

Intraoperative Radiotherapy in times of individualized medicine:

**opportunities to combine high-precision radiation technologies**

***2014 ISIORT update vision focused on electrons***



***Prof. Dr. Felipe A. Calvo  
Hospital General Universitario Gregorio Marañón  
Madrid, Spain***



***3 decades after...***

***An special tribute to Prof. Dr. Luther W. Brady***

Peter P. Yu ASCO President 51th... Messages

## **“Illumination and innovation: transforming data into learning”**

- Best clinical results = Best personal (values) results
- 30% non-USA members: diversity
- Money and politics = affordable individualized medicine

ASCO 2014 “Science and Society”



# Van der Schueren Award 2011...



3 years after...



Is radiotherapy...

Is precise radiotherapy...

Is a precise component of RT for dose-escalation...

Is an efficient alternative for RT dose-de-escalation...

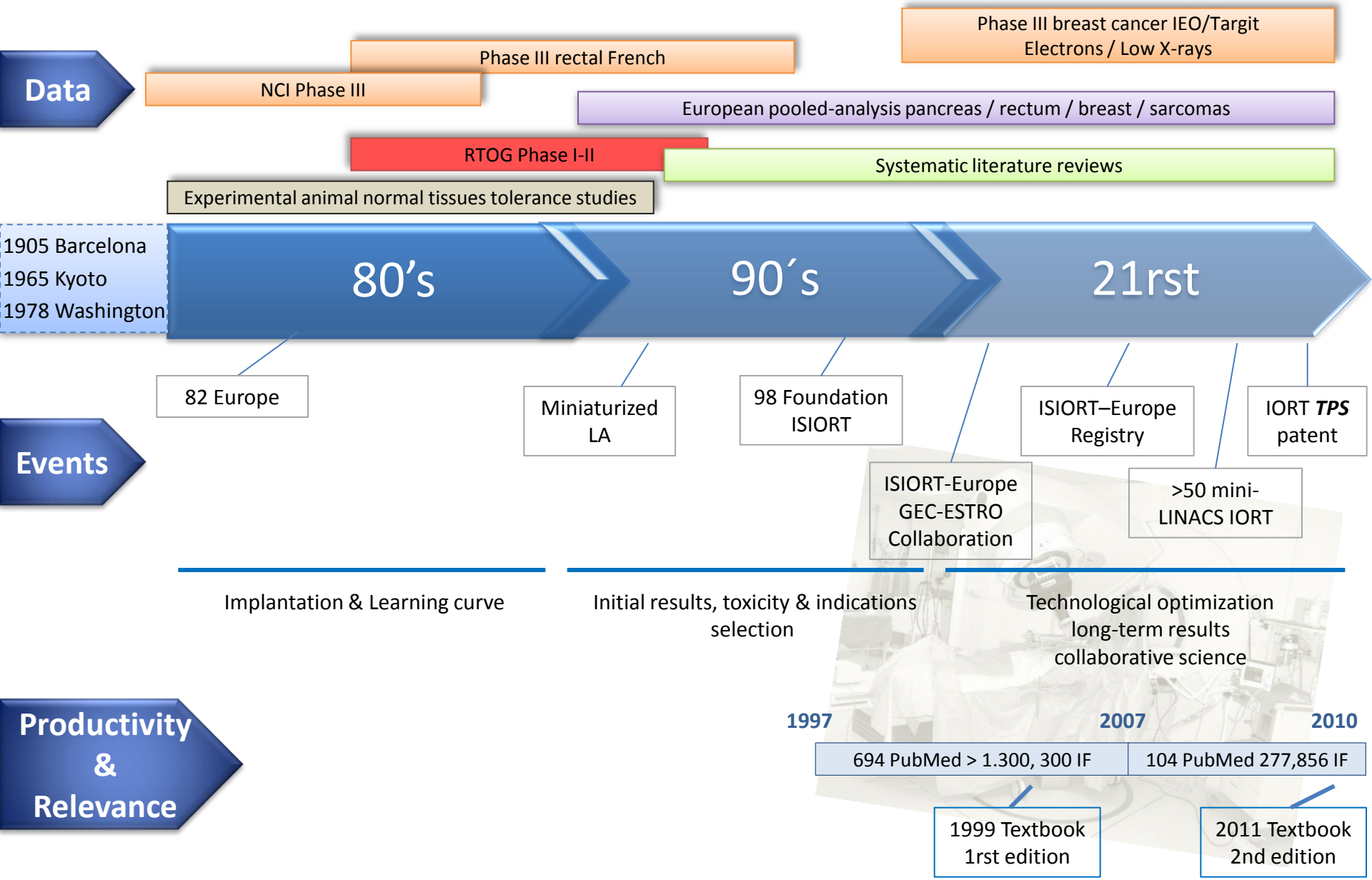
Adds a radiobiological safety margin to surgical resection...

Does not interfere with systemic therapy





# Historical Perspective

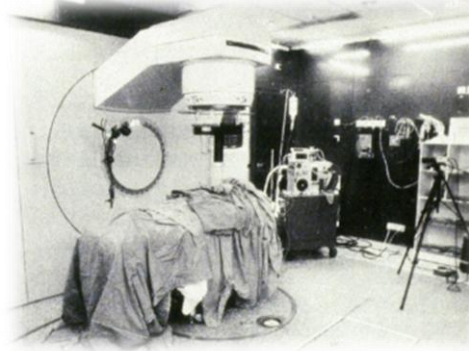
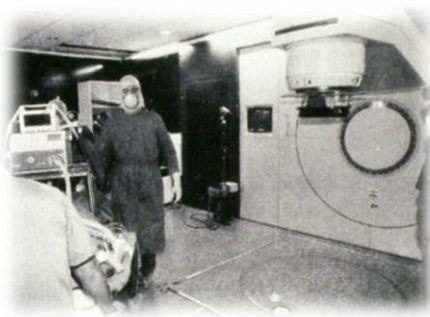
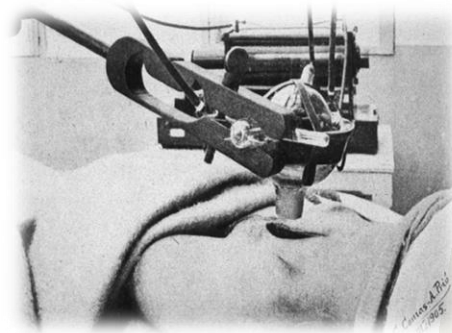


The Past

The present

The future

- Tissue tolerance knowledge
- Standardization procedures (Surgery + Radiotherapy)
- Patient transportation

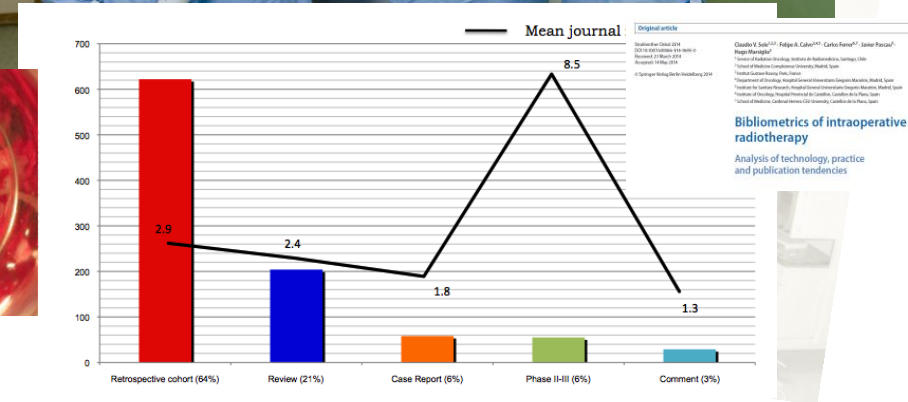
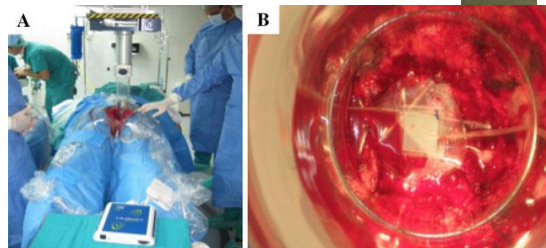
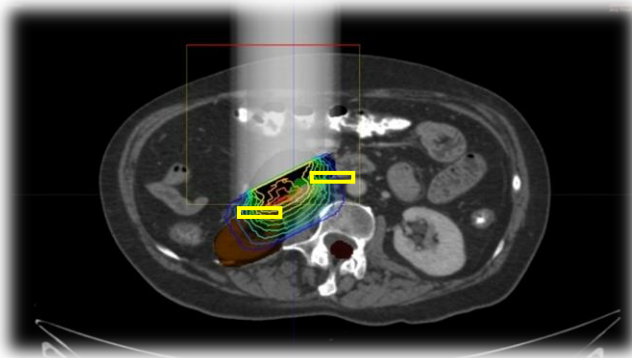


The past

The Present

The future

- Miniaturized IORT dedicated technology
- Virtual TPS IORT, *in vivo* dosimetry... (radio-surgical specific elements)
- Dose-escalation vs Dose-de-escalation alternatives trials



IORT...

Is radiotherapy... *feasible and tolerable*

Is precise radiotherapy... *able to be planned and registered*

Is a precise component of RT for dose-escalation...

*50Gy + 10/15Gy IORT LC >90% R0*

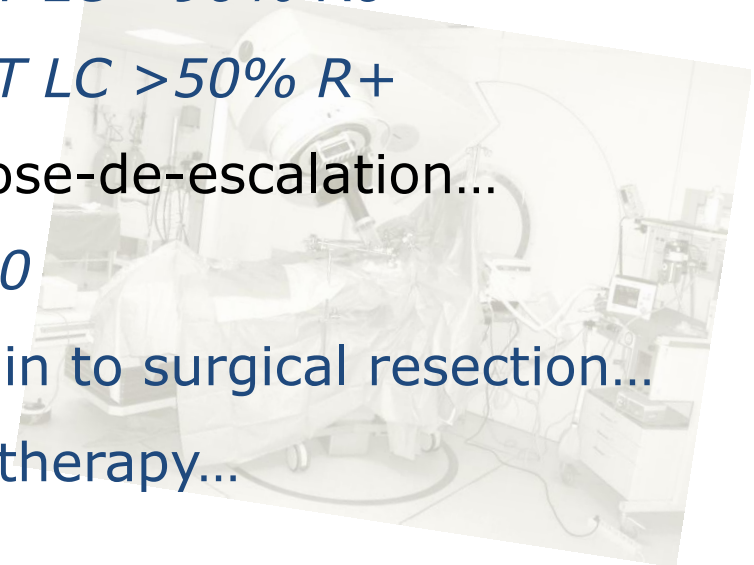
*50Gy + 10/15Gy IORT LC >50% R+*

Is an efficient alternative for RT dose-de-escalation...

*20-21Gy LC >95% R0*

Adds a radiobiological safety margin to surgical resection...

Does not interfere with systemic therapy...





The past

The present

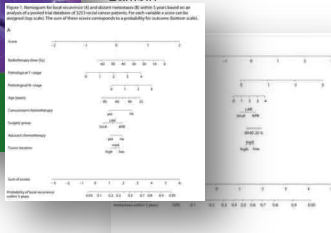
The Future

- Tailored / individualized oncology & IORT
  - Nomogram guided IORT
  - Molecular guided IORT
- "Making friends": IMRT/IGRT + IORT (super-hypofractionated RT)



A META-ANALYSIS OF SIX EUROPEAN TRIALS TO DEVELOP VALIDATED NOMOGRAMS FOR THE PREDICTION OF LOCAL CONTROL, DISTANT METASTASES AND SURVIVAL FOR LOCALLY ADVANCED RECTAL CANCER PATIENTS AFTER LONG COURSE CHEMORADIOTHERAPY

V. Vincenzo<sup>1</sup>, R. van Stiphout<sup>2</sup>, G. Lammering<sup>2</sup>, M. A. Gambacorta<sup>4</sup>, M. C. Barba<sup>4</sup>, K. Bujko<sup>5</sup>, M. Bebenek<sup>6</sup>, L. Cionini<sup>7</sup>, A. Sainato<sup>7</sup>, C. Rödel<sup>8</sup>, R. Sauer<sup>9</sup>, F. Bonnetain<sup>10</sup>, J. P. Gérard<sup>11</sup>, J. F. Bosset<sup>12</sup>, L. Collette<sup>13</sup>, P. Lambin<sup>2</sup>



Breast Cancer Res Treat (2010) 124:141–151  
DOI 10.1007/s10550-010-1115-5

CLINICAL TRIAL

**Intraoperative radiotherapy during breast conserving surgery: a study on 1.822 cases treated with electrons**

Umberto Veronesi · Roberto Orvieto · Alberto Lani · Viviana Galimberti · Stefano Zarrida · Mattia Intra · Paolo Veronesi · Paolo Arnone · Maria Cristina Leonard · Mario Cicca · Roberta Lazari · Pietro Caldarella · Nicole Rotunno · Claudio Sangalli · Fiorella Sances · Patrick Matsuyama

original article

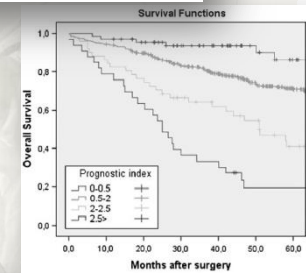
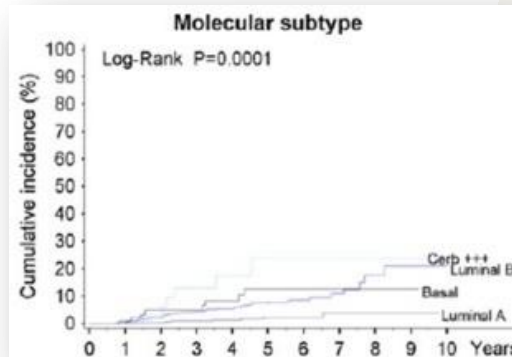
Annals of Oncology 21: 1279–1284, 2010  
doi:10.1093/annonc/mdk001  
Published online 4 November 2009

**Results of European pooled analysis of IORT-containing multimodality treatment for locally advanced rectal cancer: adjuvant chemotherapy prevents local recurrence rather than distant metastases**

M. Kusters<sup>1</sup>, V. Valentini<sup>2</sup>, F. A. Calvo<sup>3</sup>, R. Krumpal<sup>4</sup>, G. A. Nieuwenhuijzen<sup>5</sup>, H. Martijn<sup>6</sup>, G. B. Doglietto<sup>7</sup>, E. dal Valle<sup>8</sup>, F. Floeder<sup>9</sup>, M. W. Buchler<sup>10</sup>, C. J. H. van de Velde<sup>11</sup> & H. J. T. Platten<sup>1\*</sup>

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Received 19 March 2009; revised 13 September 2009; accepted 17 September 2009



Prognostic index = (age over 70 years > yes: 0.60, no: 0)  
+ (male gender > yes: 0.36, no: 0)  
+ (any downstaging > yes: 0, no: 0.30)  
+ (LN positivity > yes: 0.86, no: 0)  
+ (margin positivity > yes: 0.70, no: 0)  
+ (aCT > yes: 0, no: 0.64).

Published Ahead of Print on July 11, 2011 as 10.1200/JCO.2010.33.1595  
The latest version is at <http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2010.33.1595>

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Nomograms for Predicting Local Recurrence, Distant Metastases, and Overall Survival for Patients With Locally Advanced Rectal Cancer on the Basis of European Randomized Clinical Trials

Vincenzo Valentini, Royal G.P.M. van Stiphout, Guido Lammering, Maria Antonietta Gambacorta, Maria Cristina Barba, Marek Bebenek, Frank Bonnetain, Jean-François Bosset, Krzysztof Bujko, Luca Cionini, Jean-Pierre Gérard, Claus Rödel, Aldo Sainato, Rolf Sauer, Bruce D. Sainato, Lawrence Collette, and Philippe Lambin



- Tailored / individualized oncology & IORT
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 0360-3015/06/\$18.00

doi:10.1016/j.ijrobp.2005.09.028

**CLINICAL INVESTIGATION** Rectum

**PROGNOSTIC FACTORS FOR DISEASE-FREE SURVIVAL IN PATIENTS WITH T3-4 OR N+ RECTAL CANCER TREATED WITH PREOPERATIVE CHEMORADIATION THERAPY, SURGERY, AND INTRAOPERATIVE IRRADIATION**

JUAN A. DÍAZ-GONZÁLEZ, M.D., PH.D.,<sup>1,2</sup> FELIPE A. CALVO, M.D., PH.D.,<sup>3</sup> JAVIER CORTÉS, M.D., PH.D.,<sup>4</sup> JOSÉ L. GARCÍA-SABIDO, M.D., PH.D.,<sup>5</sup> MARINA GÓMEZ-ESPI, M.D.,<sup>6</sup> EMILIO DEL VALLE, M.D.,<sup>7</sup> FERNANDO MÚÑOZ-JIMÉNEZ, M.D.,<sup>1</sup> AND EMILIO ÁLVAREZ, M.D., PH.D.<sup>1</sup>

original article

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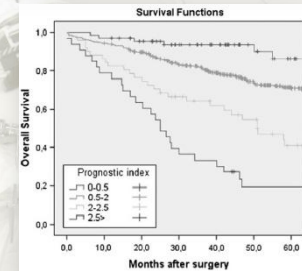
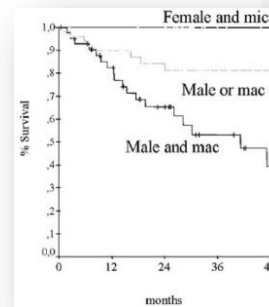
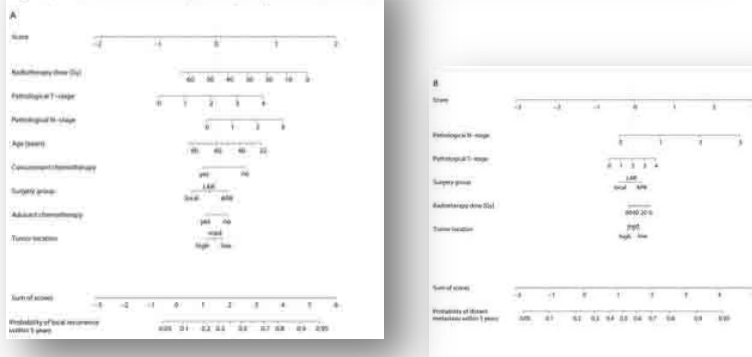
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Figure 1. Nomogram for local recurrence (A) and distant metastases (B) within 5 years based on an analysis of a pooled trial database of 3253 rectal cancer patients. For each variable a score can be assigned (top scale). The sum of these scores corresponds to a probability for outcome (bottom scale).

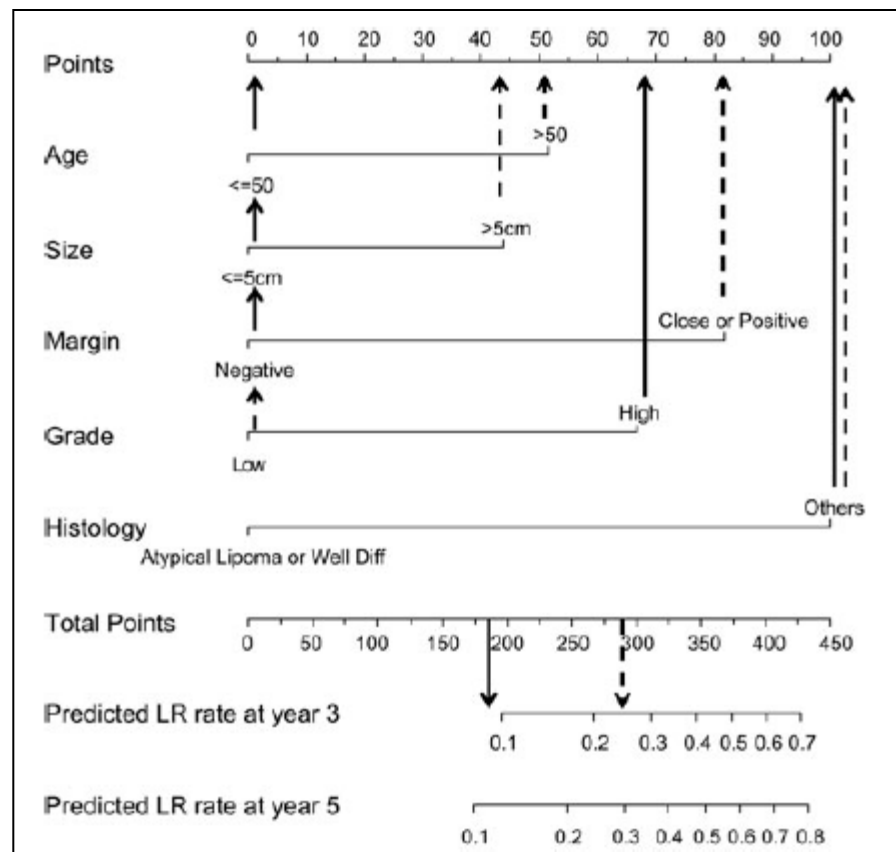


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## A Postoperative Nomogram for Local Recurrence Risk in Extremity Soft Tissue Sarcomas After Limb-Sparing Surgery Without Adjuvant Radiation

Oren Cahlon, MD,\* Murray F. Brennan, MD,† Xiaoyu Jia, MS,‡ Li-Xuan Qin, PhD,‡ Samuel Singer, MD,† and Kaled M. Alekhtiar, MD\*



(*Ann Surg* 2012;255:343–347)

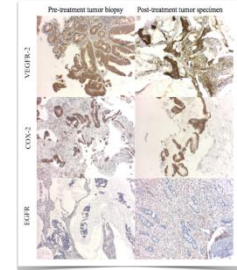
**FIGURE 4.** Two hypothetical cases. Case #1 (solid arrows) where total points were 167 based on age <50, size <5 cm, negative margin, but high grade histology yielding a predicted LR at 3 years <10%. Compared to case #2 (dashed arrows) where total points were 278 yielding a predicted 3 year LR that is 25%.

