Advances in Cervical Cancer Management

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April 14, 2012
Disclosures

• No financial disclosures
• Board member of American Brachytherapy Society
Learning Objectives:

1. Early stage cervical cancer
   - Post operative radiation
2. Locally advanced cervical cancer
   - External beam w conc chemo
3. Brachytherapy
Cervical Cancer Incidence and Deaths in the USA, 2005 - 2011*

*Source: American Cancer Society
Presentation

- Vaginal bleeding
- Discharge
- Back pain
- Superficial ulceration
- Exophytic tumor
- May spread to the vaginal fornices, parametria, bladder or rectum
Diagnostic work-up

Visible lesion:

• EUA
• Chest X-ray, CBC, Labs, Urinalysis
• Stage $> 3$: Cystoscopy, Rectosigmoidoscopy
• Optional: MRI, PET, CT, US, IVP
• Lymphangiogram not in U.S.
Manual Examination
FIGO Staging System

• Studies permitted by FIGO for staging:
  – EUA, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, IVP, CXR, skeletal x-ray

• Studies not permitted but often obtained in the U.S.: CT, MRI pelvis, PET

• If there is disagreement about parametrial invasion, the earlier stage should be chosen.

• No LN included in FIGO staging
2009 Staging revision

- Stage IIA1: upper 2/3 vag involvement with size $\leq 4\text{cm}$
- Stage IIA2: upper 2/3 vag involvement with size $> 4\text{cm}$
Prognostic Factors

- FIGO Stage
- Tumor Size
- Lymph node status
- Histology
- Smoking
- Hemoglobin $? (> 10)$
- Post-hysterectomy
  - Lymphovascular invasion
  - Percent stromal invasion
  - Parametrial extension
- Others: SCC-Ag, Age
- Predictive factors: duration of treatment, use of chemo-RT, brachytherapy
PET at diagnosis: Detection of Nodal Metastases
## Rule of 15

<table>
<thead>
<tr>
<th>Stage</th>
<th>5 yr survival</th>
<th>%+ pelvic LN</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>II</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>III</td>
<td>55</td>
<td>45</td>
</tr>
</tbody>
</table>

Prophylaxis of para-aortic LN? Not standardized
If + pelvic LN, large tumor size, LVI - prophylactic PAN RT
Resect or boost LNs >3cm
PET + LN predict survival

- 513 patients
- Stage independent
- Positive pelvic LN better than PAN

Post-treatment PET predicts survival

Schartz et al. JAMA 21;298(19):2289-95
Locally advanced cases
MR: Sag and Axial T2-weighted Images
Predictive value of MRI


• MRI at diagnosis, 2-3 weeks into EBRT; after 45Gy, 1-2 mo post Tx

• Regression ratio predictive of recurrence

• Initial MR Volume 40 cc and ratio:

• post-EB vol/initial vol <20%
  – significantly lower LC and DSS
Management of Stage IA

- Cryotherapy
- Laser Conization or Ablation
- Cold Knife Conization
- Loop Electrosurgical Excision Procedure (LEEP)
- If LVI+: Radical hysterectomy
- Trachelectomy
- Simple Cone + LND
Management of IB1: Radical Hysterectomy
Radiation or hysterectomy


• Randomized trial of 469 patients
• IB or IIA cervical cancer
• Median f/u: 87 months
• 54% of IB1 & 84% of IB2 surgical pts had adjuvant radiation for high risk features
Radiation or Hysterectomy

<table>
<thead>
<tr>
<th>5 year</th>
<th>OS</th>
<th>DFS</th>
<th>Rec</th>
<th>tox</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>83%</td>
<td>74%</td>
<td>25%</td>
<td>12%</td>
</tr>
<tr>
<td>Surgery</td>
<td>83%</td>
<td>74%</td>
<td>26%</td>
<td>28%</td>
</tr>
</tbody>
</table>

*(p=0.0004)*

SBO risk increased with LND

Viswanathan ASTRO 2012
Post-operative RT :  GOG 92
Intermediate risk factors

Sedlis et al. 1999;73:177-83.

