Minimizing Disparity in Cervical Cancer Cure Through Improved Access to Care

- The importance of radiotherapy
  Michael Milosevic, Toronto, Canada
- Global availability of brachytherapy
  Eduardo Zubizaretta, IAEA, Vienna, Austria
- Brachytherapy in low resource settings
  Supriya Sastri (Chopra), Mumbai, India
- Digital education to improve access
  Li Tee Tan, Cambridge, UK
- General discussion
Global Access to Radiotherapy for Cervical Cancer

The Critical Need for Brachytherapy

Michael Milosevic, MD

Department of Radiation Oncology, University of Toronto
Radiation Medicine Program, Princess Margaret Cancer Centre
Toronto, Canada
Disclosures

I have no conflicts of interest to disclose.
The Face of Cervical Cancer

Courtesy of Barry Rosen
Global Cervical Cancer Incidence

Estimated age-standardised rates (World) per 100,000

Source: GLOBCAN 2012
Map production: IARC
World Health Organization

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Global Cervical Cancer Morality

Without treatment, virtually all women with cervical cancer will die
WHO: Global Fight Against Cervical Cancer

Comprehensive cervical cancer control plan to eradicate and cure

**PRIMARY PREVENTION**
- Girls 9-13 years
  - HPV vaccination
- Girls and boys, as appropriate
  - Health information and warnings about tobacco use*
  - Sexuality education tailored to age & culture
  - Condom promotion/provision for those engaged in sexual activity
  - Male circumcision

**SECONDARY PREVENTION**
- Women >30 years of age
- Screening and treatment as needed
  - “Screen and treat” with low cost technology VIA followed by cryotherapy
  - HPV testing for high risk HPV types (e.g., types 16, 18 and others)

**TERTIARY PREVENTION**
- All women as needed
- Treatment of invasive cancer at any age
  - Ablative surgery
  - Radiotherapy
  - Chemotherapy

*WHO Guidance Note, 2013*
HPV Vaccination to Prevent Cervical Cancer

Population benefit of vaccination is delayed 20-30 years

**Prevented Cases**
- Strategic demand forecast (GAVI)
- Worst case
- Best case

**Prevented Deaths**
- Strategic demand forecast (GAVI)
- Worst case
- Best case
Locally Advanced Cervical Cancer

Radiotherapy cures 50-60% of patients with locally advanced disease

Delaney, 2005, Hanna, 2015
Curative Radiotherapy for Cervical Cancer

Both external beam radiotherapy and brachytherapy are essential.
Curative Radiotherapy for Cervical Cancer

Substantially improved survival with the use of brachytherapy

SEER Database
(7,359 patients)

National Cancer Database
(2,571 patients)

Han, 2013

Gill, 2014
Global Disparities in Radiotherapy Access

No radiotherapy where cervical cancer is most prevalent

IAEA Directory of Radiotherapy Centres (DiRAC)
What is the economic benefit of closing the gap between what exists today and reasonable access to radiotherapy globally?

Atun, Jaffray, Gospodarowicz

September 2015
Global Demand for Cervical Cancer Radiotherapy

10 million women will require radiotherapy in the next 20 years

Demand for External Beam Radiotherapy

Demand for Brachytherapy

Courtesy of Danielle Rodin
Radiotherapy Net Economic Benefit

Health and societal benefits translate to economic benefits

![Bar chart showing net monetary benefit (in billions) for Time Horizon: 2015-2035. The chart compares Human Capital Economic Model and Full Income Economic Model using nomimal and efficient cost models.]

Courtesy of Danielle Rodin
Key Messages

• Cervical cancer will not be eradicated for generations.
• Cervical cancer control strategies must include prevention, early detection and treatment.
• Increased treatment capacity is essential to prevent millions of women from dying.
• The combination of external beam radiotherapy and brachytherapy can cure even advanced cervical cancer.
• Radiotherapy for cervical cancer needs to be included in national cancer control planning.
Brachytherapy resource assessment: Need for an international initiative

E. Zubizarreta¹, A. Polo¹, D. Rodin²

¹International Atomic Energy Agency - IAEA, Vienna, Austria
²Princess Margaret Hospital, Toronto, Canada
Overall Survival benefit in locally advanced cervical cancer

Total: 25% increase in Overall Survival from „no brachy“ to „2D brachy“ (Han) to „3D/4D brachy“ (RetroEMBRACE)

Han et al. IJROBP 2013, 87: 111-119
Sturdza et al. R&O 2016
### The Commonwealth (CON) in numbers