The past

The present

The Future

- Tailored / individualized oncology & IORT
  - Nomogram guided IORT
  - Molecular guided IORT
- "Making friends": IMRT/IGRT + IORT (super-hypofractionated RT)

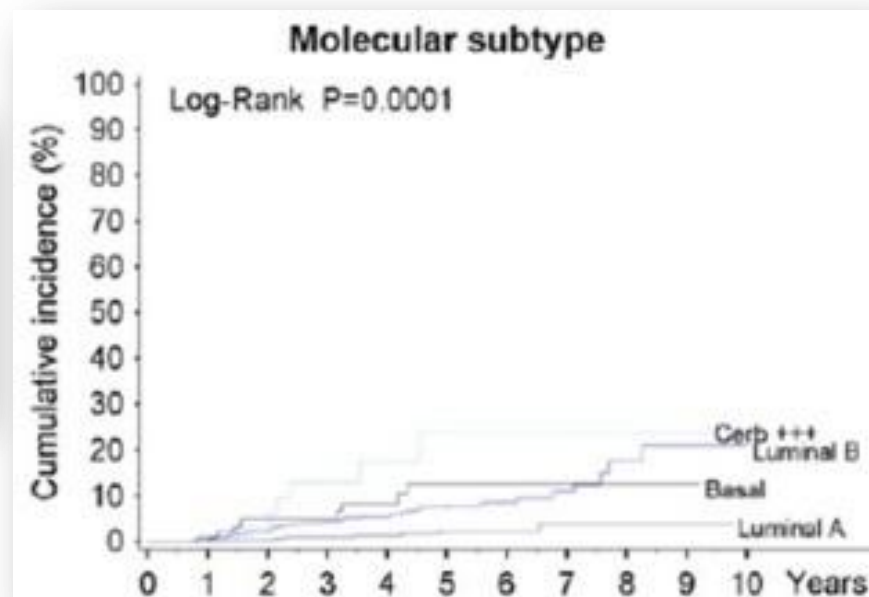


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CLINICAL TRIAL

## Intraoperative radiotherapy during breast conserving surgery: a study on 1,822 cases treated with electrons

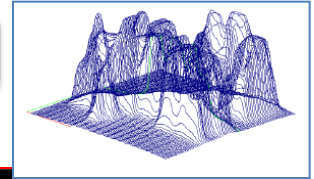
Umberto Veronesi · Roberto Orecchia · Alberto Luini · Viviana Galimberti ·  
Stefano Zurrada · Mattia Intra · Paolo Veronesi · Paolo Arnone ·  
Maria Cristina Leonardi · Mario Ciocca · Roberta Lazzari · Pietro Caldarella ·  
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The past

The present

The Future

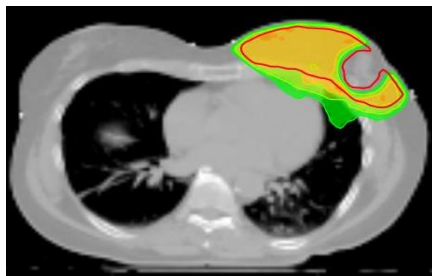
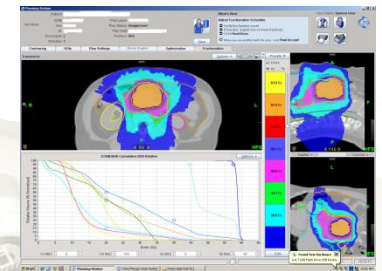
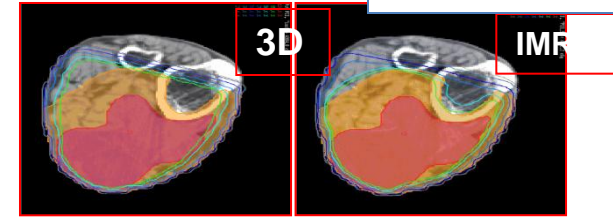


- Tailored / individualized oncology & IORT

- Nomogram guided IORT

- Molecular guided IORT

- "Making friends": IMRT/IGRT + IORT (super-hypofractionated RT)



Patient selection: based on... treatment options? ... risk?...



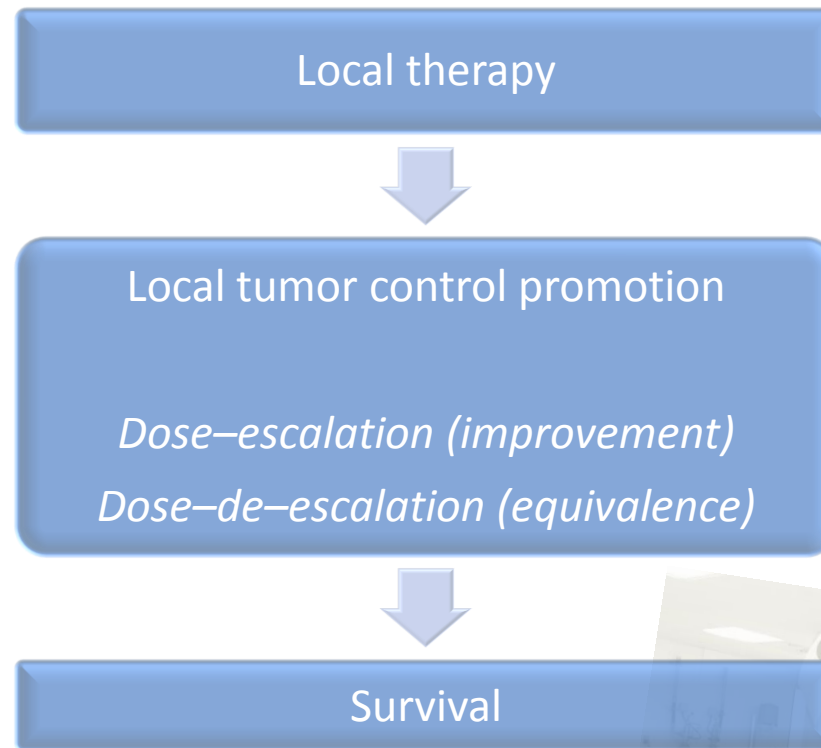


# IORT options in times of technological high-precision revolution

*Clinical opportunities...*



# Academic contribution: multidisciplinary oncology



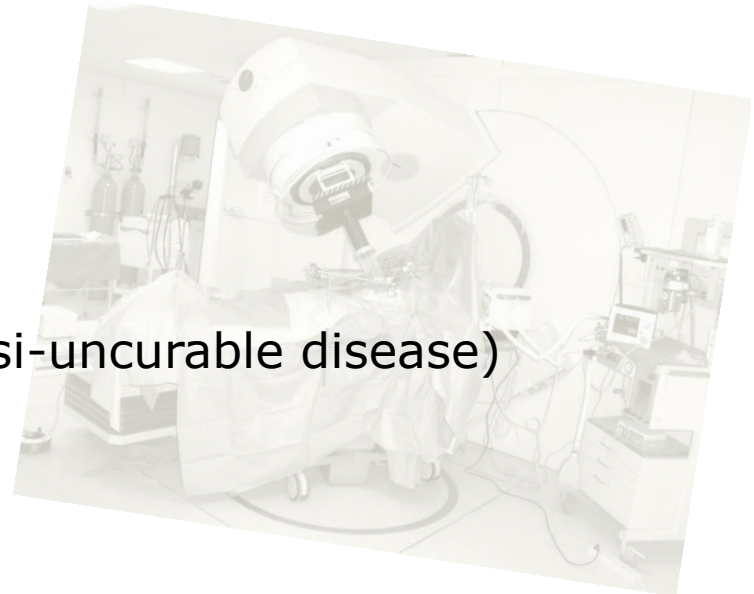
- Topography of intensification
- Dose-dense radiotherapy (shorter treatment time)
- Normal tissue tolerance balance



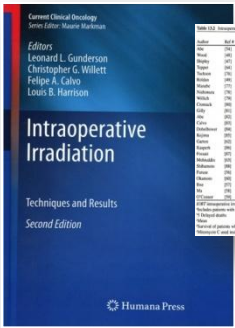


***iORT is a precise boost to be combined with high-precision RT***

- Pancreatic cancer (cuasi-uncurable disease)
- Esophago gastric
- Locally advanced rectal cancer
- Soft tissue sarcomas
- Breast cancer
- Mono-oligotopic recurrent cancer (cuasi-uncurable disease)



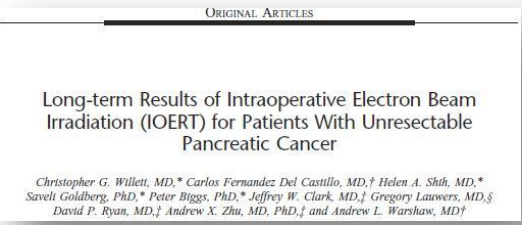
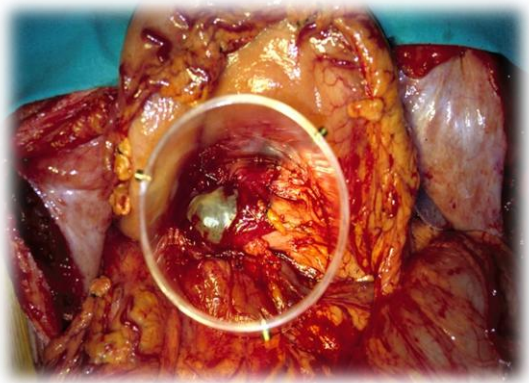
# IORT Results: Locally advanced unresectable pancreatic cancer



| Author | Institution | No. of Patients | Median Survival (months) | 1-Year Survival (%) | 2-Year Survival (%) | 3-Year Survival (%) | 4-Year Survival (%) | 5-Year Survival (%) |
|--------|-------------|-----------------|--------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| 1      | 1           | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 2      | 2           | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 3      | 3           | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 4      | 4           | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 5      | 5           | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 6      | 6           | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 7      | 7           | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 8      | 8           | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 9      | 9           | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 10     | 10          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 11     | 11          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 12     | 12          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 13     | 13          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 14     | 14          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 15     | 15          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 16     | 16          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 17     | 17          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 18     | 18          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 19     | 19          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 20     | 20          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
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| 22     | 22          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 23     | 23          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 24     | 24          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 25     | 25          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 26     | 26          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 27     | 27          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 28     | 28          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 29     | 29          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 30     | 30          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 31     | 31          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 32     | 32          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 33     | 33          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 34     | 34          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
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| 36     | 36          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 37     | 37          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 38     | 38          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
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| 42     | 42          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
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| 47     | 47          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
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| 49     | 49          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 50     | 50          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 51     | 51          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 52     | 52          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 53     | 53          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 54     | 54          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 55     | 55          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 56     | 56          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 57     | 57          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 58     | 58          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
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| 60     | 60          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
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| 66     | 66          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 67     | 67          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 68     | 68          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 69     | 69          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 70     | 70          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 71     | 71          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 72     | 72          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 73     | 73          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 74     | 74          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 75     | 75          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 76     | 76          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 77     | 77          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 78     | 78          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 79     | 79          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 80     | 80          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 81     | 81          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 82     | 82          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 83     | 83          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 84     | 84          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 85     | 85          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 86     | 86          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 87     | 87          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 88     | 88          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 89     | 89          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 90     | 90          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 91     | 91          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 92     | 92          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 93     | 93          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 94     | 94          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 95     | 95          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 96     | 96          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 97     | 97          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 98     | 98          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 99     | 99          | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |
| 100    | 100         | 10              | 12                       | 10                  | 0                   | 0                   | 0                   | 0                   |

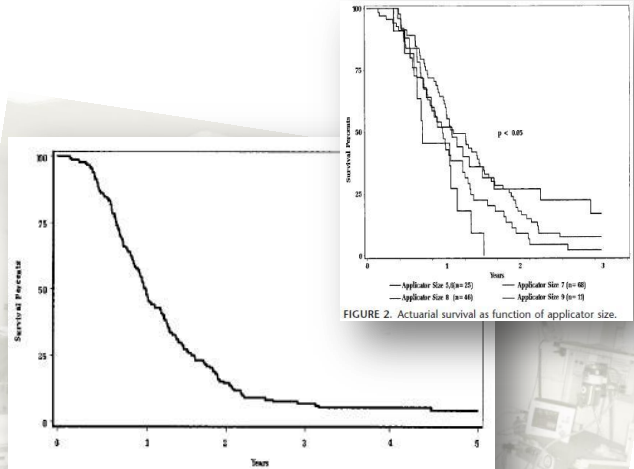
2011

1981-2005, 23 Institutions, 862 patients  
 8-16 months median survival time (12 months)  
 50-100% pain relieve effect (80%)



2005

1978-2001, 150 patients, MGH-Boston  
 13 months MST, 8 long-term survival  
 <6 cm applicator 17% 3-y OS



# IORT Results: Locally advanced unresectable pancreatic cancer

2011

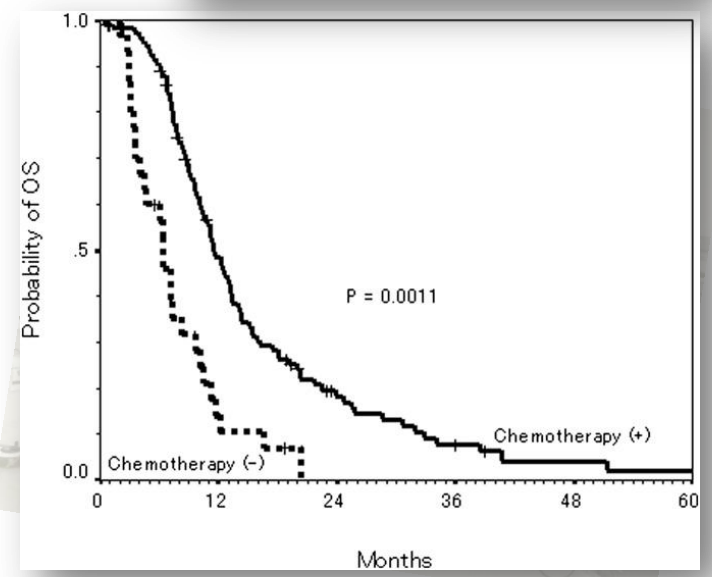
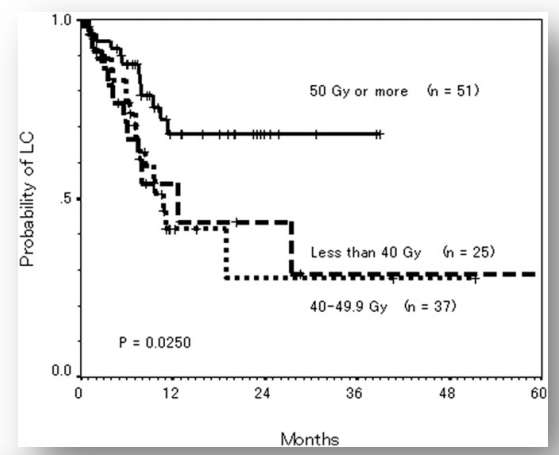


2000-2006, 144 patients, 34 institutions

Local control 51%, 2 years

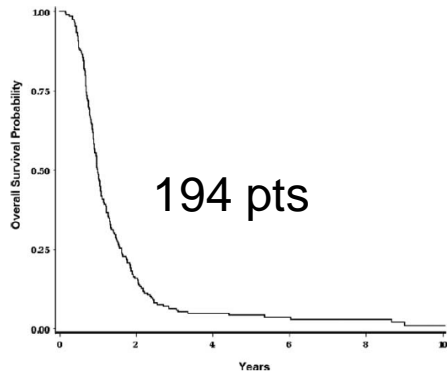
EBRT 50 Gy + IORT= LC 71%

Survival CT 18% vs 0% 2 years

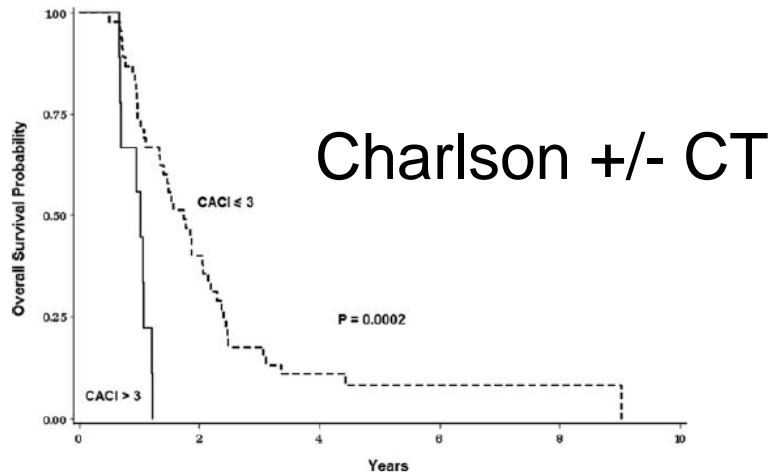


# Updated Long-Term Outcomes and Prognostic Factors for Patients With Unresectable Locally Advanced Pancreatic Cancer Treated With Intraoperative Radiotherapy at the Massachusetts General Hospital, 1978 to 2010

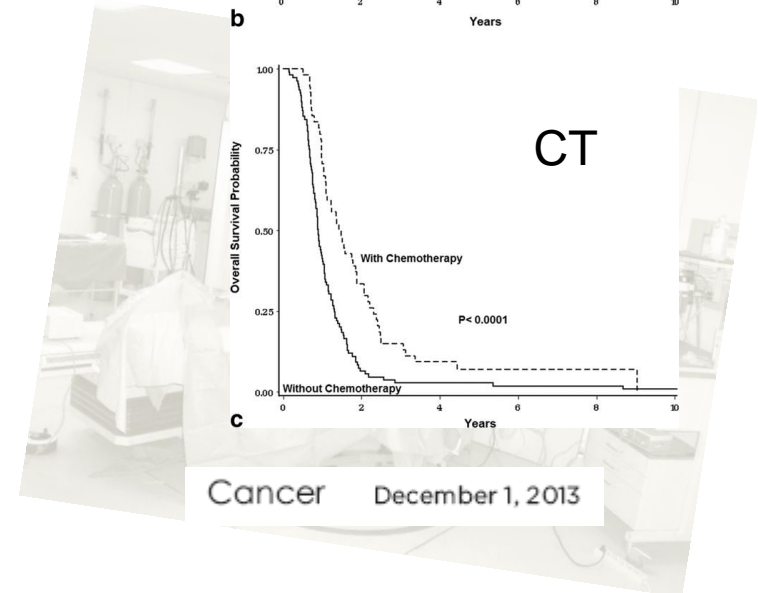
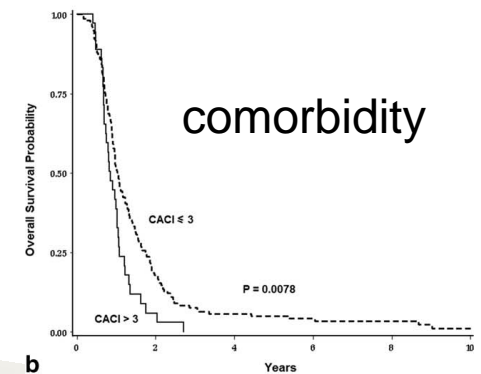
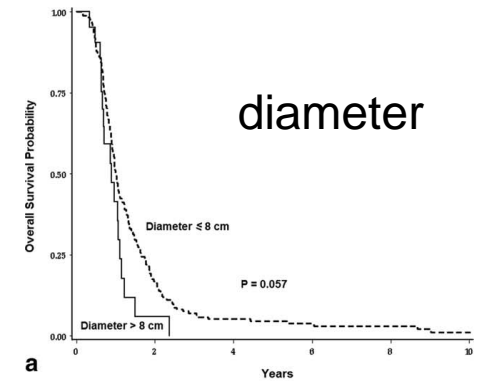
Sophie Cai, BA<sup>1</sup>; Theodore S. Hong, MD<sup>2</sup>; Saveli I. Goldberg, PhD<sup>2</sup>; Carlos Fernandez-del Castillo, MD<sup>3</sup>; Sarah P. Thayer, MD, PhD<sup>3</sup>; Cristina R. Ferrone, MD<sup>3</sup>; David P. Ryan, MD<sup>4</sup>; Lawrence S. Blaszkiwsky, MD<sup>4</sup>; Eunice I. Kwak, MD, PhD<sup>4</sup>; Christopher G. Willett, MD<sup>5</sup>; Keith D. Lillemoe, MD<sup>3</sup>; Andrew L. Warshaw, MD<sup>3</sup>; and Jennifer Y. Wo, MD<sup>2</sup>



**Figure 1.** Overall survival is shown among patients with unresectable locally advanced pancreatic cancer who were treated with intraoperative radiotherapy (N = 194).



**Figure 3.** Overall survival of patients treated with chemotherapy is shown stratified by Charlson age-comorbidity index (CACI) (N = 57).