<table>
<thead>
<tr>
<th>LVI</th>
<th>Stromal invasion</th>
<th>Tumor size</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>Deep 1/3</td>
<td>Any</td>
</tr>
<tr>
<td>+</td>
<td>Middle 1/3</td>
<td>&gt; 2cm</td>
</tr>
<tr>
<td>+</td>
<td>Superficial 1/3</td>
<td>&gt; 5cm</td>
</tr>
<tr>
<td>--</td>
<td>Deep or middle 1/3</td>
<td>&gt; 4cm</td>
</tr>
</tbody>
</table>

Need 2 of 3 features
GOG 92 update  

- Median f/u 10 years
- **46%** reduction in risk of recurrence (HR 0.54)
  - 30% improvement in overall survival (p=0.07)
  - Increases Grade 3/4 toxicity by 4.5%
  - 42% reduction in risk of progression/death
  - Reduction in adenoca 8.8% vs. 44%

Accruing GOG 263: concurrent weekly Cisplatin vs. no chemo

Viswanathan ASTRO 2012
Post-op Chemo-RT: SWOG 8797
High-risk patients

- + LN
- + Margins
- + Parametria
- 4 yr PFS
  - 63% vs. 80% (p=0.003)
- 4yr OS
  - 71% vs. 81% (p=0.007)

Peters et al. JCO 18:1606-13, 2000

Accruing RTOG 0724: adj Carbo/Taxol
Locally Advanced Cervical Cancer
Chemo-sensitization

Cell cycle

M

G1

G2

S

Taxol

Hydrea

Cis-platinum

RT sensitive

RT resistant
Cisplatinum

cis-Diammine dichloroplatinum[II]

- Cytotoxic and supra-additive with RT
- Inhibits repair of sublethal and potentially lethal RT injury
- Toxicities: renal, hematologic, GI
  - Check Creatinine – stent if obstructed
  - CBC – transfuse if Hct <30
  - Caution low performance status, medical comorbidities, nutritional status (cardiac, pulmonary)
Randomized trials of cisplatin-containing CT-RT leading to NIH clinical alert in April, 1999
**CT-RT of Cervical Cancer**

Settings in which chemoradiation has demonstrated advantage over RT alone

- Locally-regionally advanced (PAN -)
  - IB2-IVA disease
- Pre-operative (bulky IB)
- Post-operative, high risk
  - Positive nodes, margins, parametria
RT versus RT and chemotherapy

RTOG 90-01: Morris et al.
NEJM 340:1137, 1999

- IB1, IB2, IIA (N+ or ≥5cm); IIB-IVA; PAN neg (lymphangiogram or surgery)
- 403 patients
- Arm 1: Extended field RT (pelvic & PAN)
  RT dose: 45Gy pelvis and PAN + 40 Gy point A
- Arm 2: RT+CDDP 75 mg/m2 + 5FU 4g
d1-5 q3w x 3 cycles
# RTOG 90-01: 8 yr update

J Clin Oncol 22(5):872-880, 2004

<table>
<thead>
<tr>
<th></th>
<th>8yOS</th>
<th>DFS</th>
<th>LRF</th>
<th>DM</th>
<th>PAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT+CDDP+5FU</td>
<td>67%</td>
<td>61%</td>
<td>18%</td>
<td>20%</td>
<td>9%</td>
</tr>
<tr>
<td>EF RT</td>
<td>41%</td>
<td>36%</td>
<td>35%</td>
<td>35%</td>
<td>4%</td>
</tr>
</tbody>
</table>

- Only trial with RT alone arm
- Largest RR reduction (0.48)
- G3+ toxicity: 13% vs. 12% (p=0.65)
- St IB-IIA (272 pts): 78% vs. 55% (p<0.001)
- St III-IVA (117 pts): 59% vs. 47% (p=0.066)
## Weekly CDDP Chemoradiotherapy for Cervical Cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Control</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 120</td>
<td>526 (1999, 2007)</td>
<td>HU+RT</td>
<td>+++</td>
</tr>
<tr>
<td>GOG 123</td>
<td>374 (1999, 2003)</td>
<td>RT only</td>
<td>+++</td>
</tr>
<tr>
<td>NCIC</td>
<td>259 (2002)</td>
<td>RT only</td>
<td>-</td>
</tr>
</tbody>
</table>
NCIC trial: why negative?

- Smallest # patients, lowest % stage III-IV
  insufficient power to detect difference
- Shortest treatment duration
  – Improved outcome in both arms
- Anemia higher in chemotherapy arm
- Para-aortic LN staged CT only
- Only squamous cell ca
- Variable brachytherapy (HDR, MDR, LDR)
### Studies of CDDP/5FU Chemoradiotherapy

<table>
<thead>
<tr>
<th>Trial</th>
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<th>Control</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 90-01</td>
<td>(1999)</td>
<td>RT (EF)</td>
<td>+++</td>
</tr>
<tr>
<td>SWOG 87-97</td>
<td>(2000)</td>
<td>RT (postop)</td>
<td>+++</td>
</tr>
<tr>
<td>GOG 85</td>
<td>(1999)</td>
<td>HU + RT</td>
<td>+</td>
</tr>
</tbody>
</table>

