recurrence</td>
<td>Therapy completion</td>
</tr>
<tr>
<td>Groin recurrence</td>
<td>Primary tumor size</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>Primary tumor size, chemo</td>
</tr>
<tr>
<td>Overall survival</td>
<td>Therapy completion (trend), primary tumor size, chemo</td>
</tr>
</tbody>
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Conclusions

- Long-term survival achieved with definitive radiotherapy despite advanced presentations
- Local control is paramount
- Acceptable incidence of late toxicities
- Concurrent chemo may be beneficial
What radiation technique would you use?

1. AP-PA photon followed by 3D conformal boosts
2. Wide AP, narrower PA with lateral e- supplements followed by 3D conformal boosts
3. 1 or 2 followed by IMRT boosts
4. IMRT to GTV and CTV followed by sequential boost
5. IMRT to GTV and CTV with concurrent GTV boosts
Simulation

- Supine, frog-leg position,
- Vac-loc cradle
- Radio-opaque markers around lesion, urethra/clitoris, anal verge
- 5mm bolus placement
Vulvar Bolus

- TLDs to assess the need for bolus
Traditional photon/electron technique for treatment of vulva and inguinal nodes

- **Advantages:**
  - Broad coverage of targets
  - Provides some protection of femoral heads

- **Downsides:**
  - Electrons insufficient in obese cases
  - ↑ diarrhea contaminating raw vulvar surfaces
  - Unnecessary tx of large areas of skin

![Image showing photon/electron technique with 6 MV photons, 12 MeV e-, 12 MeV e-, 18 MV photons.]
Traditional photon/electron technique for treatment of vulva and inguinal nodes

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12 yrs after RT alone for T3 vulvar cancer with inguinal N+
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12 yrs after RT alone for T3 vulvar cancer with inguinal N+
IMRT for vulvar cancer - Advantages

- Advantages:
  - Ability to protect skin outside the PTV
  - Protection of central pelvic bowel, etc.
  - Ability to protect femoral heads even in obese pts
  - Concurrent boosts
IMRT for vulvar cancer - Disadvantages

- VERY steep learning curve
- Controversies about target delineation
  - Groins
  - “skin bridge”
    - (intransit lymphatics)
  - Coverage of mons
  - Vaginal coverage
  - Does entire vulva always need to be covered?
- IMRT has trouble optimizing targets that extend to the skin
  - Check air gaps!!!
What is the top border of the field?
Superior border coverage

- Pelvic nodes
- + inguinals, ECE
- + inguinals, no ECE
- - inguinals
How do you contour inguinal LNs?

- Vessels + 7mm margin…. right?
How do you contour Inguinal LN CTV

To cover ≥90% disease:
- Anteromedial ≥35 mm
- Anterior ≥23 mm
- Anterolateral ≥25 mm
- Medial ≥22 mm
- Posterior ≥9 mm
- Lateral ≥32 mm

Corresponding anatomic boundaries:
- Lateral: medial border of the iliopsoas
- Medial: lateral border of adductor longus or medial end of pectineus
- Posterior: iliopsoas muscle laterally and anterior aspect of the pectineus
- Medial / Anterior: the anterior edge of the sartorius muscle.

* Most macroscopic nodes were medial or anteromedial to the femoral vessels.

Kim et al PRO 2012
Contouring the groins – Understand the anatomy

- Relationship between nodes and vessels
  - Medial to femoral and saphenous veins
Contouring the groins – Understand the anatomy

- Usually anterior and medial to femoral and saphenous veins
Contouring the groins – Understand the anatomy

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Contouring the groins – Understand the anatomy

- Usually anterior and medial to femoral and saphenous veins
- May lie along tributaries some distance from large vessels
  - Sup. epigastric, pudendal (1°)
  - Circumflex (2°)
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- Usually anterior and medial to femoral and saphenous veins
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- Nodes anterior and posterior to vessels as they enter (exit) pelvis
Contouring the vulva

- Fiducials to define tumor, critical structures
  - EUA if vagina extensively involved
Contouring the vulva

- Fiducials to define tumor, critical structures
  - EUA if vagina extensively involved
- Unless necessary, avoid high dose to
  - Mons
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  - Medial thighs
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AP-PA