# IORT Results: pancreatic cancer post-resected

3 decades... a summary

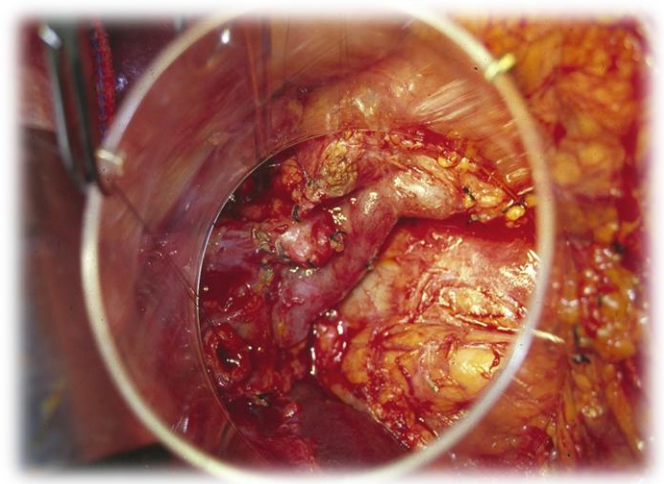
**Intraoperative Irradiation**  
Techniques and Results  
Second Edition  
Humana Press  
2011

| Author    | N   | Year | No. patients | Year of IORT | No. surviving | Median survival (mo) | 5-y survival (%) | Median survival (mo) |
|-----------|-----|------|--------------|--------------|---------------|----------------------|------------------|----------------------|
| Chelikoff | 275 | 2008 | 4            | 4            | 4             | 1                    | NA               | 1.0                  |
| Chelikoff | 275 | 2008 | 11           | 11           | 11            | 1                    | NA               | 1.0                  |
| Chelikoff | 275 | 2008 | 20           | 20           | 20            | 2                    | NA               | 1.0                  |
| Chelikoff | 275 | 2008 | 8            | 12-25        | 8             | 8                    | NA               | 1.0                  |
| Chelikoff | 275 | 2008 | 30           | 30           | 30            | 30                   | NA               | 1.0                  |
| Chelikoff | 275 | 2008 | 11           | 12-15        | 7             | 7                    | NA               | 1.0                  |
| Chelikoff | 275 | 2008 | 17           | 17           | 17            | 17                   | NA               | 1.0                  |
| Chelikoff | 275 | 2008 | 7            | 7            | 7             | 7                    | NA               | 1.0                  |
| Chelikoff | 275 | 2008 | 48           | 12-24        | 48            | 48                   | NA               | 1.0                  |
| Chelikoff | 275 | 2008 | 13           | 12-20        | 9             | 9                    | NA               | 1.0                  |
| Chelikoff | 275 | 2008 | 14           | 12-15        | 14            | 14                   | NA               | 1.0                  |
| Chelikoff | 275 | 2008 | 10           | 12-20        | 10            | 10                   | NA               | 1.0                  |
| Chelikoff | 275 | 2008 | 17           | 17           | 17            | 17                   | NA               | 1.0                  |
| Chelikoff | 275 | 2008 | 18           | 12-25        | 18            | 18                   | NA               | 1.0                  |
| Chelikoff | 275 | 2008 | 20           | 20           | 20            | 20                   | NA               | 1.0                  |
| Chelikoff | 275 | 2008 | 44           | 12-20        | 22            | 22                   | NA               | 1.0                  |
| Chelikoff | 275 | 2008 | 17           | 12-25        | 17            | 17                   | NA               | 1.0                  |

1985-2009, 778 patients, 23 Institutions

9-19 months MST (16 mo)

9%-55% local recurrence

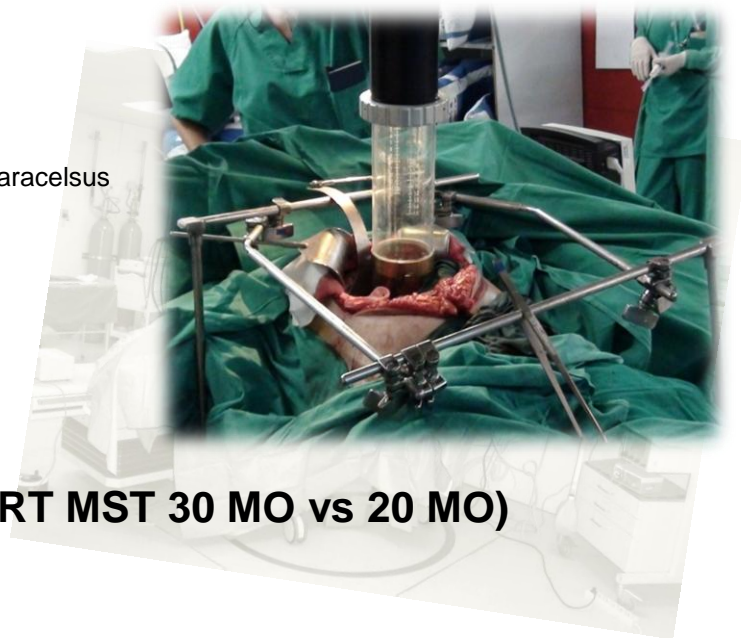


**Radiotherapy and Oncology**  
Journal homepage: www.thegreenjournal.com  
2009

1985-2006, 270 patients,

Gemelli, San Raffaele, Marañón, Heidelberg, Paracelsus

Local control @ 5-y 23% (T3-4, R2, N+)



IORT of pancreatic cancer  
Intra-operative radiotherapy (IORT) in pancreatic cancer: Joint analysis of the ISIOR-T-Europe experience  
Vincenzo Valentini<sup>1</sup>, Felipe Calvo<sup>2</sup>, Michele Reni<sup>3</sup>, Robert Krempien<sup>4</sup>, Felix Setlmayer<sup>5</sup>, Markus W. Buchler<sup>6</sup>, Valerio Di Carlo<sup>7</sup>, Giovanni B. Doglietto<sup>8</sup>, Gerd Fastner<sup>9</sup>, José L. Garcia-Sabrido<sup>1</sup>, GianCarlo Mattiucci<sup>10</sup>, Alessio G. Morganti<sup>11</sup>, Paolo Fassioni<sup>12</sup>, Falk Roeder<sup>13</sup>, Giuseppe R. D'Agostino<sup>14</sup>

2009

**OS 5-y 18% (preoperative CRT MST 30 MO vs 20 MO)**



ARTICLE IN PRESS

Radiotherapy and Oncology xx (2007) xxx–xxx  
www.thegreenjournal.com

Review

## Intraoperative radiotherapy in pancreatic cancer: A systematic review

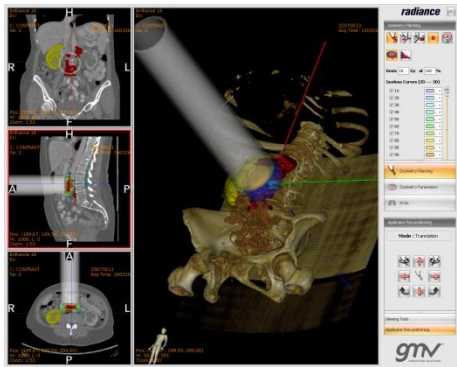
Alberto Ruano-Ravina<sup>a,b,c,\*</sup>, Raquel Almazán Ortega<sup>d</sup>, Ferran Guedea<sup>e</sup>

<sup>a</sup>Galician Agency for Health Technology Assessment, Galician Health Authority, Santiago de Compostela, Spain, <sup>b</sup>Department of Preventive Medicine and Public Health, University of Santiago de Compostela, Spain, <sup>c</sup>CIBER de Epidemiología y Salud Pública, Spain, <sup>d</sup>Research Unit, Ourense Hospital Complex, Ourense, Spain, <sup>e</sup>Department of Radiation Oncology, University of Barcelona, Spain

2008

1984-2002, 14 Journal articles, 789 patients

|                                |                    |
|--------------------------------|--------------------|
| Palliative surgery + IORT      | 0-3% OS @ 5-years  |
| Curative surgery + IORT        | 6-22% OS @ 5years  |
| Curative surgery + IORT + EBRT | 7-27% OS @ 5-years |







Original article

## Chemoradiation for resected pancreatic adenocarcinoma with or without intraoperative radiation therapy boost: Long-term outcomes

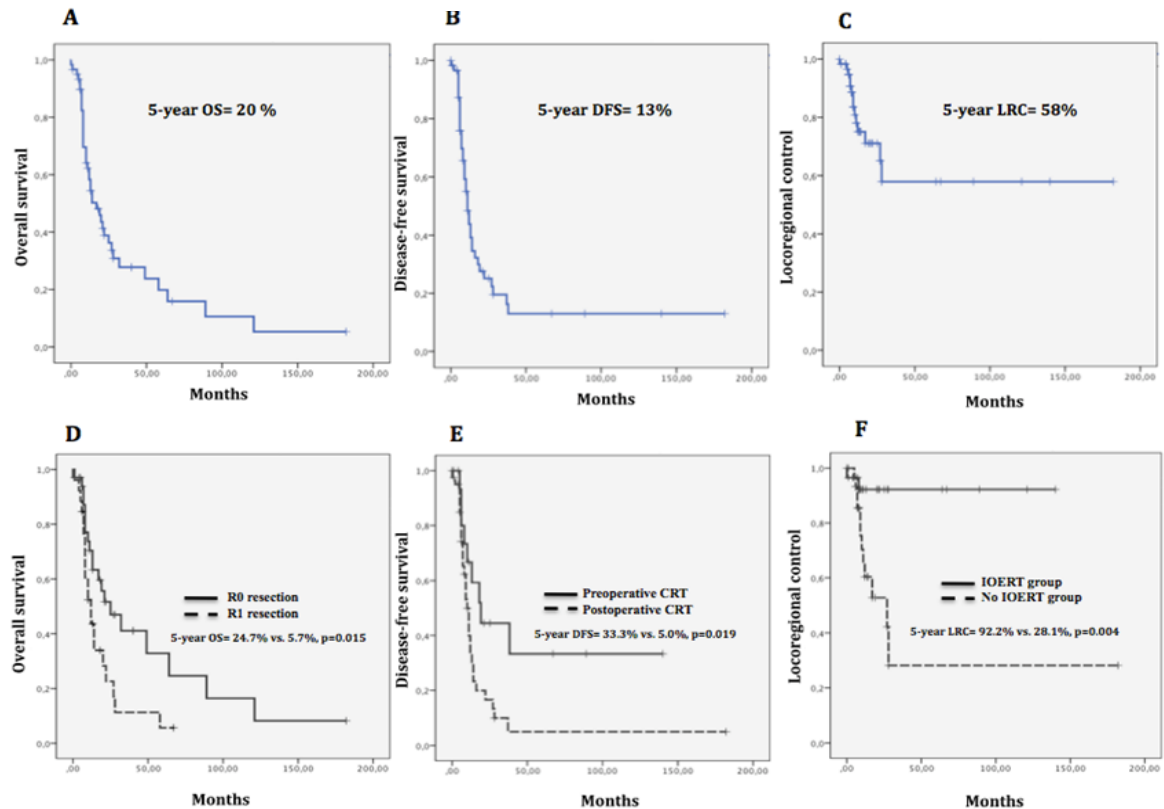
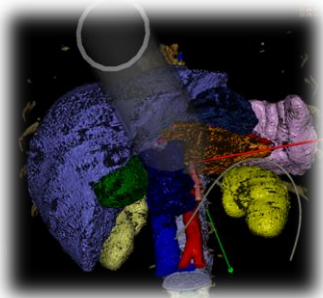
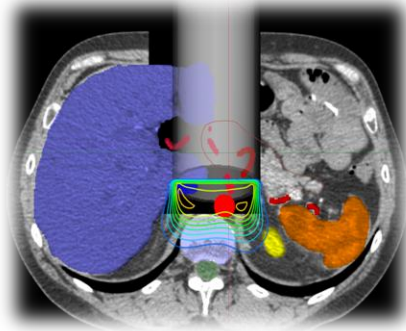


Felipe A. Calvo<sup>a,b,1</sup>, Claudio V. Sole<sup>a,b,c,d,\*</sup>, Freddy Atahualpa<sup>b,e</sup>, Miguel A. Lozano<sup>f</sup>, Marina Gomez-Espi<sup>f</sup>, Ana Calin<sup>f</sup>, Pilar Garcia-Alfonso<sup>g</sup>, Luis Gonzalez-Bayon<sup>e</sup>, Rafael Herranz<sup>f</sup>, Jose Luis Garcia-Sabrido<sup>b,e</sup>

**60 pts resected  
1995-2010  
29 non-IOERT pts  
vs  
31 IOERT pts**

**Table 4**  
Factors associated with locoregional control, disease-free survival, and overall survival in the multivariate analysis.

| Variable   | Locoregional control |       |            | Disease-free survival |       |           | Overall survival |       |           |
|--|----------------------|-------|------------|-----------------------|-------|-----------|------------------|-------|-----------|
|  | HR                   | 95%CI | P value    | HR                    | 95%CI | P value   | HR               | 95%CI | P value   |
| Preoperative staging<br>Clinical stage                   | IB–IIA               | 1.0   | 1.0–5.53   | 0.05                  | –     | –         | –                | –     | –         |
|  | IIb–III              | 2.88  |            |                       |       |           |                  |       |           |
| Microscopic surgical specimen<br>Margin resection status | R0                   | 1.0   | 1.0–9.21   | 0.05                  | 1.0   | 1.10–3.91 | 0.02             | 1.0   | 1.11–7.43 |
|  | R1                   | 3.32  |            |                       | 2.10  |           |                  | 2.87  |           |
| Chemoradiation therapy                                   | Preoperative         | –     | –          | –                     | 1.0   | 1.10–5.0  | 0.03             | –     | –         |
|  | Postoperative        | –     | –          | –                     | 2.08  |           |                  | –     | –         |
| IOERT  | Yes                  | 1.0   | 1.89–20.51 | 0.01                  | –     | –         | –                | –     | –         |
|  | No                   | 6.75  |            |                       | –     |           |                  | –     |           |



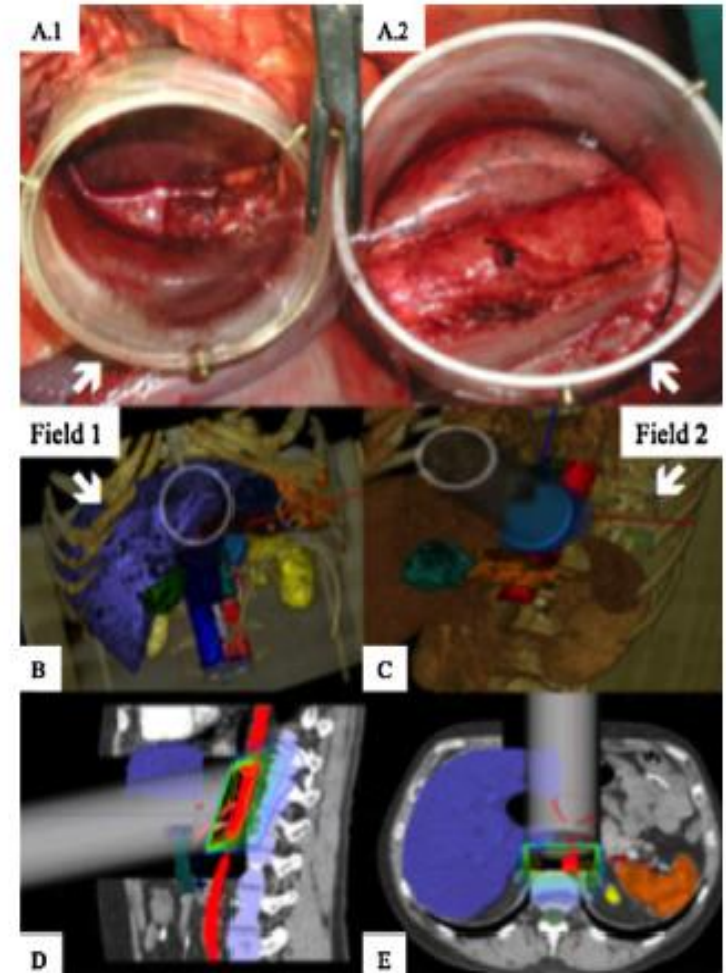
***iORT is a precise boost to be combined with high-precision RT***

- Pancreatic cancer (cuasi-uncurable disease)
- Esophago gastric
- Locally advanced rectal cancer
- Soft tissue sarcomas
- Breast cancer
- Mono-oligotopic recurrent cancer (cuasi-uncurable disease)



## Postchemoradiation Resected Locally Advanced Esophageal and Gastroesophageal Junction Carcinoma: Long-Term Outcome With or Without Intraoperative Radiotherapy

Felipe A. Calvo, MD, PhD<sup>1,2</sup>, Claudio V. Sole, MD<sup>1,2,3</sup>, Rosángela Obregón, MD, PhD<sup>2,4</sup>, Marina Gómez-Espí, Miguel A. Lozano, MD<sup>5</sup>, Luis Gonzalez-Bayon, MD, PhD<sup>4</sup>, and Jose Luis García-Sabrido, MD, PhD<sup>2,4</sup>



**FIG. 1** Intraoperative target volume view (a), 3D (b and c) and 2D (d and e) CT scan-based IOERT planning technology. Planning treatment volume (PTV) encompasses the upper abdominal lymph node area (a.1 and b), including lymph node groups of the right/left cardia, left gastric artery, celiac artery, and abdominal para-aorta (*Field 1*), and tumor bed plus inferior mediastinum (a.2 and c) (*Field 2*)



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IORT in gastric cancer

Adjuvant chemoradiotherapy with or without intraoperative radiotherapy for the treatment of resectable locally advanced gastric adenocarcinoma

Qing Zhang<sup>a</sup>, Jeremy Tey<sup>b</sup>, Lihua Peng<sup>a</sup>, Zhe Yang<sup>c</sup>, Fei Xiong<sup>a</sup>, Ruiyao Jiang<sup>a</sup>, Taifu Liu<sup>d</sup>, Shen Fu<sup>a,\*</sup>, Jiade J. Lu<sup>b</sup>

<sup>a</sup> Department of Radiation Oncology, Sixth Hospital of Jiao Tong University, Shanghai, People's Republic of China; <sup>b</sup> Department of Radiation Oncology, National University Hospital, Singapore; <sup>c</sup> Department of Surgery, Sixth Hospital of Jiao Tong University, Shanghai, People's Republic of China; <sup>d</sup> Department of Radiation Oncology, Fudan University, Shanghai, People's Republic of China

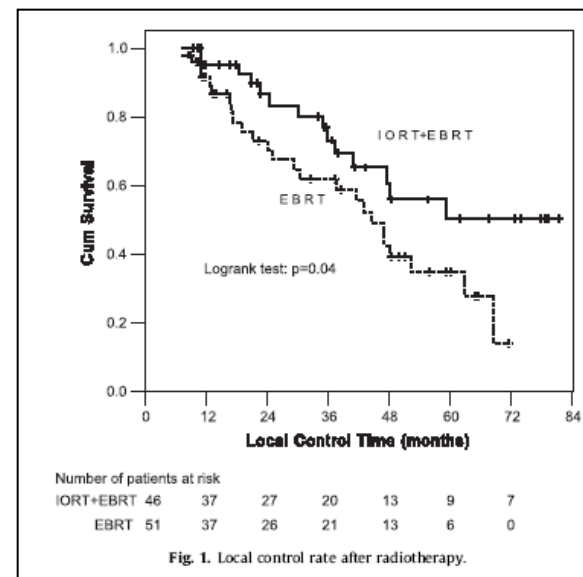
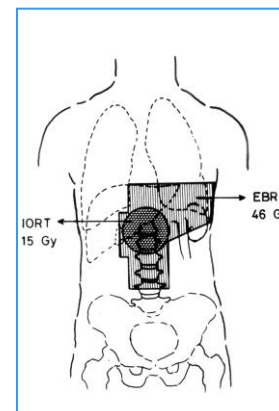


Fig. 1. Local control rate after radiotherapy.

**Table 2**  
Patterns of local regional failure after adjuvant chemoradiotherapy.

| Patterns of failure          | Group            |           |
|------------------------------|------------------|-----------|
|                              | IOERT + EBRT (%) | EBRT (%)  |
| Anastomosis                  | 8 (57%)          | 9 (36%)   |
| Posterior to pancreatic head | 4 (29%)          | 2 (8%)    |
| Hepatoduodenal ligment       | 1 (7%)           | 4 (16%)   |
| Tumor bed                    | 1 (7%)           | 7 (28%)   |
| Common hepatic artery        | 0 (0%)           | 2 (8%)    |
| Celiac axis                  | 0 (0%)           | 1 (4%)    |
| Total                        | 14 (100%)        | 25 (100%) |



**Table 3**  
Multivariate analysis for

| Variable                    | P value          |                        |                          |                       |
|-----------------------------|------------------|------------------------|--------------------------|-----------------------|
|                             | Overall survival | Local regional control | Metastatic free survival | Disease free survival |
| IOERT (Yes vs. No)          | 0.06             | 0.02                   | 0.10                     | 0.05                  |
| T (T1–2 vs. T3 vs. T4)      | <0.001           | 0.03                   | <0.001                   | <0.001                |
| N (N0 vs. N1 vs. N2 vs. N3) | <0.001           | 0.002                  | <0.001                   | <0.001                |
| R (R0 vs. R1)               | 0.07             | 0.14                   | 0.01                     | 0.006                 |

## *iORT is a precise boost to be combined with high-precision RT*

- Pancreatic cancer (cuasi-uncurable disease)
- Locally advanced rectal cancer
- Soft tissue sarcomas
- Breast cancer
- Mono-oligotopic recurrent cancer (cuasi-uncurable disease)





# IORT Results: Locally advanced rectal cancer 2014 update



2009

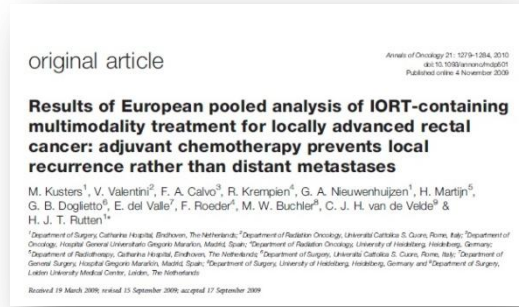
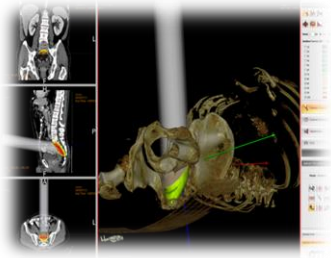
1994 – 2006

290 patients preop RT (70% CRT)

**13% local recurrence, 5% presacral,**

(distal, R+, 48% outside IORT field)

67% cancer-specific survival @ 5-years



2010

1989 – 2005

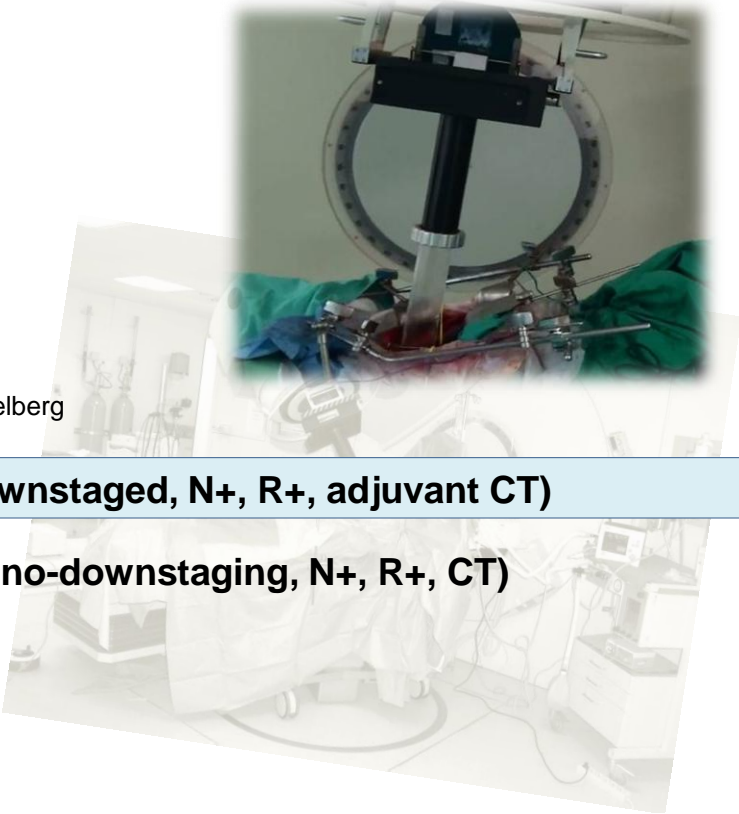
605 patients Catharina, Marañón, Gemelli, Heidelberg