Plat/5FU never compared directly with weekly CDDP
Weekly CDDP Chemoradiotherapy as the standard arm

<table>
<thead>
<tr>
<th>Trial</th>
<th>#</th>
<th>Year</th>
<th>Control</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 165</td>
<td>316</td>
<td>(2005)</td>
<td>PVI 5FU</td>
<td>++</td>
</tr>
</tbody>
</table>

(terminated early 35% failure rate)

Conclude: 5FU alone inferior to weekly CDDP

J Clin Oncol 2005;23(33):8289-95
Meta-Analysis


  - 4580 pts randomized, 3656 evaluable
- 16% absolute improvement in PFS (47% to 63%)
  - Benefit both local control and distant failures
- 12% absolute improvement in survival (40% to 52%)
  - Greater benefit for St IB-IIB
- Increased acute toxicity with CT+RT, but not late toxicity
LDR Treatment Schema

<table>
<thead>
<tr>
<th>CDDP</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>T/O #1</th>
<th>6</th>
<th>7</th>
<th>8 wks</th>
</tr>
</thead>
</table>

40-45 Gy

Boosts

External beam

HDR Treatment Schema

<table>
<thead>
<tr>
<th>CDDP</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>#1</th>
<th>#2</th>
<th>#3</th>
<th>#4</th>
<th>#5</th>
<th>6</th>
<th>7</th>
<th>8 wks</th>
</tr>
</thead>
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40-45 Gy

Boosts

External beam

Viswanathan ASTRO 9/25/08
Management of IB2-IVA

• Concurrent chemotherapy (Cisplatinum 40 mg/m2 weekly) and radiation therapy
• RT – pelvic and brachytherapy
• Pelvic – APPA or 4F, 180cGy/fraction, 45Gy, 15-18 MV.
• Boost parametria, sidewall
• Brachytherapy TD 80-90 Gy
Outback Chemotherapy

Dueñas-González A et al. JCO 2011;29:1678-1685

- Concurrent Cis + RT versus
- Concurrent Gem/Cis plus outback Gem/Cis

Kaplan-Meier estimates of (A) progression-free survival (PFS) and (B) overall survival for patients who were randomly assigned to arm A or arm B. PFS at 3 years is shown by the dotted black lines and was 74.4% for arm A and 65.0% for arm B (P = .029)
TECHNIQUES
Bowel sparing simulation

Supine
Intact cervix

Prone
Post-op pelvis

Radioth Oncol 2005;74:267-74
Lateral DRR

Could miss external iliac, pre-sacral, peri-rectal and internal iliac LN posteriorly
IMRT
http://www.rtog.org/gynatlas/main.html

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MOVEMENT
Heisenberg’s Uncertainty Principle

• The more precisely the position is determined, the less precisely the momentum is known in this instant, and vice versa.

--Heisenberg, Uncertainty paper, 1927
Heisenberg $\cong$ 4D RT

- Locate the target
- But as soon as you locate it, it moves
- Vaginal, parametrial mobility
- How much over-contouring is necessary to compensate ‘uncertainty’
- A sim CT is a STATIC image
Variation in Vaginal Position
Bladder Full vs. Empty
Parametria & change depending on volume of bladder

PTV: 1-4 cm
RTOG IMRT Atlas

- Obturator nodal contours /inferior extension
- Vaginal ITV
- Parametrial tissues
- Uterosacral ligaments/parametria
PET/CT Fusion Nodal Contour

Nodal boost 54-65 Gy
Location of Dose Limiting Structures

IMRT looks like an attractive option…

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Disadvantages of IMRT

Contouring

Need accurate contouring to avoid misses

Immobilization

Patient setup must be accurate and reproducible

Knowledge of Internal Motion

Margins could vary greatly depending on organ motion
Disadvantage.....

• Underdosing a critical region....
  – Uterosacral ligaments
  – Parametrial tissues
  – Uterine cavity

• Consequence
  – Relapse
  – DEATH
Can IMRT replace brachytherapy?

