Contact radiotherapy (Papillon) for rectal cancer

Arthur Sun Myint
Lead clinician (Papillon)
Hon. Professor in Gastroenterology
The University of Liverpool
sun.myint@clatterbridgecc.nhs.uk

SPECC
Significant Polyp & Early Colorectal Cancer

Education Centre, Good Hope Hospital, Birmingham 13th May 2016
Background

• When malignancy is identified in a polyp completion surgery is offered as this is still the gold Standard of care
• Annually 9,433 rectal cancers treated by radical resection in the UK 42 %were either pT1 or pT2
• 66% were node negative
Background

- Surgery is still the gold Standard of care
- 77% those operated on underwent major resection either APER or AR (TME)
- Only 11% were locally excised
- For early rectal cancer this approach is an over treatment
- We should not offer the same standard of surgical care for all patients with rectal cancer
WHY? - Personalised treatment

- There is increase in ageing population
- There is recognition of harm from extirpative surgery especially in elderly patients
- Earlier staged cancers are been increasingly diagnosed through National bowel cancer screening programme.
- Disease stage is changing, therefore, the concepts for management of rectal cancer treatment should changed to reduce the harm from surgery.
UK’s ageing population on the rise

Mortality & morbidity in the Elderly

Mortality 14 - 25%
Morbidity 40 - 50%
Worse with higher ASA grades

Obese

Medical co-morbidity

Fiaz O et al. Colorectal Disease (2011) 14: 1175-1182

Courtesy of Mr Simon Bach
Screen Detected Tumors by Stage

Started 2009

Stage A - polyp 22%
Stage A 26%
Stage B 25%
Stage C 26%
Stage D 1%

Polyp cancer 22%

Dukes A 48%

2500 rectal polyp cancers

This is a reality and not a dream

North West screening data

Courtesy of Prof Paul O’Toole 2012
Variations in APR rates (NHS trusts in England) 1998-2004

Time to Intervene?

27.4% of Dukes’ A had APR
4.6% of Dukes’ A had Hartmann’s
32% of Dukes’ A had stoma

E Morris, P Quirk, B Cottier et al Gut (2008)57: 1690-1697
The standard of Care for Rectal Cancer

**The Good**
- T1/T2/T3a
- N0/M0
- <3cm
- Mobile polyp

**The Bad**
- T3b <5mm
- N1/M0
- >3cm
- CRM(-) ive

**The Ugly**
- T3c+/T4
- N2/M0
- >3cm
- CRM (+) ive

Not all pts suitable for surgery

They might not want surgery
32% of Dukes’ A had APER

Time to rethink?

Early rectal cancer

Advanced rectal cancer
Time to rethink?

So, what is the alternative option?
Contact X-ray Brachytherapy

Time to rethink?

Polyp cancers

Papillon

Prof Bill Heald

Prof Jean Papillon - Lyon (1914-1993)

Minimally invasive topical radiotherapy
Selection Criteria

Patients not suitable for surgery or refuse surgery

• Rectal adenocarcinoma (early cancer) low risk
• Stage cT1 or cT2 (cT3a) confine to bowel wall
• <3cm (one third of circumference or less)
• Histologically- well to mod. differentiated
• Clinically - Mobile exophytic tumour
• Within 12cm from anal verge
• Staging- MRI (rT1/T2/T3a) / uT1(EUS)
• No suspicious lymph nodes (N0)
Exclusion Criteria

Patients not suitable for radical curative radiotherapy

- Poorly differentiated adenocarcinomas
- Mucinous tumours
- Lympho vascular invasion - LVI(+)
- Suspicious lymph nodes
- Deeply ulcerative fixed tumours
- Large tumour >50% of circumference
Contact RT delivers low energy, high dose (30Gy) small volume targeted radiation directly on the rectal tumour and kill cancer cells layer by layer at each treatment sessions every 2 weeks X 3
“Papillon RT50” contact radiotherapy machine
Treatment set up

Treatment time 1 minute

Day patient
30mm polyp cancer
Regressed by >50%
No residual tumour visible or palpable

Response sustained
Select responders after treatment

Good responders - No residual - Wait & Watch
Partial responders - Small residual - TEMS
Poor responder - Residual disease - TME