IMRT
Contouring the vulva

- Fiducials to define tumor, critical structures
  - EUA if vagina extensively involved
- Unless necessary, avoid
  - Mons
  - Medial thighs
  - Anus (if not in target)
IMRT for vulvar cancer – Disadvantages
- Challenges: Target motion, tumor regression, wt loss
- Solutions: IGRT, generous PTV, resimulation
Side Effects

- Acute
  - Epilation of pubic hair
  - Hyperpigmentation
  - Moist desquamation by 3\textsuperscript{rd} – 5\textsuperscript{th} week
  - Superinfection: Candida, others
  - Diarrhea, cystitis
RT side effects

- Chronic
  - Atrophy of skin, telangiectasia
  - Vaginal shortening, dryness
  - Femoral neck fracture < 5%
Follow-up of Stage IVB patient

>7 years after IMRT:

- Fully active 72 year-old
- NED (continuously)
- Mild rectal irritation treated with dietary fiber
- Mild L lymphedema (on side of LND)
- Fully continent, no urinary complaints
Conclusions

- Pelvic nodes should be treated definitely
- Treatment of vulvar carcinoma should be individualized
- Radiation therapy plays a very important role in the treatment of vulvar carcinoma
- Concurrent chemotherapy may have a very important role
- IMRT may reduce both acute and chronic toxicity but needs to be done well
Cervix
Global Disease

- Over 500,000 cases worldwide
- 3rd most common cause of death
- 12,000/yr new invasive Cx ca in US
Risk Factors: HPV

- High risk type (19 total)
  - 16, 18
    - HPV 18 more aggressive
      - Associated with LN involvement and DM
  - 31, 33, 35, 39, 45, 51, 52, 56, 58

- Low risk types
  - 6, 11
    - Associated with genital warts not cancer
  - 42, 43, 44
HPV and Prognosis

- 1993-2000: 327 pts. with stage IIB-IVA
- 22 HPV genotypes detected in 98.8%
- 4 most common HPV 16, 58, 18 and 33
- CCRT improved DSS most in HPV 18 and HPV 58
- Poor prognosis associated with advanced stage, age <45 and no chemo
Pre-treatment Imaging

- PET/CT
- MRI
- CT scan
FDG-PET vs. CT of paraaortic lymph nodes

PFS

Time (months)

CT– / PET–

CT+ / PET+

CT– / PET+

P < 0.0001

Cervical Cancer
Recurrence Free Survival: Pet + LN
Kidd et al. JCO, 2010;28:2108-2113

513 patients, Stage Independent, Positive pelvic LN better than PA

Stage I

Stage III
Case Presentation

- 47 yrs. old female – several months of vaginal discharge
- Pap smear – abnormal
- Biopsy – cervix and endometrial showed poorly differentiated squamous cell carcinoma
- Exam – 6 cm exophytic tumor involving the upper 1/3 of vaginal - IIA
Case Presentation
Treatment Options

- Management of nodes:
  - A. Treat with radiation therapy and boost the positive nodes – standard pelvic field
  - B. Same as A but extend the field maybe to L3 or higher
  - C. Node dissection – both pelvic and para-aortic nodes
  - D. Node dissection – just para-aortic nodes
Treatment options

- Chemotherapy options:
  - A. Neoadjuvant chemotherapy – followed by either surgery or radiation therapy
  - B. Concurrent cisplatin and radiation therapy
  - C. Concurrent cisplatin and another drug like gemcitabine or 5-FU
  - D. Concurrent cisplatin and radiation therapy followed by adjuvant chemotherapy
Surgical Staging vs. Imaging
Surgical staging - Rational

- Studies show 18-44% modification of fields after surgical staging
- GOG study – 320 pts – 21% IIB and 31% III B pts had positive para-aortic nodes
- Several recent studies have soon a possible survival benefit with surgical staging
PET Data

- Tsai et al – 28% treatment modification using PET
- Rose et al – 75% sensitivity and 92% specificity
- Yildirim et al – PET/CT – para-aortics – 75% sensitivity and 50% specificity – 25% pts. had modification of treatment
Figure 1. PET/CT findings and correlation with final pathology