- Complex internal organ motion
  - Brachy fixed to target
- Tumor response
- The proximity of critical structures leaves little room for error in EBRT planning

After 45 Gy EBRT
Brachy better than IMRT

**Brachytherapy**
Moves with patient

**IMRT**
Does not move with patient
Difficult to adjust with response
Does brachytherapy increase local control and increase survival?
Brachytherapy is Necessary

- Brachytherapy: internally delivered radiation using radioactive sources
- Supplements external beam
- Tumor control probability correlated with RT dose and cervix ca volume  
  [Fletcher, J Radiol Electrol 56:383-400, 1975]

<table>
<thead>
<tr>
<th></th>
<th>External beam only</th>
<th>External Beam + brachytherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 y Pelvic Control</td>
<td>45% 19%</td>
<td>67% 46%</td>
</tr>
<tr>
<td>4 y Survival</td>
<td>45% 19%</td>
<td>67% 46%</td>
</tr>
<tr>
<td>4 y Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lanciano JROBP 20:95, 1991</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local Control</td>
<td>40%</td>
<td>52%</td>
</tr>
<tr>
<td>Montana Cancer 57:148, 1986</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Individual Patient Assessment

• Where is the disease

• What is the patient’s anatomy
  – MRI
  – Clinical exam

• Preparation for the OR
  – Ante vs. retroversion
  – Os visible or palpable
  – Inferior extent of disease
  – Proximity of posterior uterus to both rectum and small bowel
  – Bladder
Applicators for Brachytherapy

INTERSTITIAL

A

Tandem and Ring

B

Tandem and Ovoids

C
Interstitial Brachytherapy

Fistula
Postop recurrence
Extensive distal vaginal involvement
Cervical stump Ca
IMAGING

Plain x ray

Computed Tomography (CT)

Magnetic Resonance Imaging (MRI)

- International standard 2002-2011
- BWH until 2002
- Prescribe to points

- 2002-2006 0.5T
- 2011- 3.0T
Ultrasound for Dilation

- Suspected uterine perforation
- Retroverted uterus
- Absence of endocervical canal
- Extreme anteversion of uterus

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What might appear acceptable on Xray, may not be acceptable in 3D

Posterior placement

Proper placement
RTOG O116/0128: Brachy Quality

- Asymmetry of ovoids
- Displaced ovoids
- Inappropriate packing

Viswanathan et al. IJROBP 2012; 22(1):123-31
Unacceptable Tandem

Midline on lateral film

Bisecting ovoids
# Local Recurrence

<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>2.61 (1.05, 6.45)</td>
<td>0.039</td>
</tr>
<tr>
<td>Displacement of Ovoids in Relation to Cervical Os</td>
<td>2.54 (1.11, 5.80)</td>
<td>0.027</td>
</tr>
<tr>
<td>Position of Tandem in Mid-Pelvis on Lateral Film</td>
<td>1.01 (0.43, 2.37)</td>
<td>0.98</td>
</tr>
<tr>
<td>Tandem Bisecting Ovoids on Lateral Film</td>
<td>0.68 (0.27, 1.67)</td>
<td>0.39</td>
</tr>
<tr>
<td>Appropriateness of Packing</td>
<td>1.66 (0.73, 3.77)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

*Model included pelvic/iliac, para-aortic node positive, FIGO stage

†This represents the HR of unacceptable/not evaluated scores compared to acceptable scores

## Disease-Free Survival

<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>1.43 (0.73, 2.80)</td>
<td>0.29</td>
</tr>
<tr>
<td>Displacement of Ovoids in Relation to Cervical Os</td>
<td>2.12 (1.16, 3.89)</td>
<td>0.02</td>
</tr>
<tr>
<td>Position of Tandem in Mid-Pelvis on Lateral Film</td>
<td>1.15 (0.63, 2.09)</td>
<td>0.65</td>
</tr>
<tr>
<td>Tandem Bisecting Ovoids on Lateral Film</td>
<td>0.79 (0.42, 1.48)</td>
<td>0.47</td>
</tr>
<tr>
<td>Appropriateness of Packing</td>
<td>1.95 (1.08, 3.55)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

*Model included pelvic/iliac, para-aortic node positive, and FIGO stage
†This represents the HR of unacceptable/not evaluated scores compared to acceptable scores

Standard prescription: Point A
CT-detected perforation

Slide courtesy of Dr Beriwal
Method used for dose specification to the cervix

- 73% Point A
- 12% Other
- 10% mg/hours
- 3% CTV
- 2% GTV/CTV
Point A vs. 3D

Narrow cervix

Wide cervix
Therapeutic Ratio: Balance between tumor cure and complications
GEC ESTRO recommended dose recording

Organs at risk:
D0.1cc, D2cc

Target:
D90, V100

@ 2cm difference ICRU Bladder and D2cc value
Plan required for each HDR fraction

Radioth Oncol 81:269, 2006

NORMAL TISSUE VARIATION
CT versus MR contouring


- Width of contoured tumor larger on MRI
- OAR differences depend on filling status
- Nodal dose may be estimated
- Point A constant
MR guided interstitial brachytherapy