No useful molecular bio predictive markers identified yet
University of Liverpool ‘Translational research’- genetic profile / proteonomics

Sun Myint et al Clin Oncol Vol. 19 No 9 Nov 2007
Side Effects

2009-2011 (n=100)

Acute

- Proctitis (2 patients have pain)
- Radiation ulcer (27%)

Late

- G1/G2 Bleeding - 38% (Argon 10%)
- Stenosis 0% (1% in initial cohort)
- Fistula 0% (1% in initial cohort)
- No treatment related mortality

Sun Myint A et al. Colorectal Disease (2013) Poster
## Results (T1/T2 rectal cancer)

<table>
<thead>
<tr>
<th>Country</th>
<th>Sex</th>
<th>No</th>
<th>LC</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAPILLON</td>
<td>F</td>
<td>312</td>
<td>91%</td>
<td>85%</td>
</tr>
<tr>
<td>GERARD</td>
<td>F</td>
<td>106</td>
<td>87%</td>
<td>78%</td>
</tr>
<tr>
<td>MAINGON</td>
<td>F</td>
<td>15</td>
<td>81%</td>
<td>67%</td>
</tr>
<tr>
<td>SISCHY</td>
<td>USA</td>
<td>227</td>
<td>95%</td>
<td>92%</td>
</tr>
<tr>
<td>DE GARAC</td>
<td>Canada</td>
<td>55</td>
<td>84%</td>
<td>87%</td>
</tr>
<tr>
<td>MYERSON</td>
<td>USA</td>
<td>199</td>
<td>80%</td>
<td>86%</td>
</tr>
<tr>
<td>MENDENHALL</td>
<td>USA</td>
<td>34</td>
<td>85%</td>
<td>90%</td>
</tr>
<tr>
<td>SCHILD</td>
<td>USA</td>
<td>20</td>
<td>90%</td>
<td>76%</td>
</tr>
<tr>
<td>SUN MYINT</td>
<td>UK</td>
<td>242</td>
<td>89%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Sun Myint et al Clinical Oncology (2007);19:9
# Results

Malignant Polyp (T1) local excision + post op Papillon

<table>
<thead>
<tr>
<th>Institution</th>
<th>N° Pts</th>
<th>Age</th>
<th>pTis</th>
<th>pT1</th>
<th>pT2</th>
<th>Loc Rec</th>
<th>3y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nice 2010-2014</td>
<td>12</td>
<td>73</td>
<td>1</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>95%</td>
</tr>
<tr>
<td>Clatterbridge 2009-2012</td>
<td>123</td>
<td>70</td>
<td>0</td>
<td>99</td>
<td>24</td>
<td>3</td>
<td>67%</td>
</tr>
<tr>
<td>Hull 2011-2014</td>
<td>18</td>
<td>71</td>
<td>0</td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Guilford 2014</td>
<td>4</td>
<td>68</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Nottingham 2014</td>
<td>6</td>
<td>72</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>93%</td>
</tr>
<tr>
<td>Mâcon 2011-2014</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Villeurbanne 2011-2014</td>
<td>3</td>
<td>76</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>166</strong></td>
<td><strong>72</strong></td>
<td><strong>2</strong></td>
<td><strong>137</strong></td>
<td><strong>37</strong></td>
<td><strong>3%</strong></td>
<td><strong>98%</strong></td>
</tr>
</tbody>
</table>