**12% local recurrence @ 5-y (downstaged, N+, R+, adjuvant CT)**

**68% OS @ 5-y (male, >70 years, no-downstaging, N+, R+, CT)**

“Seed and soil” adjuvant chemotherapy on LC

Prognostic index model





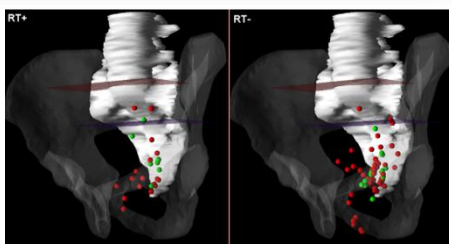
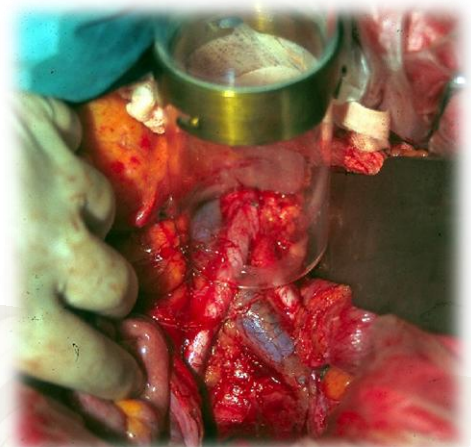


2011

1993 – 2001 / 7 French institutions

| R          | PTS | LC  | OS  | Complications |
|------------|-----|-----|-----|---------------|
| IORT (1Gv) | 73  | 91% | 70% | 29%           |
| no IORT    | 69  | 92% | 74% | 19%           |

“Technical feasibility for future phase III trials”



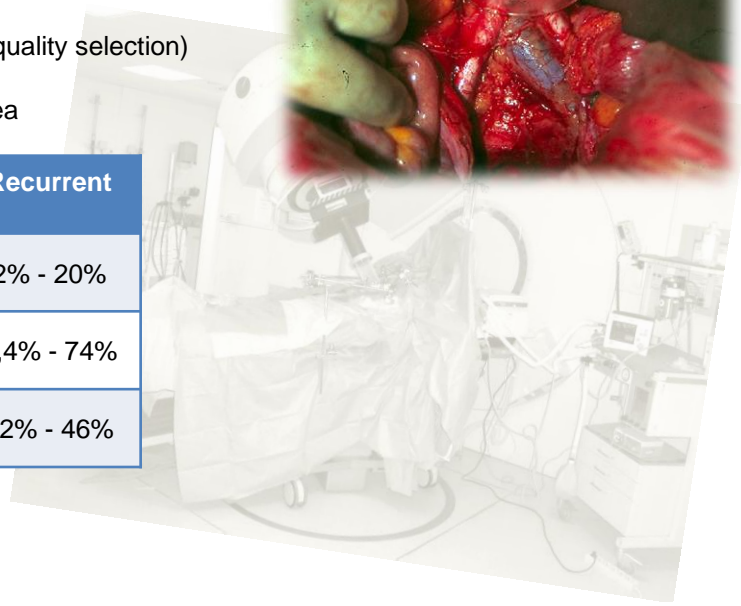
2000 – 2009 publications, 15 articles (quality selection)  
 1755 patients  
 10% reduction in LR over the IORT area



2011

| Safety           | Primary    | Recurrent  |
|------------------|------------|------------|
| Acute *          | 0,7% - 22% | 2% - 20%   |
| Late             | 11% - 30%  | 5,4% - 74% |
| Efficacy (LR 5y) | 6% - 12%   | 32% - 46%  |

\* Except incontinence evaluation

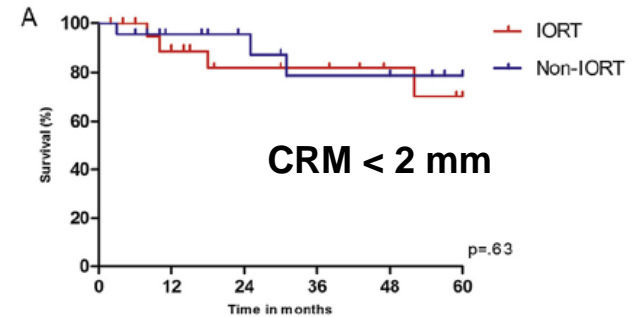
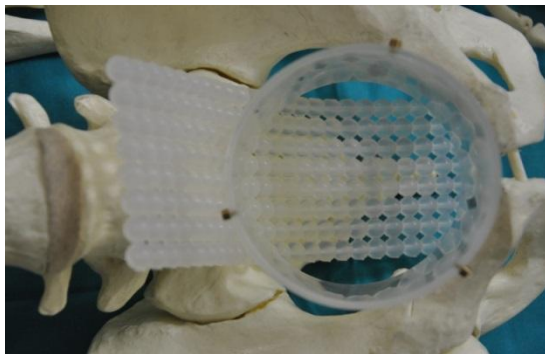
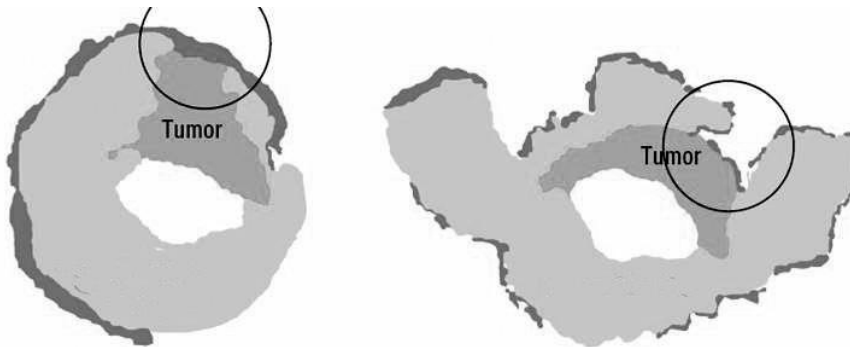


## Intraoperative Radiation Therapy Reduces Local Recurrence Rates in Patients With Microscopically Involved Circumferential Resection Margins After Resection of Locally Advanced Rectal Cancer

Wijnand J. Alberda, MD,\* Cornelis Verhoef, MD, PhD,\* Joost J. Nuyttens, MD PhD,<sup>†</sup> Esther van Meerten, MD, PhD,<sup>‡</sup> Joost Rothbarth, MD, PhD,\* Johannes H.W. de Wilt, MD, PhD,<sup>§</sup> and Jacobus W.A. Burger, MD, PhD\*

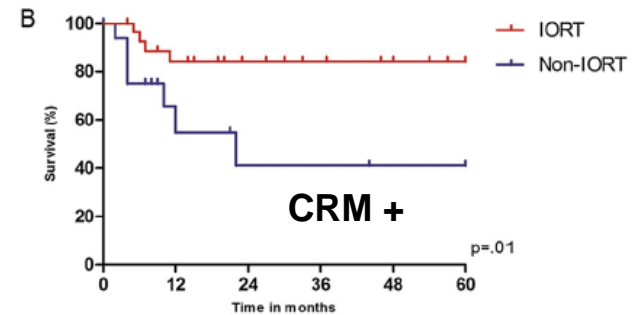
\*Department of Surgery, Division of Surgical Oncology, <sup>†</sup>Department of Radiotherapy, <sup>‡</sup>Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam; and <sup>§</sup>Department of Surgery, Division of Surgical Oncology, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands

Received Nov 8, 2013, and in revised form Jan 7, 2014. Accepted for publication Jan 10, 2014.



Patients at risk

|          |    |    |    |    |   |   |
|----------|----|----|----|----|---|---|
| IORT     | 21 | 16 | 12 | 11 | 8 | 5 |
| Non-IORT | 22 | 17 | 14 | 10 | 9 | 6 |



Patients at risk

|          |    |    |    |    |   |   |
|----------|----|----|----|----|---|---|
| IORT     | 31 | 21 | 15 | 11 | 8 | 5 |
| Non-IORT | 17 | 7  | 4  | 3  | 2 | 2 |

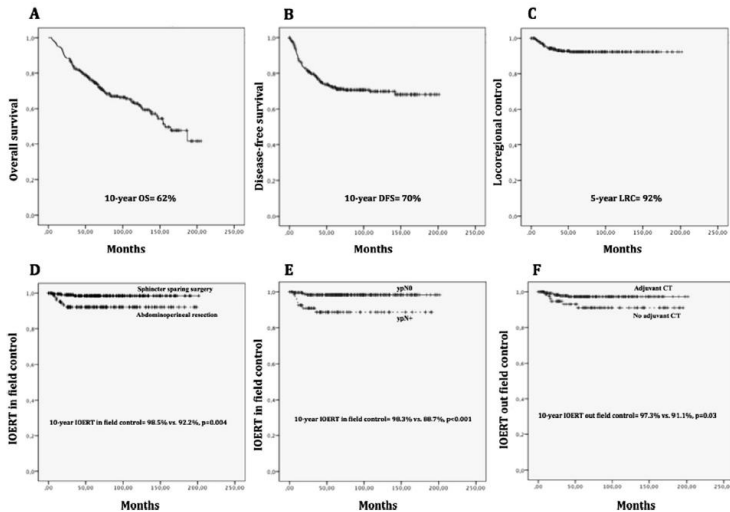
**Fig. 1.** (A) Local recurrence-free survival in patients with clear but narrow circumferential resection margins ( $\leq 2$  mm). (B) Local recurrence-free survival in patients with microscopically involved circumferential resection margins. IORT = intraoperative radiation therapy.



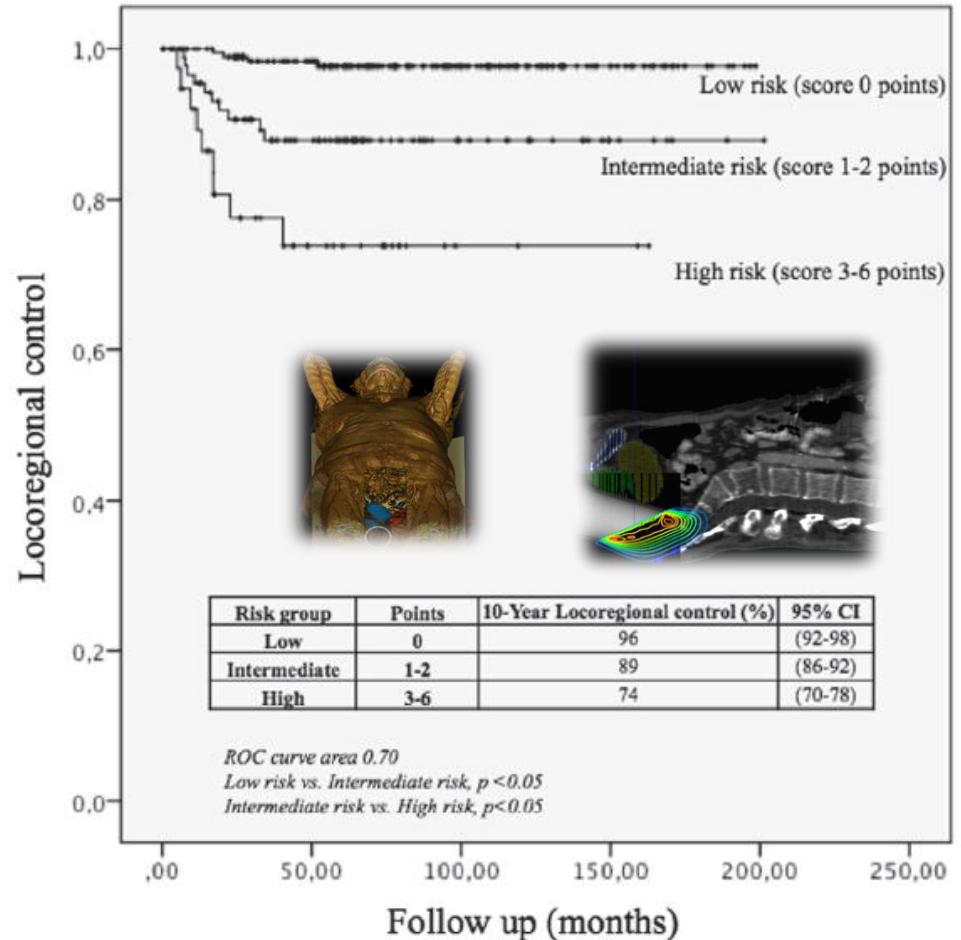
Original article

Post-chemoradiation intraoperative electron-beam radiation therapy boost in resected locally advanced rectal cancer: Long-term results focused on topographic pattern of locoregional relapse

Claudio V. Sole<sup>a,b,i,\*</sup>, Felipe A. Calvo<sup>c,d,i</sup>, Javier Serrano<sup>d,e,i</sup>, Emilio del Val<sup>d,f,i</sup>, Alberto Muñoz-Calero<sup>d,f,i</sup>, Fernando Turégano<sup>f,i</sup>, Jose Luis García-Sabrido<sup>h,i</sup>, Isabel Peligros<sup>h,i</sup>, Sofia Rivera<sup>b,j,k</sup>, Eric Deutsch<sup>b,j,k</sup>, Emilio Alvarez<sup>d,h,i</sup>



The index score was defined as weighted sum of the risk factors (distal margin < 10 mm, 1 point; R1 resection, 2 points; tumor histological grade 3, 3 points).





## Review

## Intraoperative radiotherapy in colorectal cancer: Systematic review and meta-analysis of techniques, long-term outcomes, and complications

Reza Mirnezami<sup>a</sup>, George J. Chang<sup>b</sup>, Prajnan Das<sup>c</sup>, Kandiah Chandrakumar<sup>d</sup>, Paris Tekkis<sup>a</sup>, Ara Darzi<sup>a</sup>, Alexander H. Mirnezami<sup>c,\*</sup>

<sup>a</sup> Section of Biosurgery & Surgical Technology, Department of Surgery & Cancer, Imperial College London, 10th Floor QEOM Building, St Mary's Hospital, London W2 1NY, UK

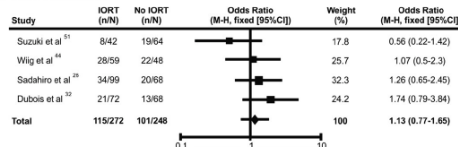
<sup>b</sup> Department of Surgical Oncology, University of Texas, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA

<sup>c</sup> Department of Radiation Oncology, University of Texas, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA

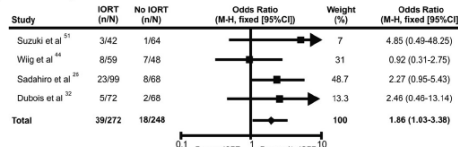
<sup>d</sup> Department of Surgery, Basingstoke and North Hampshire Hospital NHS Foundation Trust, Hampshire RG249NA, UK

<sup>\*</sup> Somers Cancer Research Building, University of Southampton Cancer Sciences Division, Southampton University Hospital NHS Trust, Tremona road, Southampton SO166YD, UK

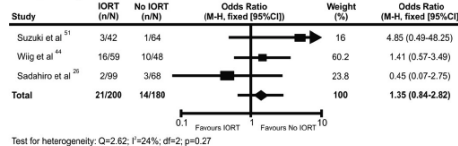
### A Total complications



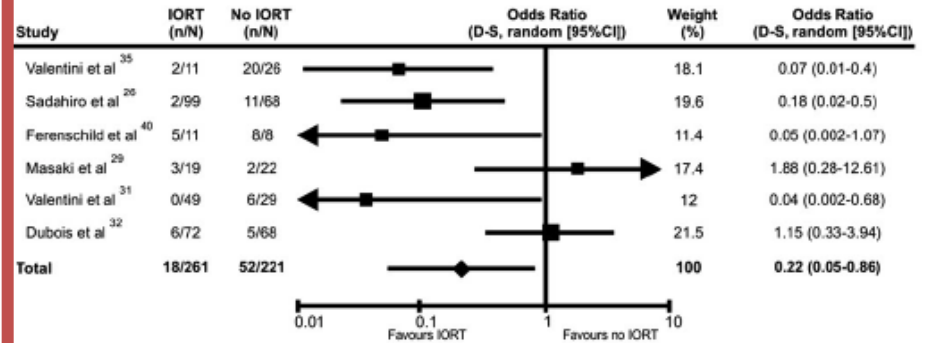
### B Wound complications



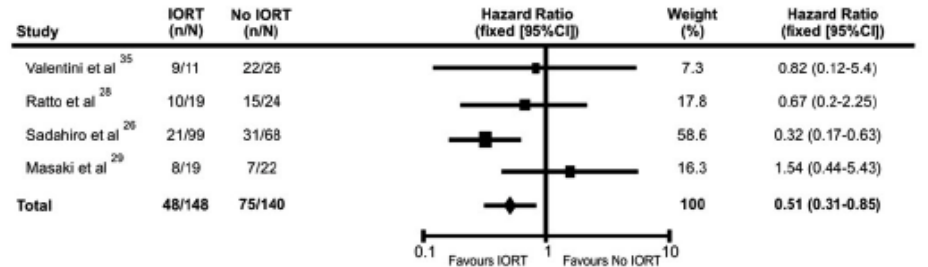
### C Urologic complications



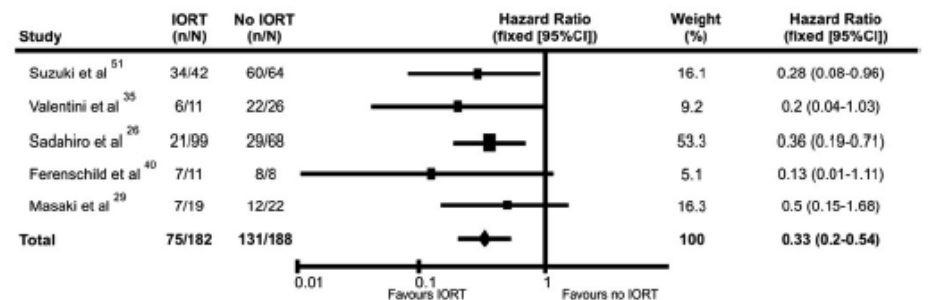
### A 5 year local control



### B 5 year disease free survival



### C 5 year overall survival



## *iORT is a precise boost to be combined with high-precision RT*

- Pancreatic cancer (cuasi-uncurable disease)
- Locally advanced rectal cancer
- Soft tissue sarcomas
- Breast cancer
- Mono-oligotopic recurrent cancer (cuasi-uncurable disease)





**Preliminary Results of a Randomized Study of Adjuvant Radiation Therapy in Resectable Adult Retroperitoneal Soft Tissue Sarcomas**

By Timothy J. Kinella, William F. Sindelar, Ernest Lock, Eli Glotstein, and Steven A. Rosenberg

Between January 1980 and September 1985, 35 adult patients with resectable retroperitoneal soft tissue sarcomas were entered on a randomized trial comparing two forms of adjuvant radiation therapy. Fifteen patients received the experimental therapy consisting of intraoperative radiotherapy (IORT) to 20 Gy using high-energy electrons followed by low-dose (35 to 40 Gy) postoperative external beam irradiation. Twenty patients received standard therapy consisting of high-dose (50 to 55 Gy) postoperative external beam irradiation. With a minimum follow-up of 15 months, there is no significant difference in the actuarial disease-free survival (DFS) and overall survival (OS) comparing the two groups (median DFS, 24 months; median OS, 38 months). At 5 years follow-up, approximately 40% of patients are alive and 20% of patients remain disease-free. Although there is a trend towards an improvement in in-field local control in the experimental arm, the predominant pattern of failure in both groups was locoregional within the retroperitoneum and/or peritoneal cavity. Acute and late radiation enteritis were significantly reduced in the experimental group. However, four experimental patients developed late (>6 months following treatment) peripheral neuropathy believed related to the use of IORT; all four recovered. We conclude that there is no difference in the therapeutic effectiveness of the combination of IORT and low-dose external beam radiation compared with conventional high-dose radiation as adjuvant treatment in retroperitoneal sarcomas, although the former appears to be less toxic. Never combined modality treatment strategies are discussed to improve the prognosis in these patients.