- Total Enrolled: N=65
- Excluded: N=5
- Eligible: N=60
  - PET/CT: Pelvic (-), Para-aortic (-), N=25
    - Para-aortic Node Status: Positive 1, Negative 24
  - PET/CT: Pelvic (+), Para-aortic (-), N=26
    - Para-aortic Node Status: Positive 7, Negative 19
  - PET/CT: Pelvic (+), Para-aortic (+), N=9
    - Para-aortic Node Status: Positive 5, Negative 4
Study Schema

Locally Advanced Cervix Cancer (Stages IB2–IVA)

FDG-PET

Radiologically Negative Pelvic/Paraaortic Nodes

Excluded

ChemoXRT with Pelvic Field

Laparoscopic Extraperitoneal Paraaortic Lymphadenectomy followed by Tailored Chemoradiation

Radiologically Positive Pelvic Nodes/Negative Paraarotic Nodes

RANDOMIZE

Radiologically Positive Paraortic Nodes

Excluded

Confirm with Biopsy then Extended-Field ChemoXRT

Whole Pelvic Chemoradiation Therapy

Primary Endpoints: Comparison of OS in two randomized arms
Secondary Endpoints: Complications (Surgical and XRT)
Disease-free survival
Treatment
Radiation Therapy

Radiotherapy is the mainstay of treatment in “advanced” disease.

Principles of treatment:

- Volume encompasses known disease and its microscopic extensions.
- Radiation dose is sufficient (85 - 90Gy dose equiv @ point A)
- Brachytherapy (LDR or HDR) must be used where possible.
- Overall treatment time should not be prolonged beyond 56 Dys.

Central recurrence:
- IB1: 1–2%
- IB2–II: 10–15%
- III: 25–30%

Death from disease:
- IB1: 10–15%
- IB2–II: 30–40%
- III: 50–60%
How can we improve?
Chemotherapy?

Neoadjuvant chemotherapy
Concurrent chemotherapy
Concurrent Chemotherapy and Radiation therapy
Relative risks of recurrence for RT with concurrent cisplatin-containing CT vs. RT ± hydroxyurea -1999

- RTOG 90-01
- GOG 120 (1)
- GOG 120 (2)
- GOG 123
- SWOG 8797
- GOG 85
RTOG 90–01

- Extended field RT vs. Pelvic RT + chemo
- Chemotherapy
  - Cisplatin 75 mg/m² + 5-FU 4 gm/m²/96 hrs
  - 68% received 3 cycles; 81% ≥ 2 cycles
- Radiation Therapy
  - Median RT dose: 85 Gy (Pt A)
  - Median duration: 58 days
  - Major deviations in RT in 16%
Pelvic RT + cisplatin/5-FU versus pelvic and paraaortic RT for high-risk cervical cancer (Morris et al. NEJM:340, 1137)

\[ P = 0.003 \]
Survival - All patients – Eifel et al., RTOG update

\[ p < 0.0001 \]

![Survival rate comparison between Chemo-RT and EFRT](chart)
Survival - Stage I–II
Eifel, et al. – RTOG update

\[ p < 0.0001 \]

79% Chemo-RT
55% EFRT
Survival - Stages III–IV – RTOG update

\[ p = 0.07 \]
**NCIC Phase III Comparison of RT ± concurrent weekly CDDP**


- **Cisplatin**
  - 40 mg/m² weekly
  - 5 cycles
  - 70% full dose on time per protocol

---

Graph showing progression-free survival with radiation therapy (RT) alone vs. RT plus cisplatin (RT+ Cisplatin). The graph indicates a comparison of outcomes over time, with the x-axis representing time in years and the y-axis representing % progression-free. The graph shows a trend line for each treatment group, with the RT+ Cisplatin group having a slightly lower % progression-free compared to the RT only group. The p-value is given as *P = 0.39.*
NCI Canada randomized trial


- Chemo only works with bad RT
- Hydroxyurea is actually harmful
- Inadequate power in Pearcey trial
  - (259 pts randomized)

<table>
<thead>
<tr>
<th></th>
<th>PDC (1 yr)</th>
<th>Survival (3 yr)</th>
</tr>
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<tbody>
<tr>
<td>RT alone</td>
<td>22%</td>
<td>66%</td>
</tr>
<tr>
<td>RT+ CT</td>
<td>17%</td>
<td>69%</td>
</tr>
<tr>
<td>p</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
</tbody>
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RT/Plat vs RT/Plat/Gem + Adjuvant Gem