- **53 states (2.38 billion pop.)**
- **39 LMIC (2.24 billion pop.)**
- **31 small states (<1.5 million pop.)**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>LMIC</th>
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<tr>
<td>Cancer cases/y</td>
<td>2.4 million</td>
<td>1.7 million</td>
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<td>Access to radiotherapy (RT)</td>
<td>66%</td>
<td>46%</td>
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<td>Additional investment needed in RT</td>
<td>3.4 billion</td>
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<td>Cervical cancer cases/y</td>
<td>209,099</td>
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<td>Cervix RT cases/y</td>
<td>167,279</td>
<td>162,688</td>
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<tr>
<td>Additional HDR afterloaders needed</td>
<td>136</td>
<td>133</td>
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Strategy for a limited investment

- Cervical cancer is the 2\textsuperscript{nd} most common cancer in females in LMIC.
- Invasive cervical cancer is highly curable with a combination of external radiotherapy (RT) + brachytherapy (BT) + chemotherapy.
- Around 80% of cervical cancer cases require RT in LMIC. 75% of these require BT.
- We identified 70 RT centres without BT in CON-LMIC (57 in India and Bangladesh).

\[\text{Graph showing survival rates for different treatments}\]
In summary

✓ 70 RT centres in CON-LMIC lack brachytherapy
✓ The capital cost of a BT service in LMIC is around US$ 1 million
✓ Each HDR afterloader can deliver 2,000 fractions/y (666 patients)
✓ 450 cases/y can be cured
✓ The cost of BT is US$ 710 per patient in LMIC (+cost of external RT)
✓ 4,500 cervical cancer patients can be cured per HDR in 10 years
✓ **315,000 additional lives could be saved in 10 years** with a limited investment of US$ 70 million and an additional operating cost of US$ 331 million (US$ 33.1 million/y)
The recommendations for a collective action

✓ Make the collective commitment that by 2025 that every young girl in the Commonwealth will have access to HPV immunisation

✓ Negotiate an affordable price for HPV vaccines on behalf of some of the low and middle income states

✓ Provide faster access to the growing body of African research into cancer

✓ Strengthen prevention and early detection strategies in the Caribbean Commonwealth countries

I recognise that the recommendations are necessarily limited in scope and the point is made politely in the position paper that these four recommendations are only the beginning of what needs to be done for cancer patients. Across the Commonwealth LMICs, training and capacity building in areas such as registration, public/professional awareness building, screening, pathology, surgery, RT, nursing, palliative care urgently need attention.

json

Unfortunately it is evident that the Commonwealth is not yet in the position to agree to act collectively to address all, or any, of these bigger issues...
Kigali, Rwanda. 2 Elekta VMAT.
1304 cervical cancer cases/y. No brachytherapy...

Courtesy of Hugo Marsiglia
IAEA projects related to brachytherapy

- CRP-study on implementation of image guided HDR brachytherapy
- Education – curriculum for brachytherapy
- Health economics
- Quality management – audits of brachytherapy services
- Directory of radiotherapy centres - DIRAC
- IAEA TC INT project on cervical cancer
- UNJGP on Cervical Cancer Prevention and Control
  - 7 UN Agencies
  - 6 countries + 10 additional African countries
Conclusion

- Even with full implementation of HPV vaccination and screening, the number of cervical cancers will continue rising in the next 20 years.

- Radiotherapy, including brachytherapy, offers a high chance of cure even for locally advanced cervical tumours.

- Investment should not only go to prevention, but also to bring additional needed resources for adequate treatment.
Thank you for your attention!
Do you have any questions?

Contact details:
Eduardo Zubizarreta,
Head, Applied Radiation Biology and Radiotherapy Section, IAEA, Austria
e.zubizarreta@iaea.org
Brachytherapy in limited resource setting: Can Triaged Care provide equivalent outcomes

– The Tata Memorial Centre Experience

Supriya Sastri (Chopra)
Professor, Radiation Oncology, Tata Memorial Hospital (India)
Estimated National Burden-New Cancers - Female

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<tr>
<th>Site Name</th>
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Relative Reduction But Absolute Increase, Shortfall of Equipment and Skilled Manpower
Recommendations from Lead Radiotherapy Groups

- Preferential use of IMRT for EBRT (??)

- MRI Based Image Based BT.

- Resource Intensive and Expensive Processes (3-4 fold process cost)

- Lack of Roadmap of how high incidence regions (LMIC) will implement it.
27,000 women would not have access (or delayed access) to External Radiation
19,000 women will not have access (or delayed access) to Brachytherapy
What Additional Needs are There for BT in India.