*J Clin Oncol 6:18-25. © 1988 by American Society of Clinical Oncology.*

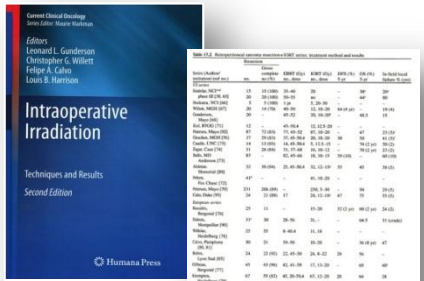
180-185, 35 patients, NCI-Bethesda

| R                   | PTS | LC (in-field) | DFS (mo) |
|---------------------|-----|---------------|----------|
| IORT (20Gy+40Gy)    | 15  | 68%           | 20       |
| no IORT (50Gy-55Gy) | 20  | 22%           | 38       |

**Acute enteritis 1 vs 12, chronic enteritis 2 vs 7, fistula 0 vs 6 (significant)**



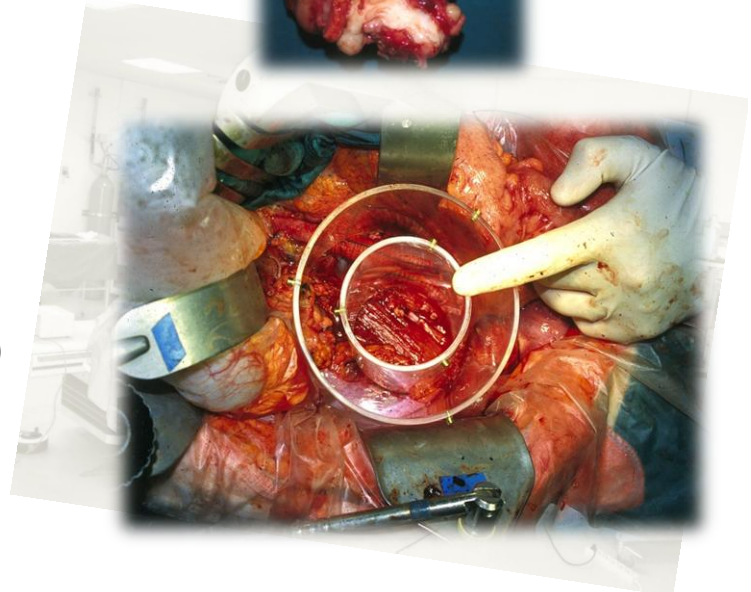
1988



1988-2008, 1173 patients, 18 Institutions

In-field failure 20%-60% (32%)

**OS @ 5-y 36%-48% (DFS 28%)**



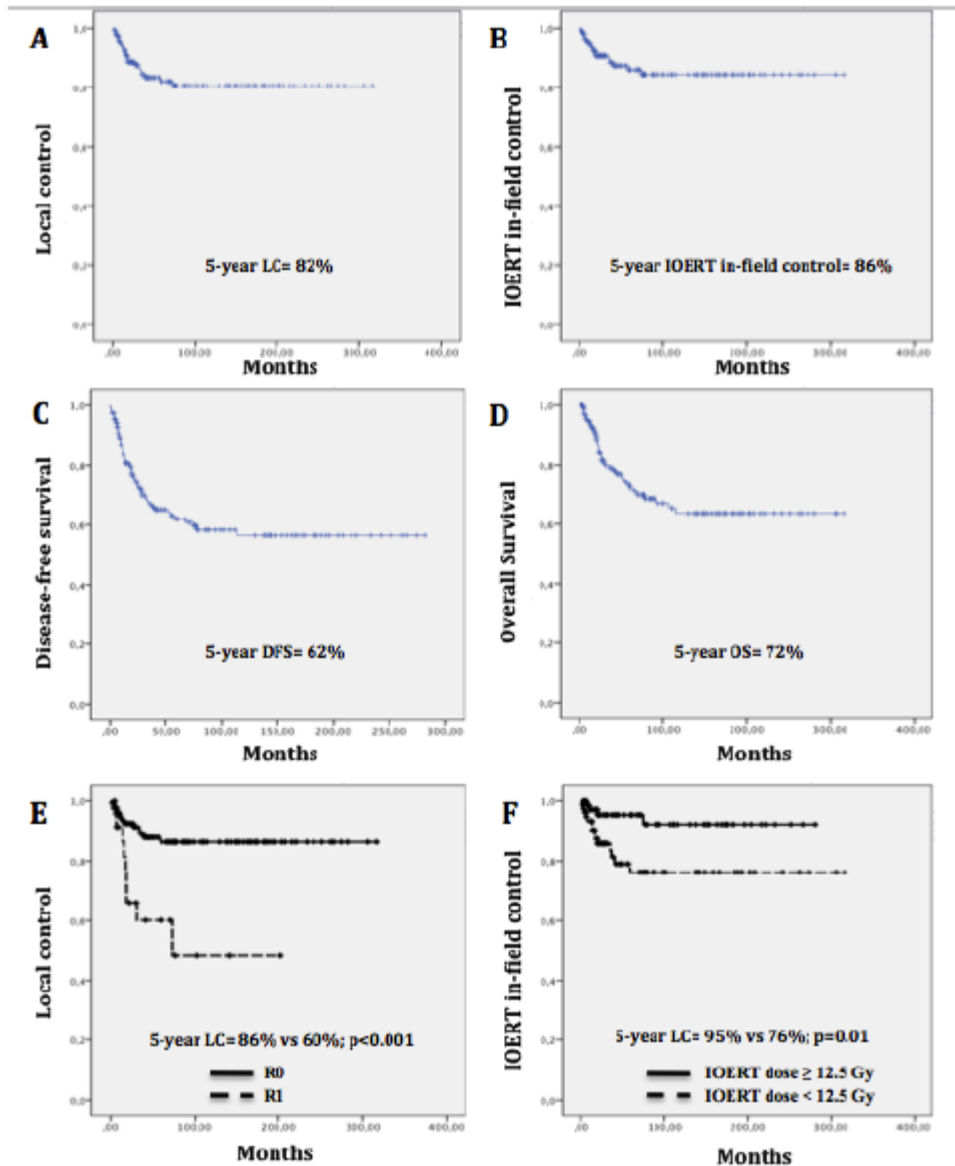
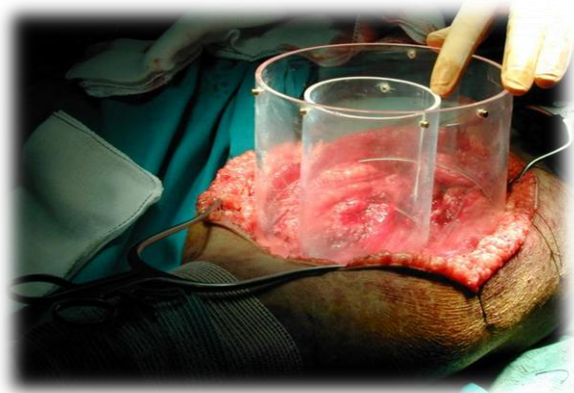
2011

# Limb-sparing management with surgical resection, external-beam and intraoperative electron-beam radiation therapy boost for patients with primary soft tissue sarcoma of the extremity

## A multicentric pooled analysis

Felipe A. Calvo<sup>1,2</sup> · Claudio V. Sole<sup>1,2,3</sup> · Alfredo Polo<sup>4</sup> · Mauricio Cambeiro<sup>5</sup> · Angel Montero<sup>4</sup> · Ana Alvarez<sup>6</sup> · Miguel Cuervo<sup>7</sup> · Mikel San Julian<sup>8</sup> · Rafael Martinez-Monge<sup>9</sup>

Strahlentherapie und Onkologie X · 2014

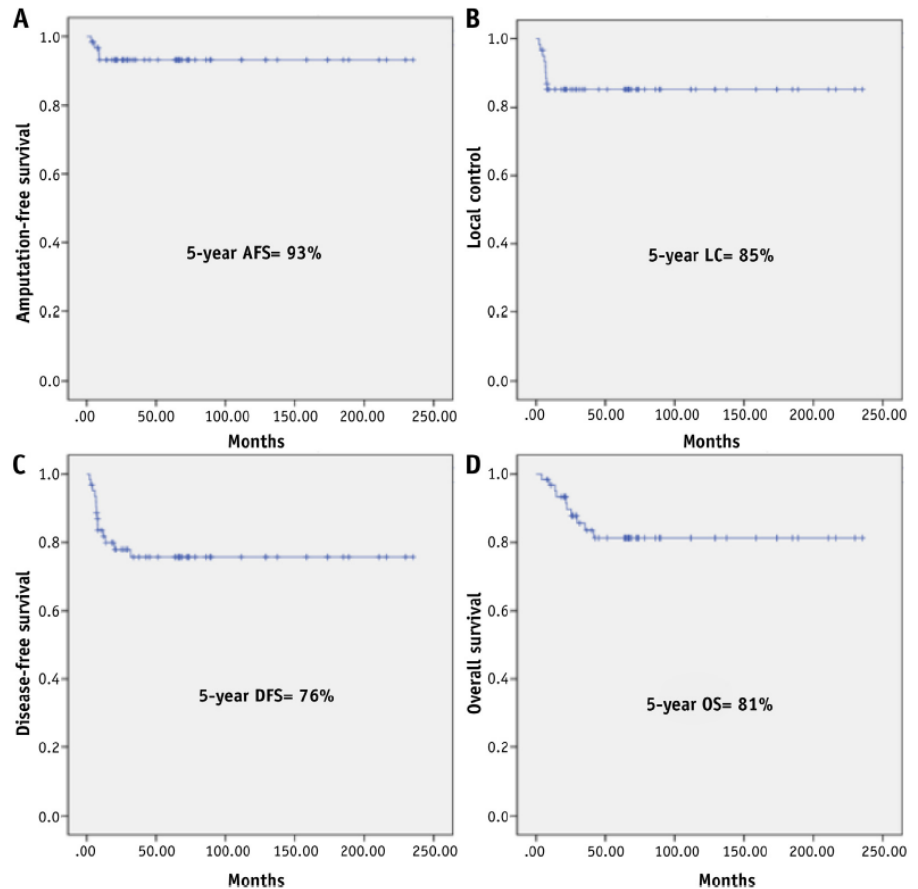




Clinical Investigation

## Anticipated Intraoperative Electron Beam Boost, External Beam Radiation Therapy, and Limb-Sparing Surgical Resection for Patients with Pediatric Soft-Tissue Sarcomas of the Extremity: A Multicentric Pooled Analysis of Long-Term Outcomes

Claudio V. Sole, MD,<sup>\*,†,‡</sup> Felipe A. Calvo, MD, PhD,<sup>\*,†</sup>  
Alfredo Polo, MD, PhD,<sup>§</sup> Mauricio Cambeiro, MD, PhD,<sup>||</sup>  
Ana Alvarez, MD,<sup>¶</sup> Carmen Gonzalez, MD,<sup>¶</sup> Jose Gonzalez, MD,<sup>#</sup>  
Mikel San Julian, MD,<sup>\*\*</sup> and Rafael Martinez-Monge, MD, PhD<sup>||</sup>



**Table 3** Factors associated with local control, disease-free survival, and overall survival in multivariate analyses

| Parameter                     | Variable | Local control |            |          | Disease-free survival |           |          | Overall survival |            |          |
|-------------------------------|----------|---------------|------------|----------|-----------------------|-----------|----------|------------------|------------|----------|
|                               |          | HR            | 95% CI     | <i>P</i> | HR                    | 95% CI    | <i>P</i> | HR               | 95% CI     | <i>P</i> |
| Presurgical variables         |          |               |            |          |                       |           |          |                  |            |          |
| Tumor size (cm)               | ≤5       | 1.0           | 1.06-11.81 | .04      | —                     | —         | —        | —                | —          | —        |
|                               | >5       | 3.03          |            |          |                       |           |          |                  |            |          |
| Microscopic surgical specimen |          |               |            |          |                       |           |          |                  |            |          |
| Histology subtype             | NRSTS    | —             | —          | —        | 1.0                   | 1.01-8.57 | .05      | —                | —          | —        |
|                               | RMS      |               |            |          | 2.88                  |           |          |                  |            |          |
| Surgery                       |          |               |            |          |                       |           |          |                  |            |          |
| Margin status                 | R0       | 1.0           | 1.06-8.22  | .04      | 1.0                   | 1.17-8.72 | .02      | 1.0              | 1.08-10.66 | .04      |
|                               | R1       | 2.32          |            |          | 2.47                  |           |          | 2.71             |            |          |

Abbreviations as in Table 2.



# Prognostic Value of External Beam Radiation Therapy in Patients Treated With Surgical Resection and Intraoperative Electron Beam Radiation Therapy for Locally Recurrent Soft Tissue Sarcoma: A Multicentric Long-Term Outcome Analysis

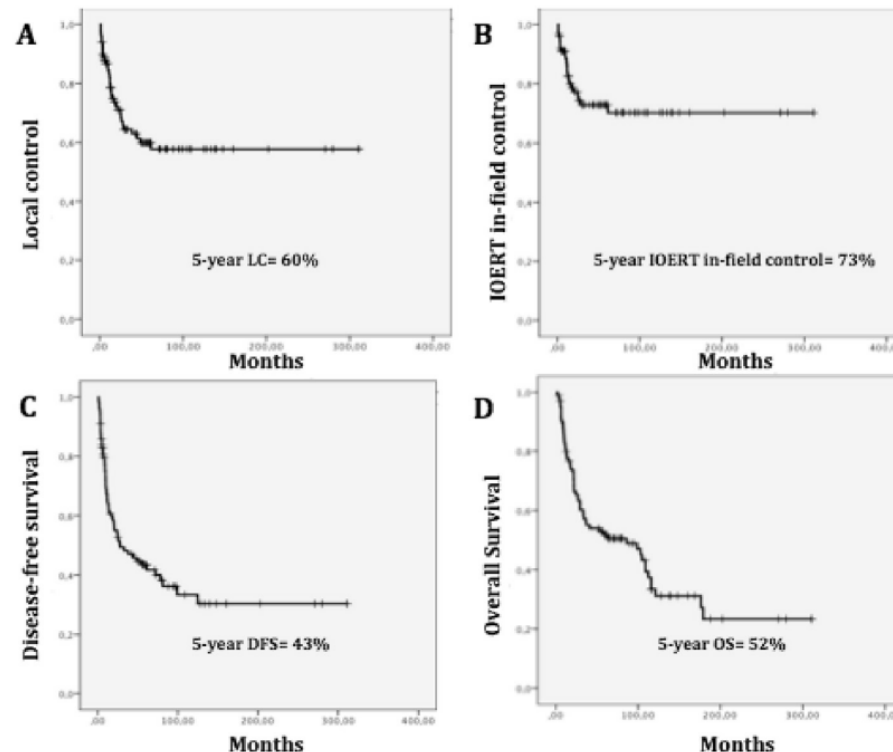
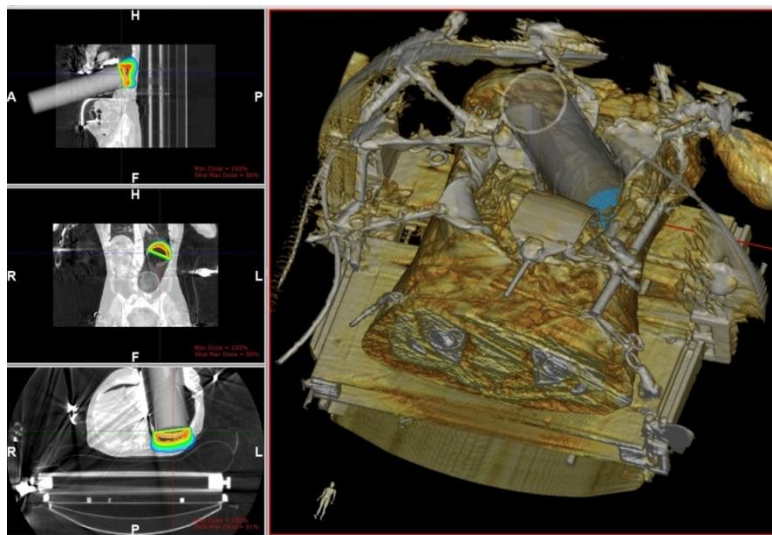
Felipe A. Calvo, MD, PhD,<sup>\*,†</sup> Claudio V. Sole, MD,<sup>\*,†,‡</sup> Mauricio Cambeiro, MD, PhD,<sup>§</sup> Angel Montero, MD,<sup>||</sup> Alfredo Polo, MD, PhD,<sup>||</sup> Carmen Gonzalez, MD,<sup>†,‡,§,||,¶</sup> Miguel Cuervo, MD,<sup>#</sup> Mikel San Julian, MD,<sup>\*\*</sup> Jose L. Garcia-Sabrido, MD, PhD,<sup>†,††</sup> and Rafael Martinez-Monge, MD, PhD<sup>§</sup>

<sup>\*</sup>Department of Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain; <sup>†</sup>School of Medicine, Complutense University, Madrid, Spain; <sup>‡</sup>Service of Radiation Oncology, Instituto de Radiomedicina, Santiago, Chile; <sup>§</sup>Service of Radiation Oncology, Clínica Universitaria, Universidad de Navarra, Pamplona, Spain; <sup>||</sup>Service of Radiation Oncology, Hospital Universitario Ramón y Cajal, Universidad de Alcalá, Madrid, Spain; <sup>¶</sup>Service of Radiation Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain; <sup>#</sup>Service of Orthopedics and Traumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain; <sup>\*\*</sup>Service of Orthopedics and Traumatology, Clínica Universitaria, Universidad de Navarra, Pamplona, Spain; and <sup>††</sup>Service of General Surgery III, Hospital General Universitario Gregorio Marañón, Madrid, Spain

**Table 4** Factors associated with local control, intraoperative electron beam radiation therapy (IOERT) in-field control, disease-free survival, and overall survival in multivariate analyses

| Parameter                             | Variable             | Local control |           |           | IOERT in-field control |        |           | Disease-free survival |           |         | Overall survival |           |         |
|---------------------------------------|----------------------|---------------|-----------|-----------|------------------------|--------|-----------|-----------------------|-----------|---------|------------------|-----------|---------|
|                                       |                      | HR            | 95% CI    | P value   | HR                     | 95% CI | P value   | HR                    | 95% CI    | P value | HR               | 95% CI    | P value |
| <b>Patient variables</b>              |                      |               |           |           |                        |        |           |                       |           |         |                  |           |         |
| Time interval from primary to LR (mo) | ≥24                  | -             | -         | -         | -                      | -      | -         | 1.0                   | -         | -       | 1.0              | -         | -       |
|                                       | <24                  | -             | -         | -         | -                      | -      | -         | 3.87                  | 1.36-7.88 | .006    | 3.44             | 1.29-7.08 | .008    |
| <b>Microscopic surgical specimen</b>  |                      |               |           |           |                        |        |           |                       |           |         |                  |           |         |
| Histologic grade                      | 1-2                  | -             | -         | -         | -                      | -      | -         | 1.0                   | -         | -       | -                | -         | -       |
|                                       | 3                    | -             | -         | -         | -                      | -      | -         | 2.41                  | 1.06-4.92 | .04     | -                | -         | -       |
| <b>Surgery</b>                        |                      |               |           |           |                        |        |           |                       |           |         |                  |           |         |
| Margin status                         | R0                   | 1.0           | 1.06-3.34 | .04       | -                      | -      | -         | 1.0                   | -         | -       | 1.0              | -         | -       |
|                                       | R1                   | 1.73          | -         | -         | -                      | -      | -         | 1.72                  | 1.11-2.83 | .03     | 2.41             | 1.21-4.21 | .02     |
| <b>IOERT technical parameters</b>     |                      |               |           |           |                        |        |           |                       |           |         |                  |           |         |
| CT treatment                          | EBRT                 | Yes           | 1.0       | -         | 1.0                    | -      | -         | -                     | -         | -       | -                | -         | -       |
|                                       | treatment to LR-STSS | No            | 2.12      | 1.18-3.23 | .02                    | 2.08   | 1.10-3.64 | .03                   | -         | -       | -                | -         | -       |

Abbreviations: CI = confidence interval; CT = chemotherapy; EBRT = external beam radiation therapy; HR = hazard ratio.





## *iORT is a precise boost to be combined with high-precision RT*

- Pancreatic cancer (cuasi-uncurable disease)
- Locally advanced rectal cancer
- Soft tissue sarcomas
- Breast cancer
- Mono-oligotopic recurrent cancer (cuasi-uncurable disease)





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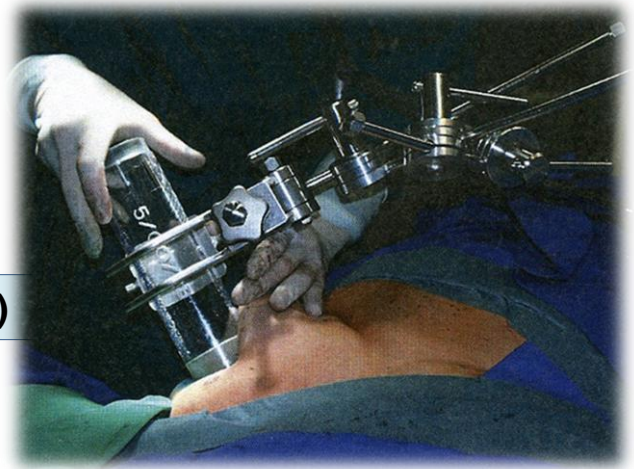
| Author               | No. patients (IORT/boost) | Selection criteria | Technique | Median IORT dose, Gy (boost) or WBRT boost, Gy | Total WBRT dose, Gy (daily dose) | Median follow-up (months) | Local recurrence % (in-breast recurrence) |
|----------------------|---------------------------|--------------------|-----------|--|----------------------------------|---------------------------|---|
| Menck et al. [16]    | 21                        | T1-2               | IORT      | 10 Gy  | 45-50 (1.8-2)                    | 71                        | 0   |
| Dobos et al. [15]    | 101 (5/96)                | T1-2               | IORT      | 10 (n.s. for control)                          | 45-50 (1.8-2)                    | 24 mo FU                  | 0 (IORT)<br>8.1 (control)                 |
| Leenanki et al. [50] | 50*                       | T1-2               | IORT      | 10   | 50 (2)                           | 109                       | 4   |
| Calzavara [26]       | 234 (12/212)              | T1-2               | IORT      | 10 (5+2)                                       |                                  |                           |   |
| Reinamer [29]        | 378 (19/359)              | T1-2               | IORT      | 9 (6+2)  |                                  |                           |   |
| hald [31]            | 204                       | T1-3               | IORT      | 12   |                                  |                           |   |
| Sodlmyer [34]        | 1,031 (pooled analysis)   | T1-3               | IORT      | 10   |                                  |                           |   |
| Valley [33]          | 300 (pooled analysis)     | <4 cm              | Low kV    | 18-20 (surface dose)                           | 45-50 (1.8-2)                    | n.s. (3-80)               | 2.8 (5-y actuarial)                       |

n.s., not stated; EBRT, external beam irradiation; pr. group, IORT neoadjuvant irradiation; EBRT, whole-breast irradiation  
\*Long-term follow-up from Dobos et al. [15]  
\*Includes patient cohorts from Calzavara et al. [26], Reinamer et al. [29]  
\*Includes patient cohorts from Krcan-Tschannacher et al. [44], Joseph et al. [32]

1997-2009, 2,301 patients, 16 Institutions

**Local recurrence (in-breast) 0-4% (1,8%)**

Median follow-up 25-109 months (70 mo)



2011

Strahlentherapie und Onkologie

Supplement Article

**IORT with Electrons as Boost Strategy during Breast Conserving Therapy in Limited Stage Breast Cancer: Results of an ISiORT Pooled Analysis**