Duenas-Gonzalez et al. ASCO 2009

IIB-IVA, PA node-ve
KPS ≥70
Statify: size, site, Co vs Linac, age

Randomize

n=259
Plat 40 mg /m² + Gem 125 mg/m² x 6 + EBRT/BT*

n=256
Plat 40mg/m² x6 + EBRT/BT *

* EBRT: 50.4GY
BT : 30-35Gy

Observe
Plat 50 mg/m² + Gem1g /m² dy 1& 8 x 2

Accrual: 10 sites, 8 countries (‘02 to ’04) –F/U to April ’08.
RT/Plat vs RT/Plat/Gem + Adjuvant Gem
Duenas Gonzalez et al. ASCO 2009

PFS

Log-rank p=0.023
Hazard ratio = 0.68
95% CI = 0.49-0.95

74% Plat/Gem/RT
P=0.029

65% Plat/RT

Gem/plat 259
Cis 256

months
0 6 12 18 24 30 36 42 48 54 mös

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

74% Plat/Gem/RT
P=0.029

65% Plat/RT

Log-rank p=0.023
Hazard ratio = 0.68
95% CI = 0.49-0.95

Gem/plat 259
Cis 256

months
0 6 12 18 24 30 36 42 48 54 mös
## RT/Plat vs RT/Plat/Gem + Adjuvant Gem

Duenas - Gonzalez et al. ASCO 2009

<table>
<thead>
<tr>
<th></th>
<th>Plat/Gem/RT</th>
<th>Plat/RT</th>
<th>p</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95%CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=259</td>
<td>n=256</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>% (n)</td>
<td>% (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>11 (29)</td>
<td>16 (42)</td>
<td>0.097</td>
<td>.64 (.39-1.07)</td>
</tr>
<tr>
<td>Distant</td>
<td>8 (21)</td>
<td>16 (42)</td>
<td>0.005</td>
<td>.45 (.26-.78)</td>
</tr>
</tbody>
</table>

Two new interventions: Gemcitabine and adjuvant courses of CT

Is benefit in ↓ distant mets. and ↑ S due to:

1. **Gem** or
2. **Adjuvant** or
3. both?
RT/Plat vs RT/Plat/Gem + Adjuvant Gem
Duenas Gonzalez et al. ASCO 2009

• Raises several questions:
  • Is intensification of chemotherapy during radiation therapy important or does it only increase toxicity
  • Was the adjuvant chemotherapy the most important addition of this study
Concomitant CT/RT for cervical cancer: An IPD meta-analysis. (25 RCT’s, 4565 pts)
C.L. Vale, J.F. Tierney et al MRC and Collaborative Grp. JCO 26,’08

Platinum CT

S. by CT type:
Main analysis
14 trials, n=3452,

HR = 0.83 p=0.017

Non-platinum CT

HR = 0.77 p=0.009

Med FU: 5.2 yrs

CT Better RT Better
Concomitant CT/RT for cervical cancer: An IPD meta-analysis. (28 RCT’s, 5852 pts)
C.L. Vale, J.F. Tierney et al MRC and Collaborative Grp. JCO 26, ’08

<table>
<thead>
<tr>
<th>Event/#</th>
<th>Hazard Ratio (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-IIA</td>
<td>HR=0.62</td>
</tr>
<tr>
<td>260/948</td>
<td>- 10% ↑</td>
</tr>
<tr>
<td>IIB</td>
<td>HR=0.61</td>
</tr>
<tr>
<td>379/966</td>
<td>- 7% ↑</td>
</tr>
<tr>
<td>IIIA-IVA</td>
<td>HR=0.81</td>
</tr>
<tr>
<td>472/914</td>
<td>- 3% ↑</td>
</tr>
<tr>
<td></td>
<td>0.5 1 1.5</td>
</tr>
</tbody>
</table>

Abs benefit at 5 years= 8% (from 60% to 68%).
Metastases Free S: ↑ 7%
L-R Free S: ↑ 9%
Survival by CT scheduling: Main analysis
14 trials, 3272 women, 1085 events
Vale et al. JCO ‘08

Concomitant CTRT only

Concomitant CTRT + Adj CT

Hazard Ratio (Fixed)

HR = 0.81 p = 0.0006
HR = 0.48 p = 0.0001
HR = 0.75 p < 0.00001
Conclusion – Chemo/RT