ICONE Group (CONTEM data base)
# Results

## T2-T3 cancers: Papillon + EBRT(CRT)

<table>
<thead>
<tr>
<th>Institution</th>
<th>N° Pts</th>
<th>Age</th>
<th>T2</th>
<th>T3</th>
<th>cCR</th>
<th>Loc Rec</th>
<th>Org pres</th>
<th>3yS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nice 2010-2014</td>
<td>16</td>
<td>84</td>
<td>10</td>
<td>6</td>
<td>16</td>
<td>1</td>
<td>15(93%)</td>
<td>70%</td>
</tr>
<tr>
<td>Clatterbridge 2009-2012</td>
<td>128</td>
<td>71</td>
<td>57</td>
<td>71</td>
<td>81</td>
<td>11</td>
<td>104(81%)</td>
<td>72%</td>
</tr>
<tr>
<td>Hull 2011-2014</td>
<td>35</td>
<td>78</td>
<td>30</td>
<td>5</td>
<td>32</td>
<td>3</td>
<td>32(91%)</td>
<td>91%</td>
</tr>
<tr>
<td>Guilford 2014</td>
<td>26</td>
<td>75</td>
<td>18</td>
<td>8</td>
<td>23</td>
<td>1</td>
<td>23(88%)</td>
<td></td>
</tr>
<tr>
<td>Nottingham 2014</td>
<td>20</td>
<td>76</td>
<td>6</td>
<td>14</td>
<td>16</td>
<td>1</td>
<td>17(85%)</td>
<td></td>
</tr>
<tr>
<td>Mâcon 2011-2014</td>
<td>14</td>
<td>70</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>3</td>
<td>9(64%)</td>
<td>78%</td>
</tr>
<tr>
<td>Villeurbanne 2011-2014</td>
<td>8</td>
<td>75</td>
<td>6</td>
<td>2</td>
<td>8</td>
<td>1</td>
<td>7(87%)</td>
<td>87%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>247</td>
<td>75</td>
<td>133</td>
<td>114</td>
<td>87%</td>
<td>11%</td>
<td>81%</td>
<td>78%</td>
</tr>
</tbody>
</table>

ICONE Group (CONTEM data base)
# Effect of dose escalation with external beam RT

<table>
<thead>
<tr>
<th>RT Dose</th>
<th>40Gy (n=46)</th>
<th>46Gy (n=52)</th>
<th>50Gy (n=36)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>13%</td>
<td>21.2%</td>
<td>30.6%</td>
<td>0.15</td>
</tr>
<tr>
<td>LRFS</td>
<td>77%</td>
<td>89.8%</td>
<td>91.3%</td>
<td>0.036</td>
</tr>
<tr>
<td>Complications</td>
<td>12.5%</td>
<td>25%</td>
<td><strong>39.4%</strong></td>
<td>0.009</td>
</tr>
</tbody>
</table>

Wiltshire et al. I.J. Rad Oncol Biol Phys Vol 60 ;No1 ;Sup 2004 abstract. 1061
### Tumour control probability (EBCRT vs EBCRT + CXB)

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Initial response</th>
<th>Organ preservation</th>
<th>Regrowth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habr Gama (2014)</td>
<td>90/183</td>
<td>49%</td>
<td>37% (68/183)</td>
<td>31%</td>
</tr>
<tr>
<td>Apelt (2015)</td>
<td>40/51</td>
<td>78%</td>
<td>NA</td>
<td>26%</td>
</tr>
<tr>
<td>Renahan (2015)</td>
<td>129(cCR)</td>
<td>15%</td>
<td>NA</td>
<td>38%</td>
</tr>
<tr>
<td>Sun Myint (2015)</td>
<td>136/200</td>
<td>68%</td>
<td>83% (166/200)</td>
<td>11%</td>
</tr>
</tbody>
</table>

2. Apelt et al. Lancet Oncology (2015); 16(8):919-927
4. Sun Myint et al. (in preparation)
Radiation Dose-Response Model (EQD 2)

Veijle group (n=222)
Brachytherapy boost

ypCR (TRG 1)
EBRT + Brachy Ir
D 50% = 92 Gy
[79-145] 95% CI
We need evidence
We need evidence

**OPERA** (phase II randomised trial)

**Inclusion**
- cT2/cT3a/cT3b
- No/N1
- Size <5cm

**Hypothesis**
- 20% difference in organ preservation between Arm A and Arm B

**End point**
- Organ preservation (3yrs)

**Mid /Low rectal cancer**

- **Arm A**
  - EBCRT + EBRT boost
  - Assessment at 14 weeks
    - cCR ‘Watch & Wait’
    - TEMS for PR

- **Arm B**
  - EBCRT + Papillon boost
  - TEMS for PR
  - TME for NR
UK NCRI Rectal Trials Portfolio