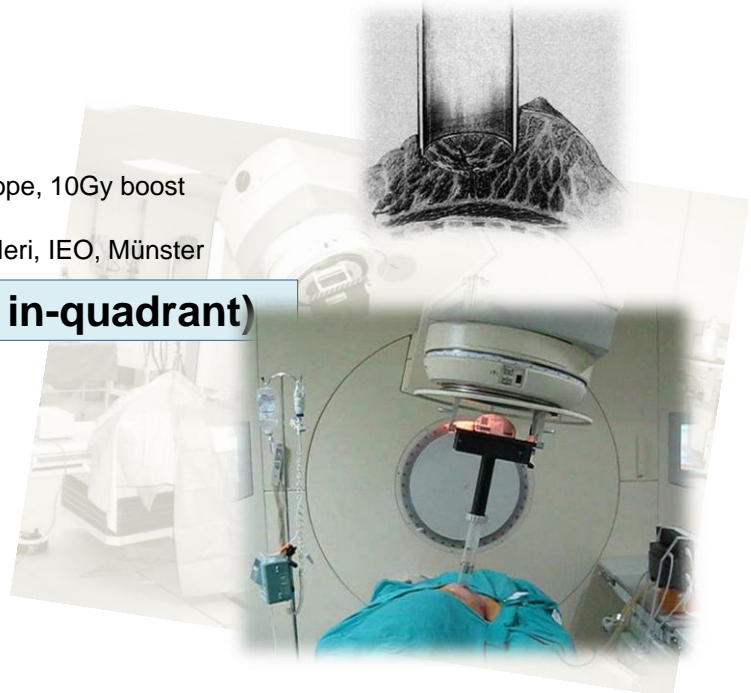
Felix Sodlmyer<sup>1</sup>, Gerd Fastner<sup>1</sup>, Florian Merz<sup>1</sup>, Heinz Deutschmann<sup>1</sup>, Roland Reit<sup>1</sup>, Christian Menzel<sup>1</sup>, Antonella Ciabattoni<sup>1</sup>, Assunta Petrucci<sup>1</sup>, Eva Hager<sup>1</sup>, Norman Martinson<sup>1</sup>, Roberto Orecchia<sup>1</sup>, Vincenzo Valentini<sup>1</sup> on behalf of the ISiORT Europe

1998-2005, 1,231 patients, ISiORT-Europe, 10Gy boost

Salzburg, Montpellier, Gemelli, San F. Neri, IEO, Münster

**1,4% in-breast recurrence (8/16 in-quadrant)**

89% OS @ 10-years (MFT 73 moths)



2007

# IORT Results: breast cancer (anticipated boost)

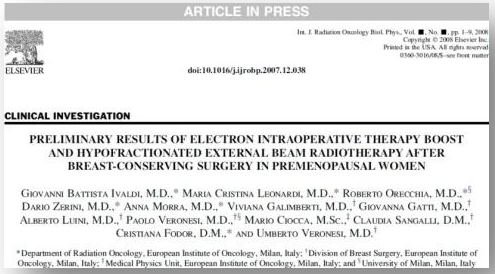


2010

1998-2005  
 300 patients  
 20Gy boost + 50Gy whole-breast

**1,7% local recurrences @ 5-years (in-breast)**

1,0% in-quadrant



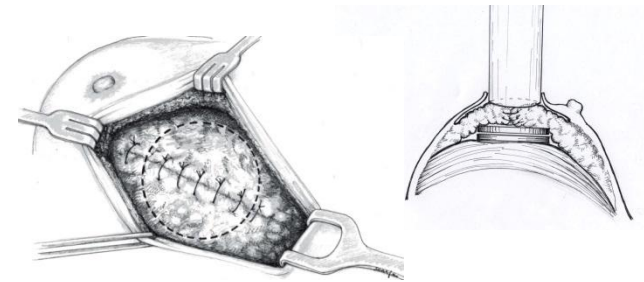
2008

2004-2007, 211 premenopausal pts (46% adjuvant CT)  
 12Gy boost + hypofractionated RT (2,85Gy x 13f)

**0% in-breast recurrence**

Maximal acute toxicity skin toxicity 67% G1, 28% G2, 4% G3





Breast cancer radiotherapy

IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: Long term results of an ISORT pooled analysis



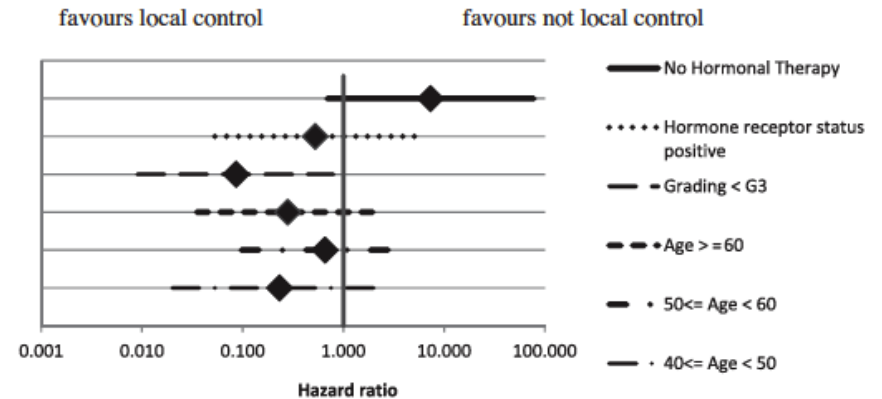
Gerd Fastner<sup>a,\*</sup>, Felix Sedlmayer<sup>a,1</sup>, Florian Merz<sup>a,1</sup>, Heinrich Deutschmann<sup>a,1</sup>, Roland Reitsamer<sup>b,c,1</sup>, Christian Menzel<sup>b,1</sup>, Christoph Stierle<sup>b,c,1</sup>, Armando Farmini<sup>b,c,1</sup>, Torsten Fischer<sup>b,c,1</sup>, Antonella Ciabattini<sup>d,1</sup>, Alessandra Mirri<sup>d,1</sup>, Eva Hager<sup>e,1</sup>, Gabriele Reinartz<sup>f,1</sup>, Claire Lemanski<sup>i,1</sup>, Roberto Orecchia<sup>g,1</sup>, Vincenzo Valentini<sup>h,1</sup>

<sup>a</sup> Department of Radiotherapy and Radio-Oncology; <sup>b</sup> Department of Special Gynecology; <sup>c</sup> Department of Gynecology, Paracelsus Medical University, Salzburg, Austria; <sup>d</sup> Department of Radiotherapy, San Filippo Neri Hospital, Rome, Italy; <sup>e</sup> Department of Radiotherapy, Landeskrankenhaus Klagenfurt, Austria; <sup>f</sup> Department of Radiotherapy, University Clinic Münster, Germany; <sup>g</sup> Department of Radiotherapy, European Institute of Oncology, Milano, Italy; <sup>h</sup> Department of Radiotherapy, Università Cattolica S. Cuore, Rome, Italy; <sup>i</sup> Department of Radiotherapy, Montpellier, France

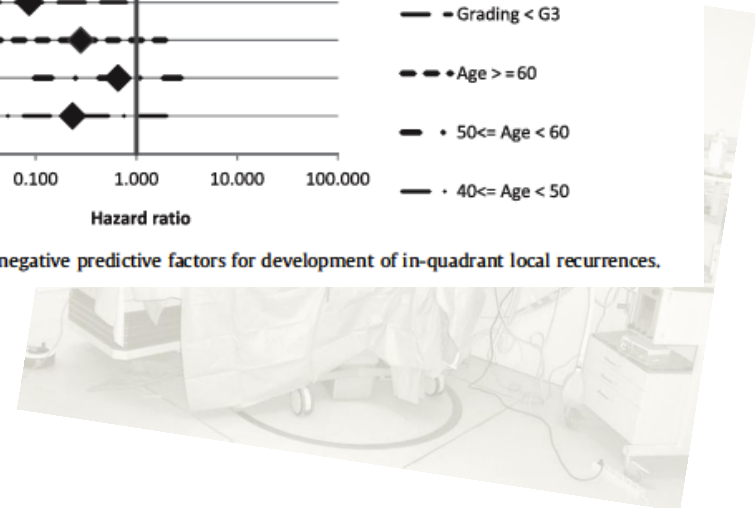


**Table 3**  
Local-recurrences depending on age separated in four groups.

| LR        | Age   | Pts/%    | FUP: median/range (mths) | LR: pts/% | Annual |
|-----------|-------|----------|--------------------------|-----------|--------|
| <i>IB</i> | <40   | 53/4.8   | 74.48 (16.50–126.00)     | 2/3.7     | 0.64%  |
|           | 40–49 | 234/21.1 | 75.89 (4.80–187.90)      | 5/2.1     | 0.34%  |
|           | 50–59 | 326/29.3 | 72.90 (3.80–208.50)      | 4/1.2     | 0.21%  |
|           | ≥ 60  | 496/44.6 | 73.03 (3.48–215.00)      | 5/1.0     | 0.16%  |
| <i>IQ</i> | <40   |          |                          | 2/3.7     | 0.64%  |
|           | 40–49 |          |                          | 2/0.85    | 0.14%  |
|           | 50–59 |          |                          | 2/0.61    | 0.10%  |
|           | ≥ 60  |          |                          | 2/0.40    | 0.06%  |
| <i>OQ</i> | <40   |          |                          | 0/0       | 0      |
|           | 40–49 |          |                          | 3/1.27    | 0.21%  |
|           | 50–59 |          |                          | 2/0.61    | 0.10%  |
|           | ≥ 60  |          |                          | 3/0.60    | 0.09%  |

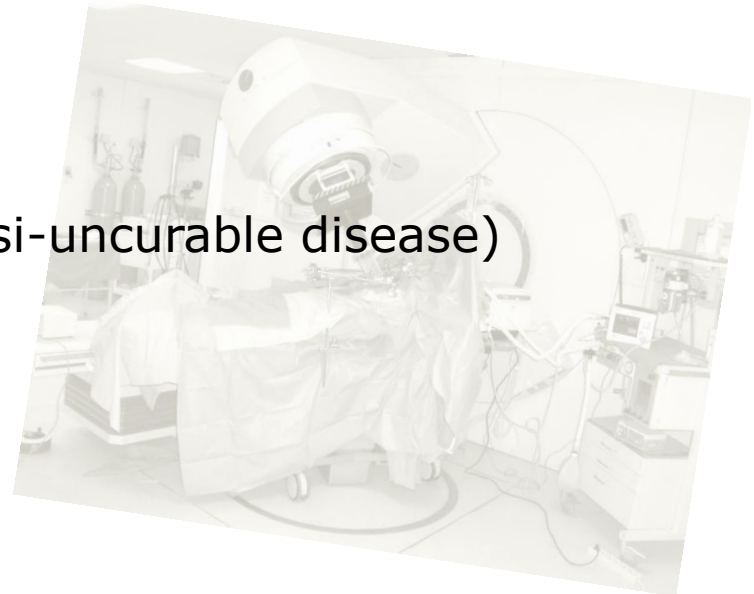


**Fig. 2.** Forrest – Plot: negative predictive factors for development of in-quadrant local recurrences.



## *iORT is a precise boost to be combined with high-precision RT*

- Pancreatic cancer (cuasi-uncurable disease)
- Locally advanced rectal cancer
- Soft tissue sarcomas
- Breast cancer
- Mono-oligotopic recurrent cancer (cuasi-uncurable disease)





# IORT Results: colo-rectal recurrent cancer Mayo Clinic

3 decades... a summary



1981-2008, Mayo Clinic (>25 years experience)

607 patients (rectal 70%), recurrent 45% previous RT, R0 85%

**LC 68% @ 5-y, 30% OS**  
**Central-control vs prior EBRT**  
 (18% vs 14%)  
**R0/R+ (11% vs 9%)**

Survival affected by Rstatus, CT, before/after 1997

2011

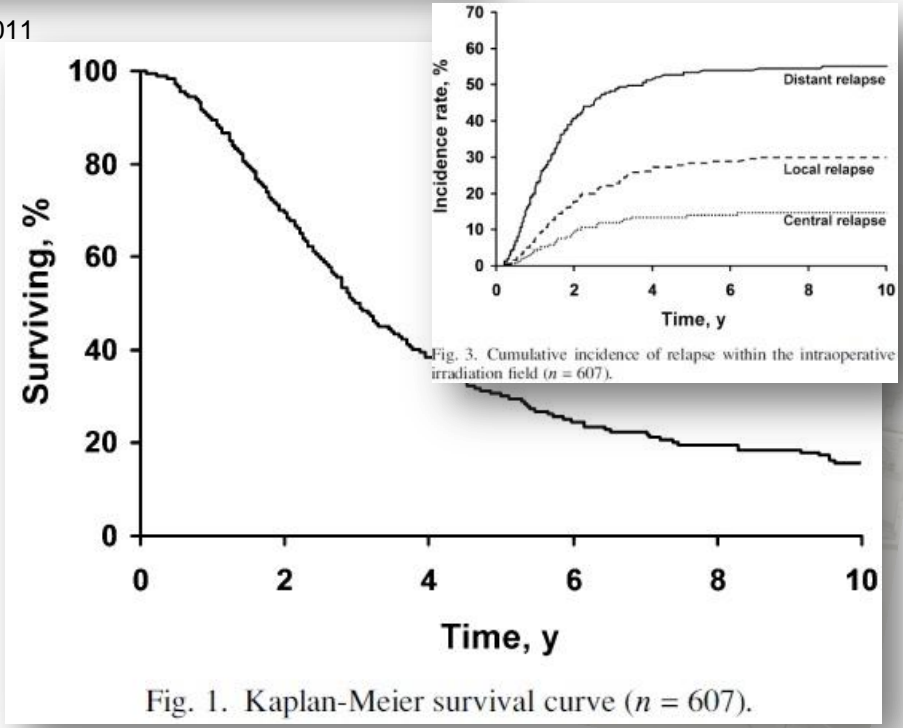


Fig. 1. Kaplan-Meier survival curve (n = 607).



# Oligo-recurrent cancer: oligotopic extrapelvic sites



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## Surgery and intraoperative electron radiotherapy in recurrent or metastatic oligotopic extrapelvic cancer: Long-term outcome

F.A. Calvo<sup>a,f,g,\*</sup>, M.E. González<sup>b,g</sup>, C. González-San Segundo<sup>c,f</sup>, L. González-Bayón<sup>d,f</sup>,  
M.A. Lozano<sup>c</sup>, J.A. Santos-Miranda<sup>c,f</sup>, E. Álvarez<sup>c,f</sup>, J.L. García-Sabrido<sup>d,f</sup>

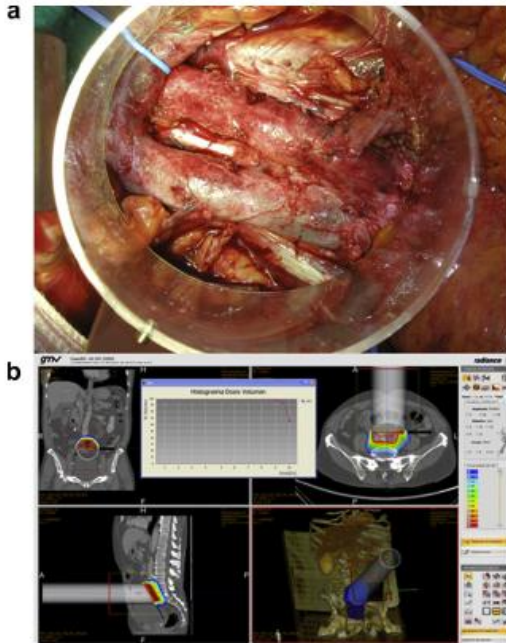


Figure 1. (a) IOERT in a case of oligotopic metastasis of testicular cancer to the para-aortic nodes. After resection, the circular applicator (8 cm in diameter) is placed in the tumor bed area containing the vascular structures and soft tissues, which is the region at risk for recurrence. Non-involved dose-sensitive organs and tissues are temporarily displaced from the target area. (b) Two- and 3-dimensional and dose-volume histogram representation of an IOERT procedure in a case of paraaortic recurrence (radiance system). A left lateral lead protection was used to decrease radiation to the ipsilateral ureter.

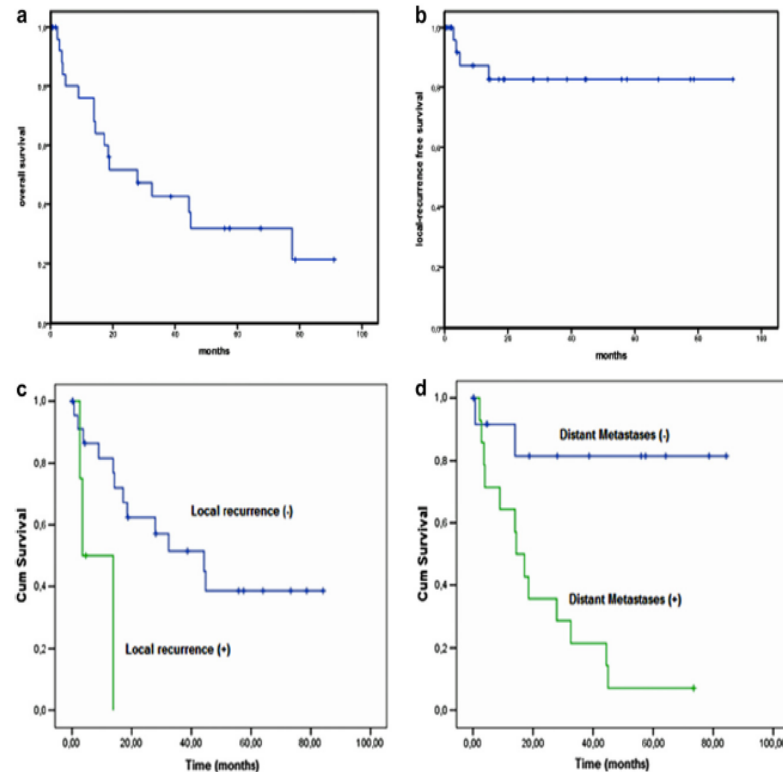


Figure 2. (a) Overall survival. (b) local recurrence-free survival. (c and d) Five-year overall survival according to disease progression pattern: (c) Local recurrence (39.5% and 0% for patients with local recurrence,  $p = 0.012$ ) and (d) distant metastases (8% and 81.5% in patients without distant metastases,  $p = 0.003$ ).

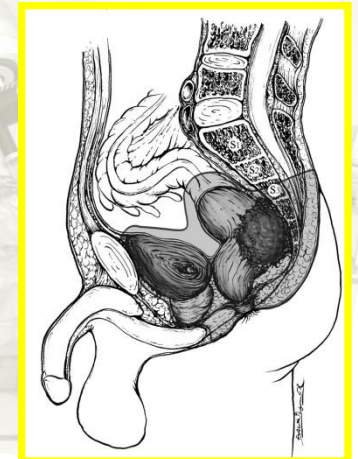
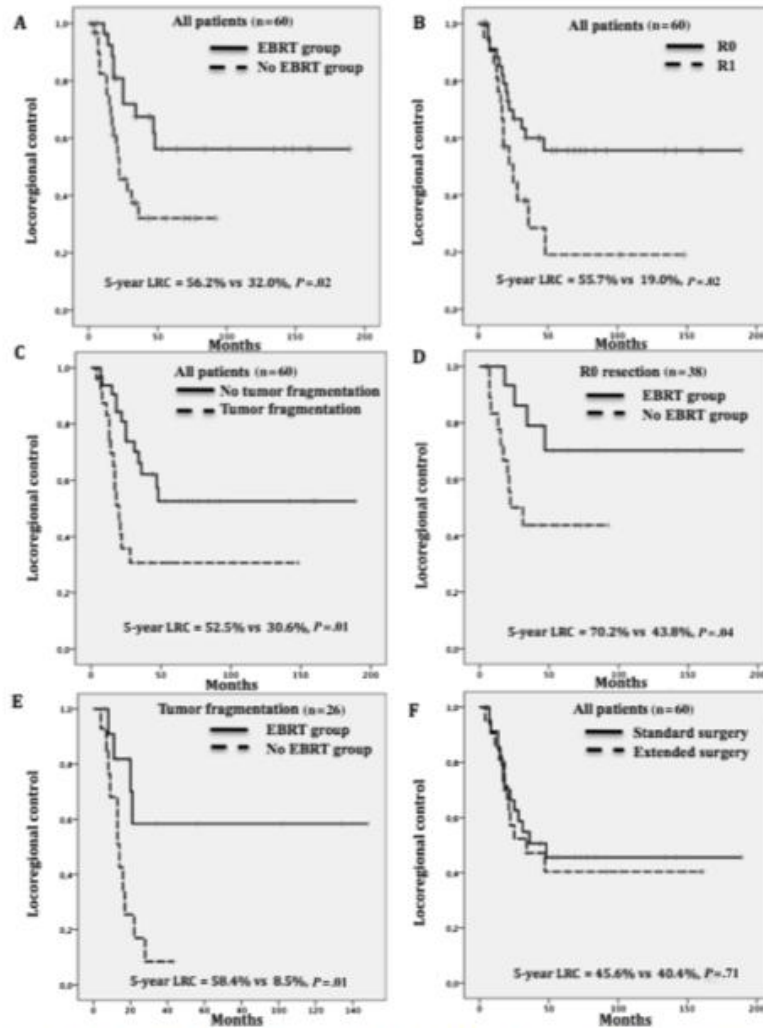


# Oligo-recurrent rectal cancer

Clinical Investigation: Gastrointestinal Cancer

## Prognostic Impact of External Beam Radiation Therapy in Patients Treated With and Without Extended Surgery and Intraoperative Electrons for Locally Recurrent Rectal Cancer: 16-Year Experience in a Single Institution

Felipe A. Calvo, MD, PhD,<sup>\*,§,||</sup> Claudio V. Sole, MD,<sup>\*,§,||,¶</sup>  
Pedro Alvarez de Sierra, MD, PhD,<sup>†,||</sup> Marina Gómez-Espí, MD,<sup>\*,†,§</sup> Jose Blanco, MD,<sup>\*,§</sup>  
Miguel A. Lozano, MD,<sup>\*,†,§</sup> Emilio del Valle, MD,<sup>†,§</sup> Marcos Rodriguez, MD,<sup>†,§</sup>  
Alberto Muñoz-Calero, MD,<sup>†,§</sup> Fernando Turégano, MD,<sup>†,§</sup> Rafael Herranz, MD,<sup>\*,†,§,||</sup>  
Luis Gonzalez-Bayon, MD, PhD,<sup>†,§</sup> and Jose Luis García-Sabrido, MD, PhD<sup>†,§,||</sup>



**Fig. 2.** Locoregional control according to external beam radiation therapy (EBRT) to the recurrent tumor (A), margin status (B), tumor fragmentation (C), EBRT to the recurrent tumor in R0 patients (n = 38) (D), EBRT to the recurrent tumor in patients with tumor fragmentation (n = 26) (E), and surgical (standard/extended) resection (F).