- Five studies positive – one not – NCI recommends concurrent chemo/rt with cisplatin
- Meta-analysis – benefit in stage IB2-IIB, but only 3% in stage III
- Where to go from here?
  - New drugs – other drugs
  - Adjuvant chemotherapy
  - New ways to treat with cisplatin
Adjuvant chemotherapy?
Other ways to give Cisplatin?
KGOG/GOG 263 for intermediate risk Cervical Carcinomas

Radical Hysterectomy – risk factors – deep stromal invasion, LVSI, G3

Pelvis RT

Pelvic RT + weekly Cis

Enrollment – 151/280 pts.
RTOG/GOG 0724 – for high-risk Cervical Carcinoma

Radical hysterectomy – positive nodes, positive parametrium

Weekly cis + RT

Weekly cis + RT + 4 courses of Carbo/Taxol

Enrollment – 92/350
Patients with stage IB₁ & positive nodes, IB₂, II, IIIB or IVA cervical cancer who have given informed consent

Eligible patients

RANDOMISE

Max 6 weeks

Arm A – Control Arm
Concurrent chemoradiation

Arm B – Intervention Arm
Concurrent chemoradiation followed by adjuvant chemotherapy

Follow up 3 monthly for 2 years, and then 6 monthly for 3 years (5 years follow up in total)
Weekly Cisplatin vs. Q 3 Weeks Cisplatin

- Phase II trial from Korea found a slight survival advantage to Q3 week cisplatin
- TAKO – randomized trial in Korea and Thailand
- Advantage for developing countries – less resources needed
- Possible advantage for patients – less n/v
TACO

(Tri-weekly Administration of Cisplatin in LOcally Advanced Cervical Cancer)

Cervical cancer

Locally advanced cervical cancer
Stage IB2, IIB-IVA

Randomization

Control Arm; Weekly Cisplatin 40mg/m2 6 cycles

Study Arm; Tri-weekly Cisplatin 75mg/m2 3 cycles
Improvement in Radiation Therapy

- IMRT and Image-base Brachytherapy
Bladder filling
ITV/PTV on full bladder includes a significant amount of bladder
ITV/PTV on empty bladder includes a significant amount of bowel superiorly.
Rectal Filling
Tumor Regression – Intact Cervix

- Green Color wash – original cervix volume – full bladder
- Forest green – original cervix – empty bladder
- Red – final cervix – full bladder
- Maroon – final cervix – empty bladder
- Other colors – cervix volume from weekly CT scan while on treatment
Intact Cervix - Reponses to treatment
Beadle et al

- 16 pts - weekly serial ct scans and one with implant
  - Mean start cervical volume - 97 cc (range 37-302 cc)
  - Mean end cervical volume - 32 cc (range 11.8-83.3)
  - Reduction of 62% no matter what stage
  - Median change in 20 days
IMRT - Limitation

- Organ motion and tumor regression (IGRT)
- Accurate target delineation
- Very few clinical outcome studies
- Big Question – how much improvement and at what risk? Is it worth the expense?
- Larger studies needed to see if IMRT really will reduce toxicity
INTERTECC Trial

- Phase II/III Trial of IMRT (45-50.4 Gy) with Concurrent Weekly Cisplatin
- Stage I-IVA, Postop or Intact
- Primary Endpoint: Acute G3 Heme + G2 GI Toxicity
- Target Accrual: 91 (Phase II) + 334 (Phase III) = 425
- Phase II: Single Arm (Lead-In)
- Phase III: Randomized Trial of IMRT vs. 4-Field Box
- Central IMRT QA (MDA and Wash U.)
- Coordinating Site: Center for Advanced Radiotherapy Technologies (CART) / Clinical Translational Research Institute (CTRI) - UCSD
Brachytherapy
Important of Implant Placement