- Interstitial reconstruction CT vs. MR
  - Patients must be imaged with legs down
- Protection of bladder or rectum
  - No inadvertent insertion of interstitial catheter into bladder or rectum noted on CT after MR
MR-Interstitial Outcomes

- 25 patients
- 15 recurrent ca
- Interstitial brachytherapy
- 0.5 T MR
- No LR
- 2 yr PFS 65%
- 2 yr OS 60%
Recommendations based on MR-imaging

- GTV – T2 bright areas
- HR-CTV – cervix + visible/palpable disease at brachy
- IR-CTV – 1 cm margin around HR-CTV + initial sites of involvement

**Viswanathan ASTRO 2012**
MR T/R Brachytherapy Outcomes

Rad Onc 2011:100:116-123

- 156 patients
- Historical comparison
- Med FU 42 mo
- CR 97%
- Significant ↑
  - 3y OS 53 to 68%
  - CSS 62 to 74%
  - Tumors > 5cm
    - OS 28 to 65%

Pötter et al. Rad Oncol 2007
Tumor control related to dose


- **D90 for HRCTV > 87 Gy**
  - LR 4% (3 of 68)

- **D90 for HRCTV \leq 87 Gy**
  - LR 20% (15 of 73)

- The effect was most pronounced in patients that had tumors >5cm with a poor response
The OR and MR rooms of AMIGO

Advanced Multimodality Image Guided Operating (AMIGO) Suite
P41 RR019703 – National Center for Image Guided Therapy (NCIGT) 2005-2015
Ferenc Jolesz, MD
Clare Tempany, MD
3T MR Treatment Planning
Standard vs Optimized Plan
**Biologically Equivalent Dose**

Equivalent Dose in 2 Gy Fractions (EQD2)

\[
BED = n d \left(1 + \frac{d}{\alpha/\beta}\right) / \left(1 + \frac{2}{\alpha/\beta}\right)
\]

\[
EQD2 = \frac{BED}{1.2}
\]

- \(n = \# \text{ fractions}\)
- \(d = \text{dose/fraction}\)
- \(\alpha/\beta\) for tumor ~ 10
- \(\alpha/\beta\) for normal tissue ~ 3

**Example:**

\[(5 \text{ fractions}) \times (5.5 \text{ Gy}) \times (1 + 5.5 \text{ Gy}/10) / 1.2 = 35.5 \text{ Gy}_{10}\]
HDR Doses (after 45 Gy EB)

- 6 Gy x 5
- 7 Gy x 4
- 8 Gy x 3

Consider lower doses with concurrent chemo

- 5.0 Gy x 5 - small volume disease
- 5.5 Gy x 5 - large volume disease
## Standard Fractionation and EQD2 values

<table>
<thead>
<tr>
<th>Fractional Dose</th>
<th>#</th>
<th>EQD2</th>
<th>EB+EQD2</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 Gy</td>
<td>2</td>
<td>28.5</td>
<td>73</td>
</tr>
<tr>
<td>8 Gy</td>
<td>3</td>
<td>36</td>
<td>80</td>
</tr>
<tr>
<td>7 Gy</td>
<td>4</td>
<td>39.7</td>
<td>84</td>
</tr>
<tr>
<td>6 Gy</td>
<td>5</td>
<td>40</td>
<td>84</td>
</tr>
<tr>
<td><strong>5.5 Gy</strong></td>
<td><strong>5</strong></td>
<td><strong>35.5</strong></td>
<td><strong>80</strong></td>
</tr>
<tr>
<td>6 Gy</td>
<td>4</td>
<td>32</td>
<td>76</td>
</tr>
</tbody>
</table>
DVH analysis and late side effects


• Rectum: D2cc rectum >75 Gy predicted > G2 side effects

• Sigmoid: No dose limit identified given low number of sigmoid specific side effects

• Bladder: D2cc >95 Gy appeared to increase side effects though further analysis needed
Strategize your approach

• Experience matters
  – Training programs
• Follow guidelines
• Standardize approach

“I like to practice before I start acupuncture treatment!”
Follow-Up

• Pelvic examination and pap smears at regular intervals
  – Every 3 months for the first 2 years
  – Every 4 months the 3rd year
  – Every 6 months years 4th and 5th
  – Yearly thereafter

Biopsy if evidence of new lesions or abnormal pap smear
Imaging studies as needed
Vaginal Dilator
Summary: Cervical Cancer

- Screening effective
- Treatment effective
  - Pre-invasive
  - Invasive
  - RT very effective
- Individualize care
  - Emphasizes role as a comprehensive oncologist

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