## Multidisciplinary therapy for patients with locally oligo-recurrent pelvic malignancies

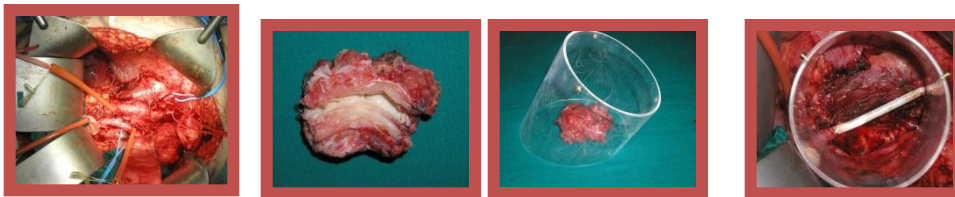
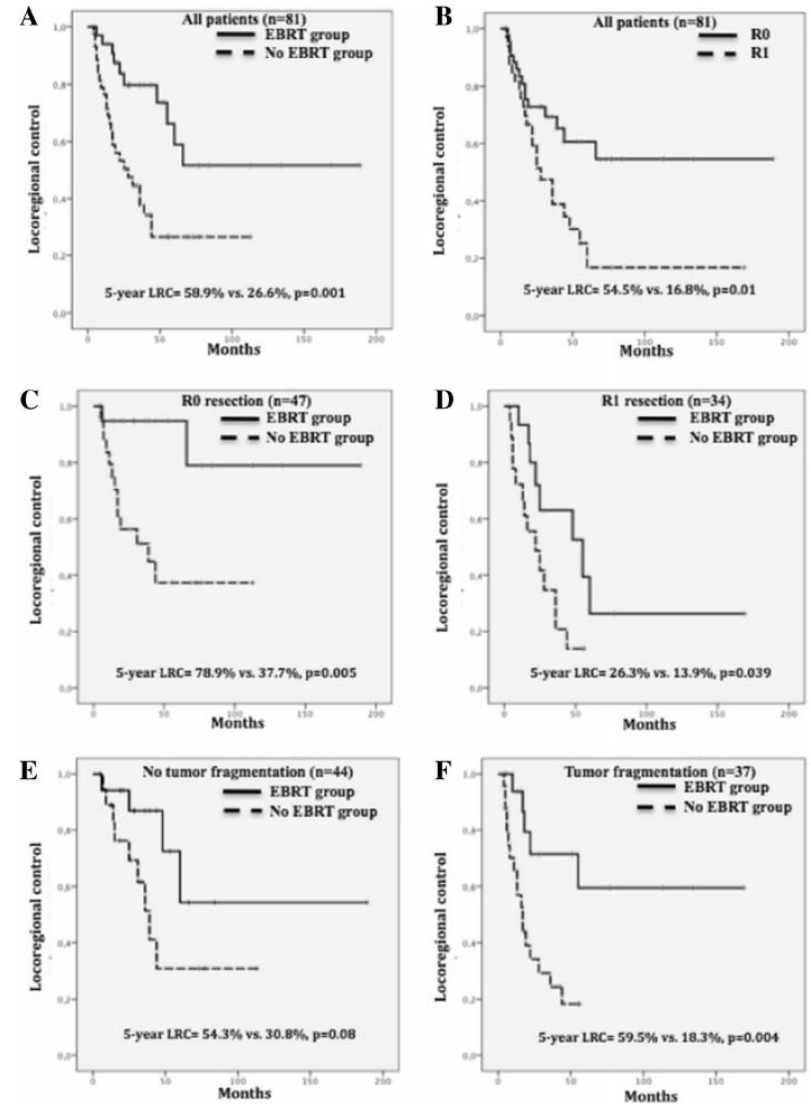
Claudio V. Sole · Felipe A. Calvo ·  
 Pedro Alvarez de Sierra · Rafael Herranz ·  
 Luis Gonzalez-Bayon · Jose Luis García-Sabrido

J Cancer Res Clin Oncol

**Table 4** Correlations between macroscopic/microscopic pathology characteristics and IOERT technical parameters

| Pathology/IOERT            | Surgical specimens | Applicator size<br>Median/range | IOERT dose (Gy)<br>Median/range | IOERT energy (MeV)<br>Median/range |
|----------------------------|--------------------|---------------------------------|---------------------------------|------------------------------------|
| Total number of fragments  |                    |                                 |                                 |                                    |
| 1                          | 37                 | 8/5–15                          | 12.5/10–15                      | 10/6–15                            |
| 2                          | 16                 | 9/5–12                          | 12.5/10–15                      | 12/6–18                            |
| 3                          | 15                 | 7/5–12                          | 12.5/10–15                      | 12/6–18                            |
| 4                          | 5                  | 8/6–15                          | 12.5/10–12.5                    | 12/6–12                            |
| 5                          | 3                  | 7/5–10                          | 12.5/12.5–15                    | 15/10–18                           |
| 6                          | 5                  | 8/6–15                          | 12.5/12.5–15                    | 10/8–18                            |
| T <sub>max</sub> size (cm) |                    |                                 |                                 |                                    |
| 1–3                        | 22                 | 7/5–9                           | 12.5/10–15                      | 9/6–15                             |
| 3.5–6                      | 35                 | 8/5–12                          | 12.5/10–15                      | 12/6–15                            |
| 6.5–24 <sup>a</sup>        | 26                 | 10/7–15                         | 12.5/10–15                      | 12/6–18                            |

<sup>a</sup> 1-field PTV, 13 patients;  
 2-field PTV, 13 patients







## Intraoperative electron beam radiotherapy and extended surgical resection for gynecological pelvic recurrent malignancies with and without external beam radiation therapy: Long-term outcomes

F.A. Calvo<sup>a,b,g,1</sup>, C.V. Sole<sup>a,b,c,g,\*</sup>, M.A. Lozano<sup>a,d,g</sup>, L. Gonzalez-Bayon<sup>e,g</sup>, C. Gonzalez-Sanseguno<sup>a,d,g</sup>, A. Alvarez<sup>d,g</sup>, J. Blanco<sup>d,g</sup>, A. Calín<sup>d,g</sup>, S. Lizarraga<sup>f,g</sup>, J.L. García-Sabrido<sup>b,e,g</sup>

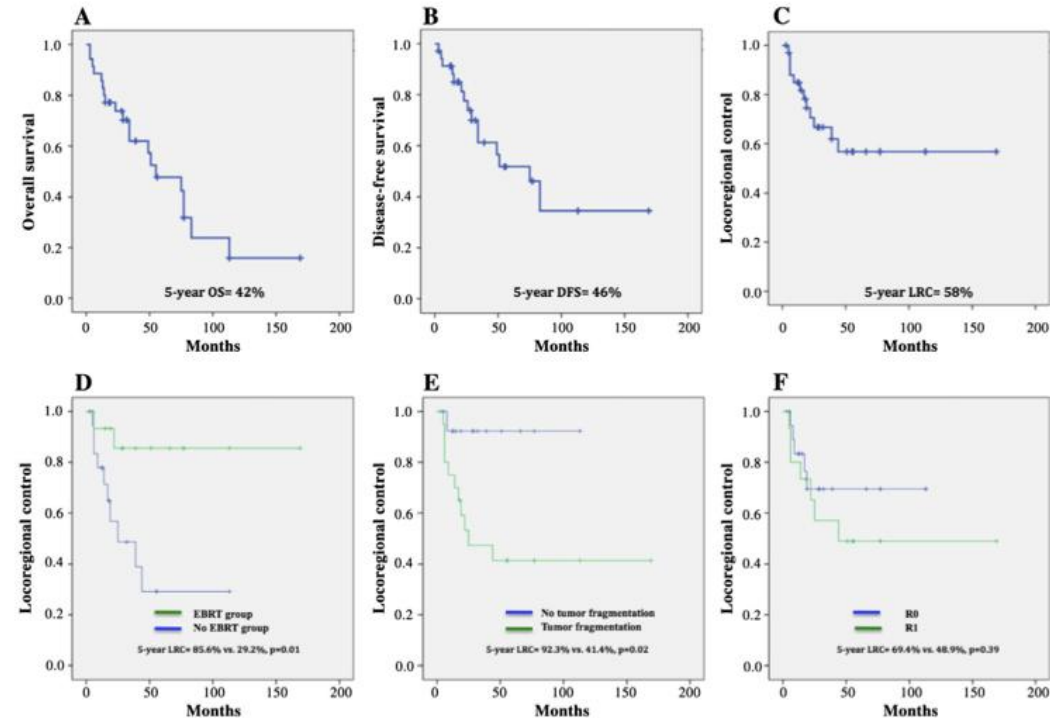
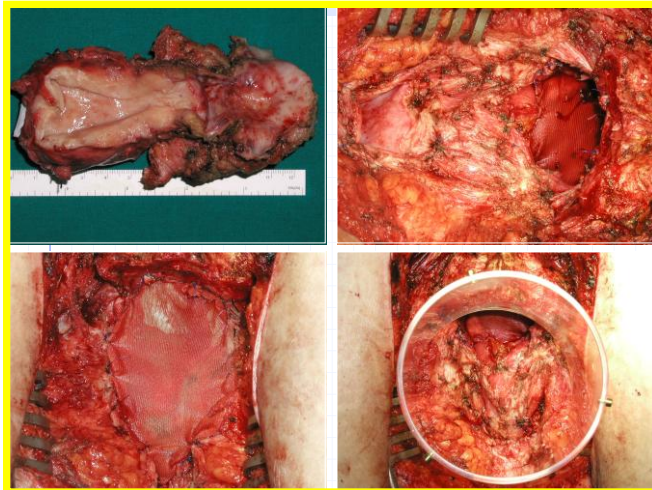
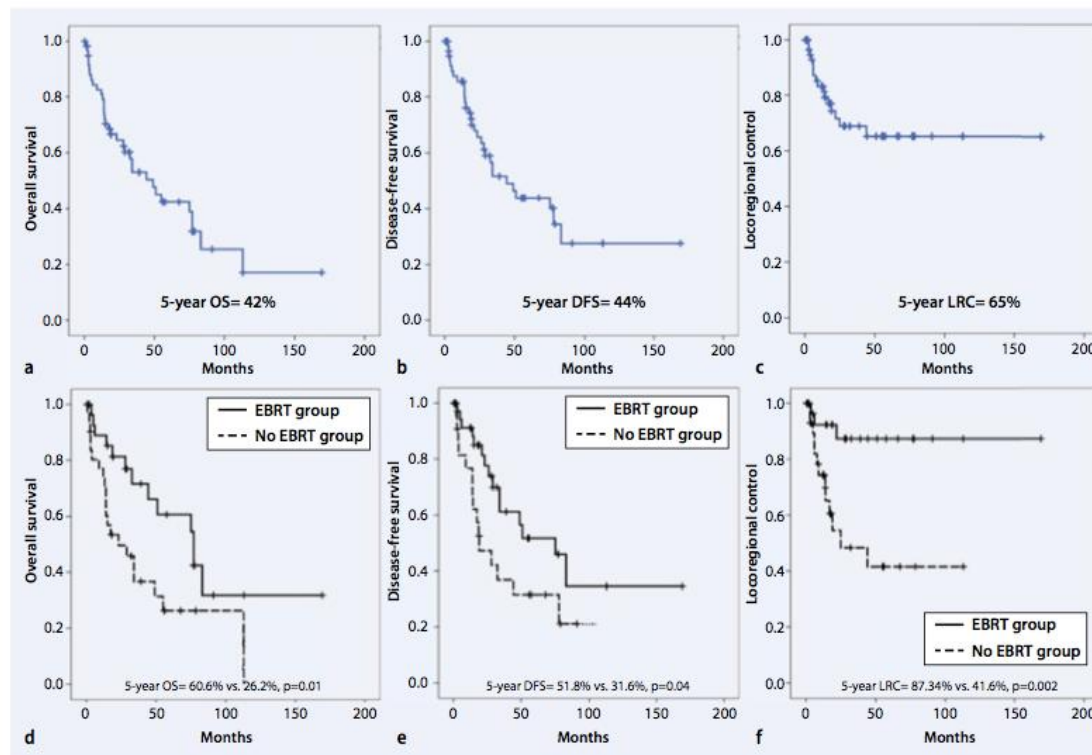
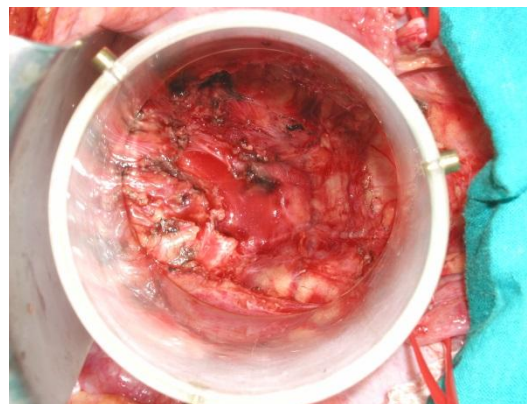


Fig. 1. Kaplan-Meier curves for all 35 patients for overall survival (A), disease-free survival (B), local-regional control (C), locoregional control according to EBRT to the recurrent tumor (D), tumor fragmentation (E) and margin status (F).

# External-beam radiation therapy after surgical resection and intraoperative electron-beam radiation therapy for oligorecurrent gynecological cancer

## Long-term outcome

C.V. Sole<sup>1,2,3,7</sup> · F.A. Calvo<sup>1,2,7</sup> · M.A. Lozano<sup>1,4,7</sup> · L. Gonzalez-Bayon<sup>5,7</sup> · C. Gonzalez-Sanseguno<sup>1,4,7</sup> · A. Alvarez<sup>4,7</sup> · S. Lizarraga<sup>6,7</sup> · J.L. García-Sabrido<sup>2,5,6</sup>



**Fig. 1** ▲ Kaplan–Meier curves of all patients (n=61) for overall survival (a), disease-free survival (b) and local-regional control (c). Overall survival (d), disease-free survival (e) and local-regional control (f) according to EBRT treatment to the local relapse or not



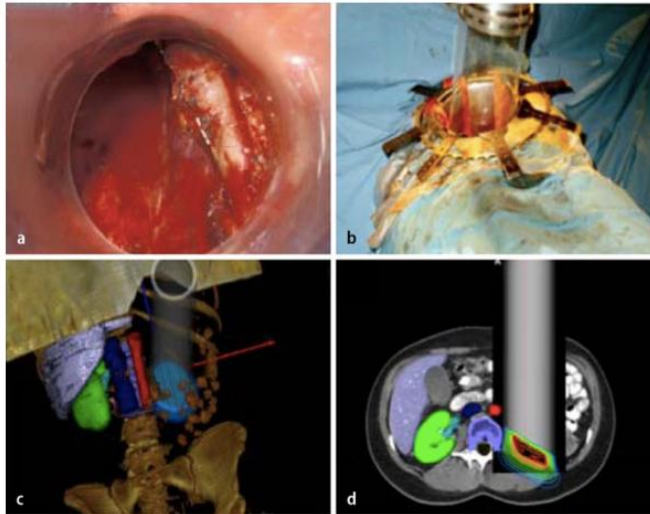


# Oligo-recurrent + / - locally advanced renal cancer

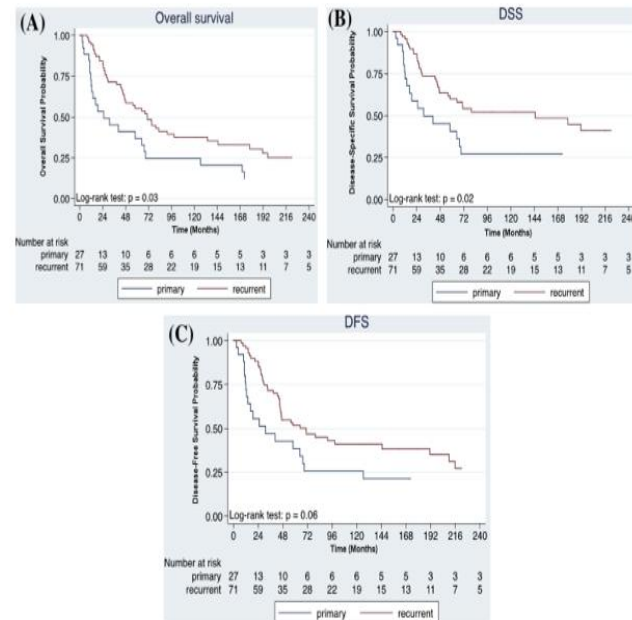
## Clinical Investigation: Genitourinary Cancer

### Outcomes in a Multi-institutional Cohort of Patients Treated With Intraoperative Radiation Therapy for Advanced or Recurrent Renal Cell Carcinoma

Jonathan J. Paly, BS,\* Christopher L. Hallemeier, MD,<sup>†</sup> Peter J. Biggs, PhD,\*  
Andrzej Niemierko, PhD,\* Falk Roeder, MD,<sup>‡</sup> Rafael Martínez-Monge, MD,<sup>§</sup>  
Jared Whitson, MD, MAS,<sup>||</sup> Felipe A. Calvo, MD,<sup>¶</sup> Gerd Fastner, MD,<sup>#</sup>  
Felix Sedlmayer, MD,<sup>#</sup> William W. Wong, MD,\*\* Rodney J. Ellis, MD,<sup>††</sup>  
Michael G. Haddock, MD,<sup>‡</sup> Richard Choo, MD,<sup>‡</sup> William U. Shipley, MD,\*  
Anthony L. Zietman, MD,\* and Jason A. Efstathiou, MD, DPhil\*



**Fig. 3** **a, b** Postnephrectomy tumor bed. An IORT applicator defining the target area (12 cm diameter). Note that normal sensitive intra-abdominal tissues and structures have been displaced from the renal fossae. **c, d** Treatment planning for an IOERT procedure on the renal fossae area (radiance technology)



**Fig. 2.** (A) Overall survival after intraoperative radiation therapy (IORT). (B) Disease-specific survival after IORT. (C) Disease-free survival after IORT.

## ***iORT alone is the only component of high-precision RT***

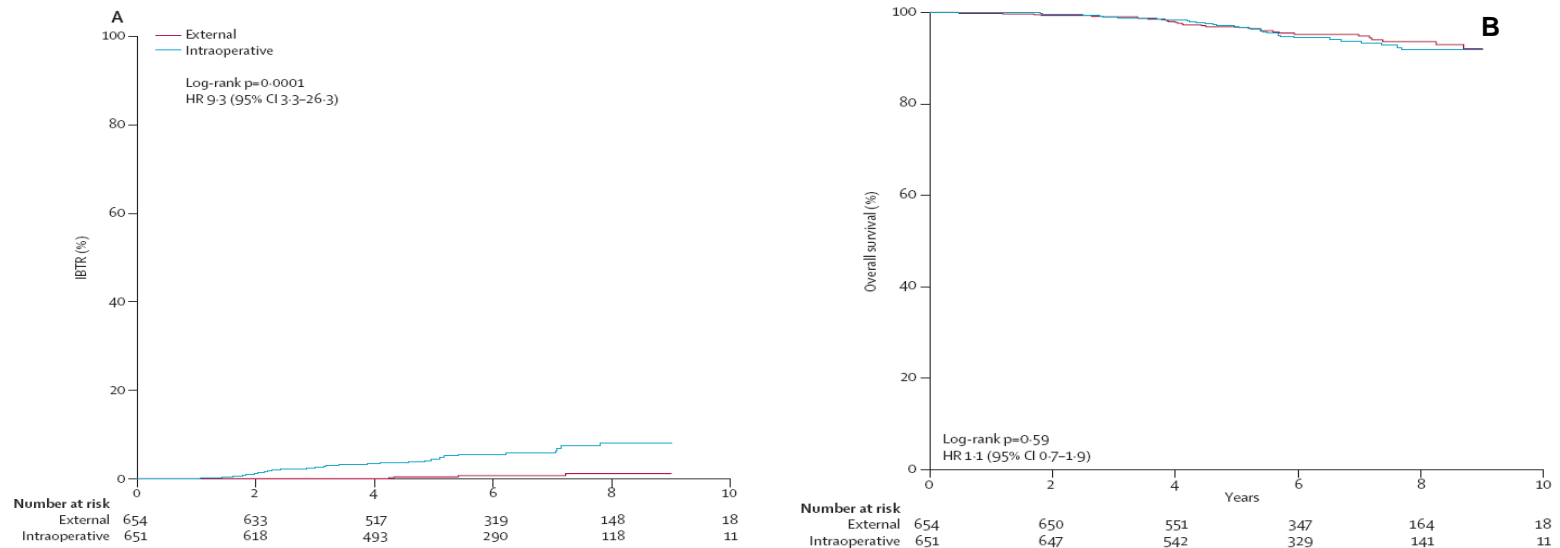
- Breast cancer
- Rectal cancer
- Pancreatic cancer
- Gastric cancer
- Oligorecurrences



# Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial



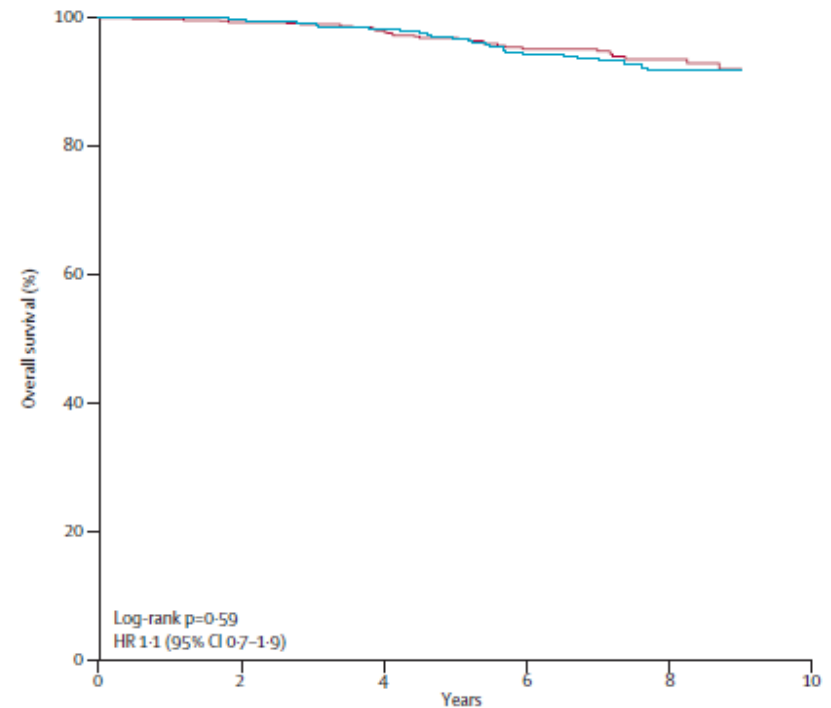
Umberto Veronesi, Roberto Orecchia, Patrick Maisonneuve, Giuseppe Viale, Nicole Rotmensz, Claudia Sangalli, Alberto Luini, Paolo Veronesi, Viviana Galimberti, Stefano Zurrada, Maria Cristina Leonardi, Roberta Lazzari, Federica Cattani, Oreste Gentilini, Mattia Intra, Pietro Caldarella, Bettina Ballardini



**Figure 2: Cumulative incidence of (A) ipsilateral breast tumour recurrence and (B) overall survival (intention-to-treat population)**  
HR=hazard ratio.