- LR
  - symmetry of ovoids ($p = 0.03$)
  - Displacement of ovoids to os ($p = 0.04$)
- DFS
  - Displacement of ovoids to os ($p = 0.01$)
  - Inappropriate placement of packing ($p = 0.03$)
## Important of Implant placement – DFS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR (95% C.I.)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetry of Ovoids to Tandem</td>
<td>2.33 (1.14, 4.75)</td>
<td>0.02</td>
</tr>
<tr>
<td>Dipplacement of Ovoids in relationship to OS</td>
<td>1.81 (0.89, 3.69)</td>
<td>0.10</td>
</tr>
<tr>
<td>Positions of Tandem in Mid-pelvis</td>
<td>0.77 (0.39, 1.50)</td>
<td>0.44</td>
</tr>
<tr>
<td>Tandem Bisecting Ovoids</td>
<td>0.71 (0.36, 1.38)</td>
<td>0.31</td>
</tr>
<tr>
<td>Appropriateness of Packing</td>
<td>1.13 (0.56, 2.29)</td>
<td>0.73</td>
</tr>
</tbody>
</table>
Image-Based Brachytherapy for Gynecologic Cancers

- Define the disease
- Define the normal tissues at risk
- Shape the dose distribution accordingly

• Potter R¹, Dimopoulos J¹, Kirisits C¹, Georg P¹, Knocke T¹, Lang S¹,
• Waldhausl C¹, Weitmann H¹, Reinthaller A², Wachter S¹

¹Radiotherapy and Radiobiology, Medical University of Vienna, Vienna, Austria;
²Gynecology and Obstetrics, Medical University of Vienna, Vienna, Austria
Results - Pötter et al

- 1998-2000 - prescribe to ICRU points
- 2001-2004 - 90% covering HR-CTV (80-85 Gy)
- OARS - all DVH - minimum to max exposed tissue - 2 cm³
  - 75 Gy to rectum and sigmoid
  - 90 Gy to bladder
  - No dose calculated for vagina
Conclusions - Image-base brachytherapy

- Pötter, et al - with Image-base brachytherapy
  - Increase dose by 10%
  - Decrease G3/G4 toxicity by 5%
  - Improvement in OS and LC
- Need larger multicenter studies with longer follow-up - on-going in Europe - Embrace
### CT-base Image Guided Brachytherapy

Charra-Brunad et al. Radiother Oncol 103(2012):305-313

<table>
<thead>
<tr>
<th>Mode of Treatment</th>
<th>Imaging During BT</th>
<th>LC (%)</th>
<th>DFS (%)</th>
<th>OS (%)</th>
<th>Grade 3-4 Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>BT + SX</td>
<td>X-ray</td>
<td>92</td>
<td>87</td>
<td>95</td>
<td>15</td>
</tr>
<tr>
<td>BT + SX</td>
<td>CT</td>
<td>100</td>
<td>90</td>
<td>96</td>
<td>8.9</td>
</tr>
<tr>
<td>XRT/BT + SX</td>
<td>X-ray</td>
<td>85</td>
<td>73</td>
<td>85</td>
<td>13</td>
</tr>
<tr>
<td>XRT/BT + SX</td>
<td>CT</td>
<td>93</td>
<td>77</td>
<td>86</td>
<td>9.0</td>
</tr>
<tr>
<td>XRT/BT</td>
<td>X-ray</td>
<td>74</td>
<td>55</td>
<td>65</td>
<td>23</td>
</tr>
<tr>
<td>XRT/BT</td>
<td>CT</td>
<td>79</td>
<td>60</td>
<td>74</td>
<td>3</td>
</tr>
</tbody>
</table>

All with significant P values except for OS
DVH Thresholds

- D2cc Rectum – 70-75 Gy
- D2cc Sigmoid – 70-75 Gy
- D2cc Bladder – 90-100 Gy
- D2 cc Bowel - < 60 Gy
- Target – D90 > 90%
DVH analysis and late side effects
Georg et al. IJROBP 2011;79 (2):356-62

- For Rectum, D2cc > 75 Gy predicted ≥ G2 side effects
- No dose limit for sigmoid was identified given low number of sigmoid specific side effects
- For bladder, D2cc > 95 Gy appeared to increase side effects though further analysis needed.
Future Directions (where definitive RT used):

1. Optimize RT – IMRT? Image base brachytherapy?

2. Cisplatin not necessary - use other agents e.g. 5 Fu/Mit C. – or different way to give cisplatin that may be more easier in developing countries

3. Explore adjuvant as well as concurrent CT to ↓ distant metastases (especially in adenoca) – large Outback trial through GCIG

4. Identify ‘better’ agents targeting specific molecular/environmental characteristics.

5. Identify who fails and sites of failure to select patients for different strategies.