Rectal Cancer

The Good
T1/T2/ N0 <3cm
TREC

The Bad
T3cCRM(-) N1
COPERNICUS
BACCUS

The Ugly
T3/T4CRM(+) N2
ARISTOTLE

OPERA (<5cm T2/T3a T3b N0 /N1)
Multi disciplinary team meeting

Doctors Knows Best

MDT

Shared decision making with patients

Informed Consent

No patient involvement

Age
PS
comorbidity

“No decisions about me without me”
Patient’s Choice

"I'M SORRY DOCTOR, BUT AGAIN I HAVE TO DISAGREE."
Some patients do prefer a box than a bag
The Future

Must learn to think outside the box

- Training
- Governance
- Guidelines
- Protocols

Advances in Technology
New Innovations
- TEMS
- Papillon
New Concepts in treatment
  Minimally invasive - Less Harm

Change in stage of disease
  50% early stage (25% polyps)

Standard of Care
Rectal Cancer - “When not to operate”
Evolving concepts in rectal cancer management

An International Consensus Meeting Champalimaud Foundation
February 2014 Lisbon
October 2014 Milan
March 2015 Basingstoke

Heald et al. Consensus statement. Colorectal Disease(2014);16:334-36
Low-energy contact X-ray brachytherapy (the Papillon technique) for early-stage rectal cancer

Issued: September 2015

NICE interventional procedure guidance 532
guidance.nice.org.uk/ipg532

NICE IP Guidance 532(2015)
1 Recommendations

1.1 In patients for whom surgery is not considered suitable, current evidence on the efficacy and safety of low-energy contact X-ray brachytherapy (CXB; the Papillon technique) for early-stage rectal cancer is adequate to support the use of this procedure, provided that normal arrangements are in place for clinical governance, consent and audit.

1.2 In patients for whom surgery is considered suitable, but who choose not to have an operation, the evidence on safety is adequate but the evidence on efficacy is inadequate. Therefore this procedure should only be used for these patients with special arrangements for clinical governance, consent and audit or research.
NICE Care pathway for Stage 1 rectal cancer

Managing local colorectal tumours:

1. Patient with diagnosed colorectal cancer

   1. Patients with resectable primary rectal tumours
   4. Patients with unresectable or borderline resectable colon or rectal tumours

   1. Information about stage 1 rectal cancer

   5. Treatment options

   5. Non surgical option
   7. Surgery to remove resectable tumours

6. Deciding whether to offer further treatment

   8. Ongoing care and support

NICE Colorectal Guidelines (2016)
Proposal for Contact radiotherapy

• Low risk early rectal cancer (<6cm) cT1/cT2/cT3a
• Small mobile cancers (<3cm)
• Elderly patients (80+ years)
• Younger patients with high surgical risk (CPX)
• No suspicious Lymph nodes
• Discuss at early rectal cancer MDT
• Offer patient treatment options after MDT

www.clatterbridgecc/professionals/papillon training course
Centres with Papillon facility in the UK

- Clatterbridge 1993
- Hull 2010
- Guildford 2014
- Nottingham 2014
- London
- Wolverhampton
- Devon
- Cardiff
- Colchester
- Newcastle

Hull team started 2010

Clatterbridge Papillon training courses started 2010 and runs annually in October
Treatment Options

It is another fine balance - Life changing

Benefits
- Cure
  Not at any cause
- Survival
  QOL-Living beyond cancer

Harm
- Recurrence
- Death
- Complications

2cmT2 N1M0
MDT
Conclusions

• CXB (Papillon) boost reduced local recurrence to 11.7% after achieving cCR compared to 30-40% in those who had EBCRT alone.

• Organ preservation of 86% for the whole group is much higher than any ‘watch and wait’ studies published so far.

• A randomised trial OPERA has been set up to evaluate this further.
Conclusions

• Papillon has acceptable toxicity and is now recommended by NICE for patients not suitable for surgery.
• Papillon should be consider as a treatment option for elderly patients with early rectal cancer.

NICE IP Guidance 532(2015)
Take home message

• Avoid extirpative surgery in elderly patients with early rectal cancer. Consider Papillon first.
• Explain & offer treatment options to the patients
• Patients prefer to avoid surgery and a stoma if they have a choice for their treatment.

Please give patients a choice?
Thank You

Arthur Sun Myint
Lead clinician
Hon. Professor
The University of Liverpool

sun.myint@clatterbridgecc.nhs.uk