Approx 40-45 Brachytherapy units: overall deficit is taken into account.

If geographical deficit is taken into account almost 80 BT units needed in India

With the current

27,000 women would not have access (or delayed access) to External Radiation

19,000 women will not have access (or delayed access) to Brachytherapy
CT and MRI Scan Availability: India

CT Scan Availability

MRI Scan Availability

No Data in Public Domain: WHO

Most of the Radiotherapy Centres have access to CT scanners

Source: WHO
• MRI Units/million population

20-51 Scanners/million population

India: 3 CT scanners/Million population
0.6 scanners/ million population

No. of CT & MRI Scans per 1 million of population

Huge upside for technical penetration

Courtesy: Harpal Singh, Fortis India Presentation 2013
Less Resource Intensive Procedures
2011-2014

USG-X Ray Based Procedures

CT-X Ray Based Procedures

CT Based Procedures

MRI Based Procedures

Mahantshetty, 2005, 2018
Can Triaged Care Provide Equivalent Outcomes

Patients with locally advanced cervical cancer (n=339)

External Radiation and Chemotherapy

- Complete Response
- Good Response in Parametrium

- Significant Residual disease in Parametrium
  - Advanced Resource Intensive Procedure MRI Based Procedures (N=17)
Selective use of Advanced MRBT in 10%

MR Based BT 100%

Resource Intensive

Less Resource Intensive

IJROBP, Mahantshetty et al
Tata 2017 (EMBRACE Cohort)

Mittal, Chopra, et al JGO
Tata 2017

N=339
Out of Clinical Trial Cohort Point A Based

N=100
TATA EMBRACE COHORT
Conclusion

- EBRT+ Brachytherapy is essential for cure of cervical cancer.

- Alternatives to advanced BT like ultrasound and CT lead to equivalent controls.

- Need to systematically investigate low cost technologies in regions of resource deficit.

- Resource mapping is needed to understand the feasibility of systematic BT implementation in high incidence regions.
Improving access to brachytherapy education using digital platforms

Dr Li Tee TAN
Consultant Oncologist
Cambridge University Hospitals, UK
Disclosure of interest

• Co-owner of Cambridge Medicine Online Limited
Challenges for healthcare education

- Increasing complexity of treatments
- Shorter working hours
- Limited study leave budgets

- Effectiveness?
  - Changes practice
  - Teaches transferable principles
  - Improves outcomes
E-learning

“Pros”
• Reach many
  – Any time, any where, any place
• Learn through practice and repetition
  – Unlimited case scenarios

“Cons”
• Expensive
  – Repackage factual information
  – High fidelity simulation tools
• Inferior to face-to-face instruction
  – Only suitable for theoretical knowledge
  – Cannot teach practical skills
EMBRACE-II international cervical cancer study

- Intensity modulated radiotherapy (IMRT)
- MRI based image-guided brachytherapy (IGBT)
EMBRACE-II international cervical cancer study

For expert centres practising high level radiotherapy
EMBRACE-II (66 centres, 25 countries)
Participation criteria

• Compliance questionnaire
  – Satisfactory clinical practice and infrastructure

• “Dummy runs” for radiotherapy quality assurance
  – Contouring
  – Dose planning
Radiotherapy protocol deviations were associated with a statistically significant decrease in overall survival ($p < 0.001$) and treatment failures ($p = 0.009$).
IMRT contouring dummy run

- One contouring case

**Contour online**
- Tumour volumes
- Normal organs

**Reviewed online**
- Two TMG members (Vienna, Aarhus, Utrecht, Leiden, Cambridge)
IMRT dose planning dummy run

• One dose planning case
Online education programme (all participants)

• Contouring
  – Two practice cases
  – Contouring atlas
  – Questionnaire (personal experience)

• Dose planning
  – Two practice cases
  – Questionnaire (personal experience)

• Quizzes
RTQA + CME programme (www.ccmo.co.uk)

• Open source learning management system
  – Automated registration
  – Track user activity

• Costs
  – Set-up £10,000
  – Annual £1,000
Addenbrooke’s Contouring Tool

• High fidelity online contouring tool
  – Functionality of clinical software
  – Three educational modes (self-study, workshop, exam)
  – Track user activity

• Costs
  – Development £100,000
  – Update ???
IMRT contouring evaluation

- 78 oncologists (66 centres, 25 countries)
  - 32 (41%) passed at first attempt
  - 33 (42%) one revision
  - 5 (6%) more than one revision
  - 8 (10%) awaiting resubmission

Duke, et al. ESTRO 37, Barcelona 2018
Average score at first attempt (maximum = 2)

2 = minimal discrepancy
1 = moderate discrepancy (clinically significant)
0 = major discrepancy

Tumour volumes
ITV-45 = compensation for organ motion

“New” concept
ITV-45 = compensation for organ motion

Q5 Do you currently use the concept of an ITV when contouring IMRT for cervix cancer?
CTV-T LR = uterus, parametrium, vagina

Conflicting guidelines
CTV-T LR = uterus, parametrium, vagina

- **GYN IMRT Consortium**
  - Medial edge of internal obturator muscle/ischial ramus
  - Can overlap with CTV-E (nodes)

- **EMBRACE II**
  - Medial edge of internal iliac and obturator vessels
  - Cannot overlap with CTV-E (nodes)
CTV-E = microscopic disease in lymph nodes

Change in practice?
CTV-E = microscopic disease in lymph nodes
IMRT CME uptake

- Quiz: 31.1% COMPLETED, 17.8% ACCESSED, 68.9% NOT ACCESSED
- Practice case 1: 24.4% COMPLETED, 57.8% ACCESSED, 42.2% NOT ACCESSED
- Practice case 2: 15.6% COMPLETED, 40.0% ACCESSED, 60.0% NOT ACCESSED
- Atlas & contouring guide: 100.0% ACCESSED
## Quiz 1

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50% 75% 52% 63% 75% 75% 67% 38% 88% 75%
A 75-year-old woman has a 3 cm adenocarcinoma with no uterine extension and no pathological nodes. Where should the superior border of the CTV-E be contoured?

Select one:
- A. Common iliac bifurcation
- B. Aortic bifurcation ✓
- C. Mid-sacroiliac joint
- D. Bottom of L5
- E. Top of L5

This patient is in the intermediate risk lymph node group because she has an adenocarcinoma. The superior border should therefore be at the aortic bifurcation.

Protocol reference: Table 9.1, pg 41.

The correct answer is: Aortic bifurcation
IMRT dose planning evaluation

- 67 submissions
  - 24 (36%) passed at first attempt
  - 23 (34%) one revision
  - 10 (15%) more than one revision
  - 10 (15%) awaiting resubmission

Seppenwoolde, et al. (manuscript submitted)
IMRT dose planning evaluation

Passed plans (57)

Minor revisions (21)

Major revisions (33)

Conformality

- Passed
- Passed, improvement possible
- Minor
- Major
- Wrong/missing
Conformality

• New concept
  – To reduce dose to bowel and bladder

• Change in practice
  – Achieved by relaxing coverage criteria for planning target volume
Clinical impact

Dose to bowel
What we have learnt

- Not sufficient to just provide educational content
- Cannot make assumptions about learning needs
- Causes of discrepancies multifactorial
Good contouring

• Image interpretation

• Conceptual understanding
  – New concepts

• “Mental models”
  – Change in practice
“Learn from learners”

- Check prior knowledge & experience
- Create learning activities
- Adapt learning activities
- Monitor user activity & performance
Mini-Contour

- Low fidelity tool
  - Essential functionality
  - Selected slices
- <5 mins per exercise

- Instant feedback on contours to users

Patient: FIGO IIb Cervix SCC
Involvement:
Anterior vaginal involvement
Distal parametrium
Hydronephrosis
Treatment:
Standard EBRT + Brachytherapy
BT: Vienna II

-> Please contour the GTV on the marked slice

Cost <£1,000

Comments from users
Education research

- **Acceptability**
  - User uptake and surveys

- **Assessments**
  - Automated
  - Significance of discrepancies

- **Feedback**
  - Reference contours
  - “Hot spots”

- **Learning environment & content**
  - Self-study, online, live
  - Number of practice cases
  - Delivery (lectures, webinars, video, quizzes, high/low fidelity tools)

- **Integrated**
  - “Living protocol”
E-learning

“Pros”

- Reach many
  - Any time, any where, any place
- Learn through practice and repetition
  - Unlimited case scenarios
- Encourage participation
  - Blended learning
  - Deadlines
  - Gamification
  - Incentives

“Cons”

- Expensive
  - Repackage factual information
  - High fidelity simulation tools
- Inferior to face-to-face instruction
  - Only suitable for theoretical knowledge
  - Cannot teach practical skills
- Inexpensive
  - Existing sources of information & assessments
  - Low fidelity tools
- Can teach practical skills
Thank you for your attention