# IOeRT 21 Gy - ELIOT

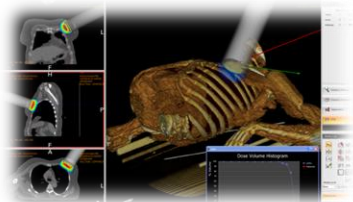
|                     | EBRT            | ELIOT            | p             |
|---------------------|-----------------|------------------|---------------|
| <b>RL- 5 y</b>      | <b>4 (0.4%)</b> | <b>21 (2.5%)</b> | <b>0.0003</b> |
| New 1° ipsi         | 0               | 14 (1.9%)        | 0.0001        |
| TOTAL LOCAL         | 4 (0.4%)        | 35 (4.4%)        | <0.0001       |
| Relapse Axilar/gang | 2 (0.3%)        | 9 (1%)           | 0.03          |
| LRR                 | 6 (0.8%)        | 44 (5.4%)        | <0.0001       |
| Contralateral       | 13 (1.7%)       | 8 (1.1%)         | 0.34          |
| Metastases          | 35 (4.8%)       | 33 (5.1%)        | 0.94          |



**Interpretation** Although the rate of IBTR in the intraoperative radiotherapy group was within the prespecified equivalence margin, the rate was significantly greater than with external radiotherapy, and overall survival did not differ between groups. Improved selection of patients could reduce the rate of IBTR with intraoperative radiotherapy with electrons.

# IORT alone Result: Breast cancer (De-escalation studies)

3 decades... a summary



Breast Cancer Res Treat (2010) 124:141–151  
DOI 10.1007/s10549-010-1115-5

CLINICAL TRIAL

**Intraoperative radiotherapy during breast conserving surgery: a study on 1,822 cases treated with electrons**

Umberto Veronesi · Roberto Orecchia · Alberto Luini · Viviana Galimberti · Stefano Zurrida · Mattia Intra · Paolo Veronesi · Paolo Arnone · Maria Cristina Leonardi · Mario Ciocca · Roberta Lazzari · Pietro Caldarella · Nicole Rotmensz · Claudia Sangalli · Daniele Sancs · Patrick Maisonneuve

2010

2000-2008, 1.822 patients, IEO-Milan, T<2,5cm

21Gy alone, MFT 36 months

1,3% in-breast ipsilateral, 2,3% in-quadrant, 89 OS @ 10-y

LC influenced by age, size, N, Cerb+++, grade, perineural

## ACCELERATED PARTIAL BREAST IRRADIATION CONSENSUS STATEMENT FROM THE AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO)

Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 4, pp. 987–1001, 2009

|                           | All  | ASTRO GUIDELINES |            |            |                | Ext-RT IEO (Botteri) |
|---------------------------|------|------------------|------------|------------|----------------|----------------------|
|                           |      | Suitable         | Cautionary | Unsuitable | Not assessable |                      |
| Patients                  | 1822 | 295 (16%)        | 690 (38%)  | 812 (45%)  | 25 (1%)        |                      |
| Person-y                  | 4    | 1016             | 2409       | 2837       | 101            |                      |
| Person-y                  | 7    | 1091             | 2613       | 3157       | 116            |                      |
| Local rel                 | 1    | 3                | 21         | 50         | 2              |                      |
| 5-year rate*              | 6.0% | 1.5%             | 4.4%       | 8.8%       | 9.9%           |                      |
| <b>Luminal A</b>          |      |                  |            |            |                |                      |
| Patients                  | 648  | 118              | 271        | 251        | 8              | 733                  |
| Person-year-DFS           | 2330 | 436              | 948        | 916        | 30             |                      |
| Loco-regional relapses    | 8    | 2                | 3          | 3          | 0              |                      |
| 5-year rate*              | 1.7% | 2.3%             | 1.6%       | -          | 0.31           |                      |
| <b>Luminal B</b>          |      |                  |            |            |                |                      |
| Patients                  | 977  | 176              | 318        | 474        | 9              | 1127                 |
| Person-year-DFS           | 3371 | 576              | 1101       | 1650       | 44             |                      |
| Loco-regional relapses    | 50   | 1                | 10         | 38         | 1              | 15                   |
| 5-year rate*              | 7.4  | 0.9%             | 4.5%       | 11.5%      | 11.4           | 1.13                 |
| <b>HER2</b>               |      |                  |            |            |                |                      |
| Patients                  | 53   | -                | 25         | 28         | 0              | 118                  |
| Person-year-DFS           | 176  | -                | 82         | 94         | -              |                      |
| Loco-regional relapses    | 6    | -                | 3          | 3          | -              | 6                    |
| 5-year rate*              | 17.0 | -                | 18.3%      | 16.0%      | -              | 5.69                 |
| <b>Triple negative</b>    |      |                  |            |            |                |                      |
| Patients                  | 137  | -                | 74         | 58         | 5              | 208                  |
| Person-year-DFS           | 469  | -                | 276        | 175        | 17             |                      |
| Loco-regional relapses    | 12   | -                | 6          | 1          | 1              | 7                    |
| 5-year rate*              | 12.8 | -                | 9.1%       | 17.1%      | 29.4           | 2.66                 |
| <b>Distant metastases</b> |      |                  |            |            |                |                      |
| Patients                  | 34   | 3                | 8          | 22         | 1              |                      |
| 5-year rate*              | 2.7% | 1.5%             | 1.7%       | 3.9%       | 5.0%           |                      |
| <b>Deaths</b>             |      |                  |            |            |                |                      |
| Patients                  | 47   | 3                | 13         | 30         | 1              |                      |
| 5-year rate*              | 3.4% | 1.4%             | 2.5%       | 4.8%       | 4.3%           |                      |

|                           | All   | GEC-ESTRO GUIDELINES |                     |                   |                | Ext-RT IEO (Botteri) |
|---------------------------|-------|----------------------|---------------------|-------------------|----------------|----------------------|
|                           |       | Good candidates      | Possible candidates | Contra-indication | Not assessable |                      |
| Patients                  | 1822  | 572 (31%)            | 268 (15%)           | 965 (53%)         | 17 (1%)        |                      |
| Person-y                  | 4     | 1838                 | 847                 | 3602              | 76             |                      |
| Person-y                  | 7     | 1979                 | 911                 | 4001              | 86             |                      |
| Local rel                 | 1     | 7                    | 12                  | 56                | 1              |                      |
| 5-year rate*              | 6.0%  | 1.9%                 | 7.1%                | 7.6%              | 6.6%           |                      |
| <b>Luminal A</b>          |       |                      |                     |                   |                |                      |
| Patients                  | 648   | 206                  | 129                 | 306               | 7              | 733                  |
| Person-year-DFS           | 2330  | 676                  | 396                 | 1231              | 27             |                      |
| Loco-regional relapses    | 8     | 0                    | 2                   | 6                 | 0              | 3                    |
| 5-year rate*              | 1.7%  | 0.0%                 | 2.5%                | 2.4%              | 0.0%           | 0.31                 |
| <b>Luminal B</b>          |       |                      |                     |                   |                |                      |
| Patients                  | 977   | 301                  | 122                 | 548               | 6              | 1127                 |
| Person-year-DFS           | 3371  | 954                  | 402                 | 1987              | 27             |                      |
| Loco-regional relapses    | 50    | 3                    | 10                  | 36                | 1              | 15                   |
| 5-year rate*              | 7.4%  | 1.6%                 | 12.4%               | 9.1%              | 18.5%          | 1.13                 |
| <b>HER2</b>               |       |                      |                     |                   |                |                      |
| Patients                  | 53    | 16                   | 1                   | 36                | 0              | 118                  |
| Person-year-DFS           | 176   | 40                   | 0                   | 135               | 0              |                      |
| Loco-regional relapses    | 6     | 1                    | 0                   | 5                 | 0              | 6                    |
| 5-year rate*              | 17.0% | 12.5%                | -                   | 18.5%             | -              | 5.69                 |
| <b>Triple negative</b>    |       |                      |                     |                   |                |                      |
| Patients                  | 137   | 47                   | 16                  | 71                | 3              | 208                  |
| Person-year-DFS           | 469   | 161                  | 49                  | 241               | 19             |                      |
| Loco-regional relapses    | 12    | 3                    | 0                   | 9                 | 0              | 7                    |
| 5-year rate*              | 12.8% | 9.3%                 | 0.0%                | 18.7%             | 0.0%           | 2.66                 |
| <b>Distant metastases</b> |       |                      |                     |                   |                |                      |
| Patients                  | 34    | 5                    | 1                   | 27                | 1              |                      |
| 5-year rate*              | 2.7%  | 1.4%                 | 0.6%                | 3.7%              | 6.6%           |                      |
| <b>Deaths</b>             |       |                      |                     |                   |                |                      |
| Patients                  | 47    | 5                    | 4                   | 38                | 0              |                      |
| 5-year rate*              | 3.4%  | 1.3%                 | 2.2%                | 4.7%              | 0.0%           |                      |



# Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial

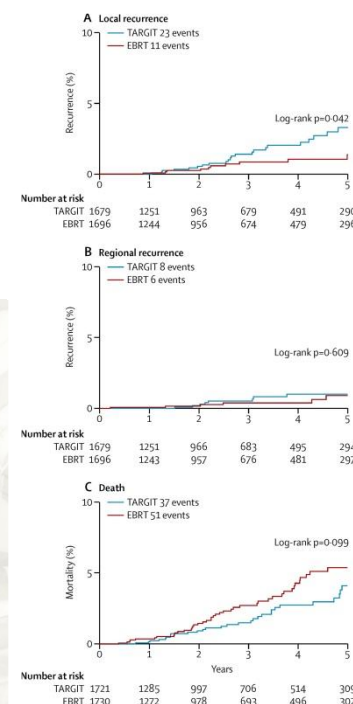


Jayant S Vaidya, Frederik Wenz, Max Bulsara, Jeffrey S Tobias, David J Joseph, Mohammed Keshtgar, Henrik L Flyger, Samuele Massarut, Michael Alvarado, Christobel Saunders, Wolfgang Eiermann, Marinos Metaxas, Elena Sperk, Marc Sütterlin, Douglas Brown, Laura Esserman, Mario Roncadin, Alastair Thompson, John A Dewar, Helle M R Holtveg, Steffi Pigorsch, Mary Falzon, Eleanor Harris, April Matthews, Chris Brew-Graves, Ingrid Potyka, Tammy Corica, Norman R Williams, Michael Baum, on behalf of the TARGIT trialists' group

|                               | Events; 5-year cumulative risk (95% CI) |                    | Absolute difference* |
|-------------------------------|---|--------------------|----------------------|
|                               | TARGIT                                  | EBRT               |                      |
| <b>All patients</b>           |   |                    |                      |
| Local recurrence (n=3375)     | 23; 3.3% (2.1-5.1)                      | 11; 1.3% (0.7-2.5) | 12 (2.0%)            |
| Any other recurrence (n=3375) | 46; 4.9% (3.5-6.9)                      | 37; 4.4% (3.0-6.4) | 9 (0.5%)             |
| Death (n=3451)                | 37; 3.9% (2.7-5.8)                      | 51; 5.3% (3.9-7.3) | -14 (-1.4%)          |
| <b>Prepathology†</b>          |   |                    |                      |
| Local recurrence (n=2234)     | 10; 2.1% (1.1-4.2)                      | 6; 1.1% (0.5-2.5)  | 4 (1.0%)             |
| Any other recurrence (n=2234) | 29; 4.8% (3.1-7.3)                      | 25; 4.7% (3.0-7.4) | 4 (0.1%)             |
| Death (n=2298)                | 29; 4.6% (1.8-6.0)                      | 42; 6.9% (4.3-9.6) | -13 (-2.3%)          |
| <b>Postpathology‡</b>         |   |                    |                      |
| Local recurrence (n=1141)     | 13; 5.4% (3.0-9.7)                      | 5; 1.7% (0.6-4.9)  | 8 (3.7%)             |
| Any other recurrence (n=1141) | 17; 5.2% (3.0-8.8)                      | 12; 3.7% (1.9-7.0) | 5 (1.5%)             |
| Death (n=1153)                | 8; 2.8% (1.3-5.9)                       | 9; 2.3% (1.0-5.2)  | -1 (0.5%)            |

TARGIT=targeted intraoperative radiotherapy. EBRT=external beam radiotherapy. \*In Kaplan-Meier point estimate at 5 years (TARGIT minus EBRT). †TARGIT given at same time as lumpectomy. ‡TARGIT given after lumpectomy, as separate procedure.

**Table 1:** Results of primary (local recurrence in the conserved breast), secondary (death), and exploratory (any other recurrence) outcomes for all patients and the two strata as per timing of randomisation and delivery of TARGIT



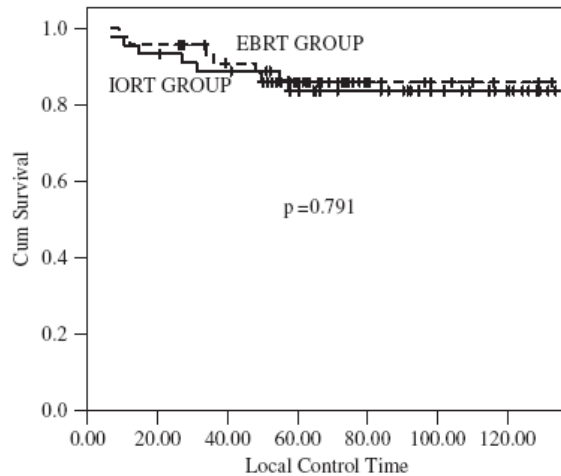
## ***iORT alone is the only component of high-precision RT***

- Breast cancer
- Rectal cancer
- Pancreatic cancer
- Gastric cancer
- Oligorecurrences

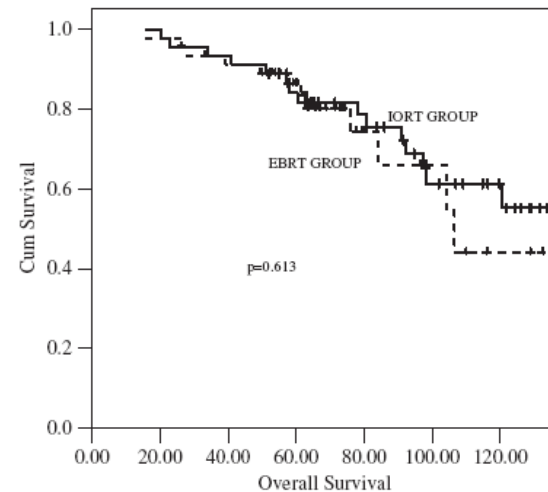


# Intraoperative Radiotherapy in the Combination of Adjuvant Chemotherapy for the Treatment of pT3N0M0 Rectal Cancer After Radical Surgery

Qing Zhang, MD,\* Jeremy Tey, MD,† Zhe Yang MD,‡ Ping Li, MD,\* Lihua Peng, MD,\*  
Ruiyao Jiang BS,\* Fei Xiong BS,\* Shen Fu, MD, PHD,\* and Jiade J. Lu, MD, MBA†



**FIGURE 1.** Local control rates between the IORT group and the EBRT group. Cum indicates cumulative; EBRT, external beam radiotherapy; IORT, intraoperative radiotherapy.



**FIGURE 2.** Overall survival between the IORT group and the EBRT group. Cum indicates cumulative; EBRT, external beam radiotherapy; IORT, intraoperative radiotherapy.

## ***iORT alone is the only component of high-precision RT***

- Breast cancer
- Rectal cancer
- Pancreatic cancer
- Gastric cancer
- Oligorecurrences



# IORT Results: Locally advanced unresectable pancreatic cancer

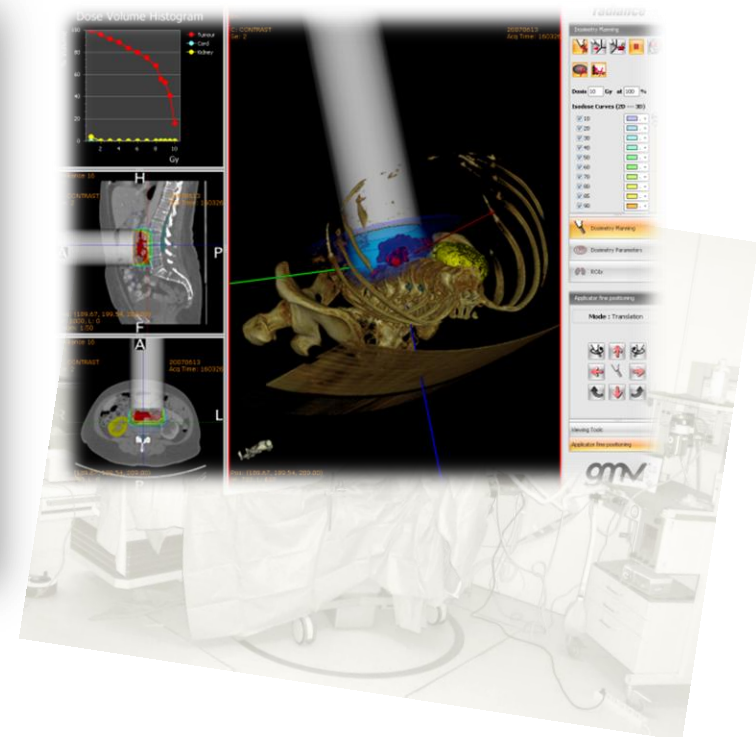
2000-2006, 870 patients, 34 Institutions

21% investigational protocol, 44% EBRT

76% concomitant gemcinabine, 75% IORT dose > 25Gy



2011





## ***iORT alone is the only component of high-precision RT***

- Breast cancer
- Rectal cancer
- Pancreatic cancer
- Gastric cancer
- Oligorecurrences



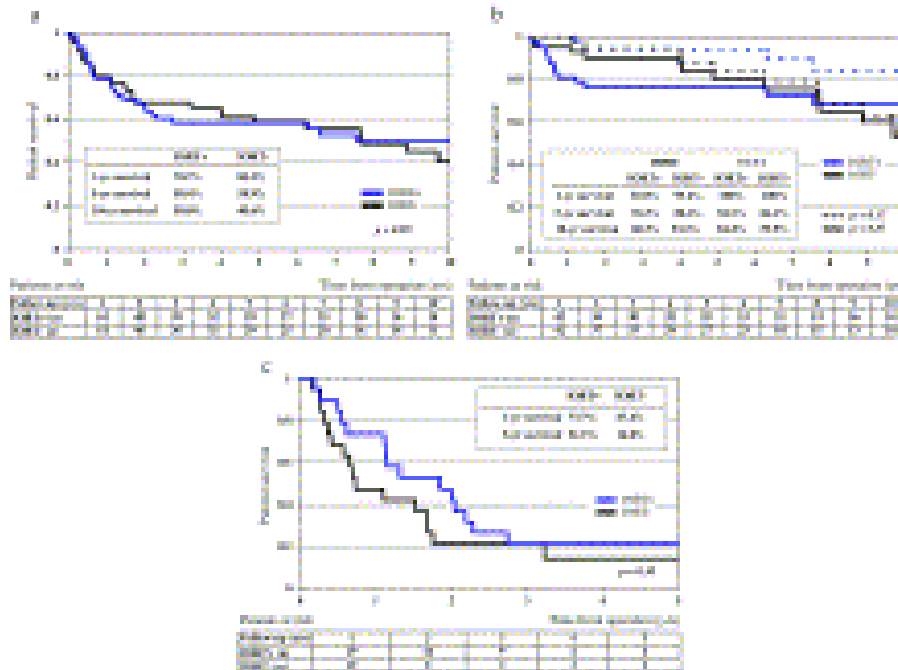
**CLINICAL INVESTIGATION**

**Stomach**

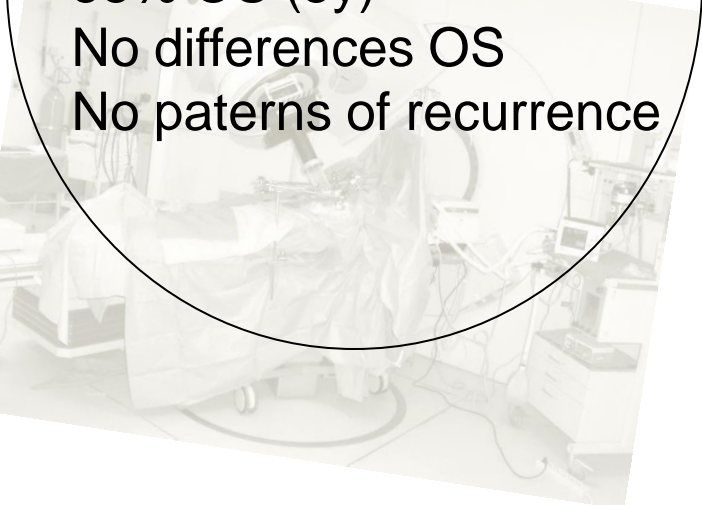
**LONG-TERM RESULTS AFTER INTRAOPERATIVE RADIATION  
 THERAPY FOR GASTRIC CANCER**

OLIVER DROGNITZ, M.D., PH.D.,\* KARL HENNE, M.D.,† CHRISTIAN WEISSENBERGER, M.D., PH.D.,†  
 GREGOR BRUGGMOSER, M.D., PH.D.,† HEIKE GÖBEL, M.D.,† ULRICH THEODOR HOPT, M.D., PH.D.,\*  
 HERRMANN FROMMHOLD, M.D., PH.D.,† AND GÜNTHER RUF, M.D., PH.D.\*

\*Department of Surgery, Division of General and Visceral Surgery, †Department of Radiotherapy, and  
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84 patients  
 23 Gy 9-15 MeV  
 Single dose  
 58% OS (5y)  
 No differences OS  
 No patterns of recurrence



## ***iORT alone is the only component of high-precision RT***

- Breast cancer
- Rectal cancer
- Pancreatic cancer
- Gastric cancer
- Oligorecurrences (STS)



## Intraoperative radiotherapy-containing multidisciplinary management of trunk-wall soft-tissue sarcomas

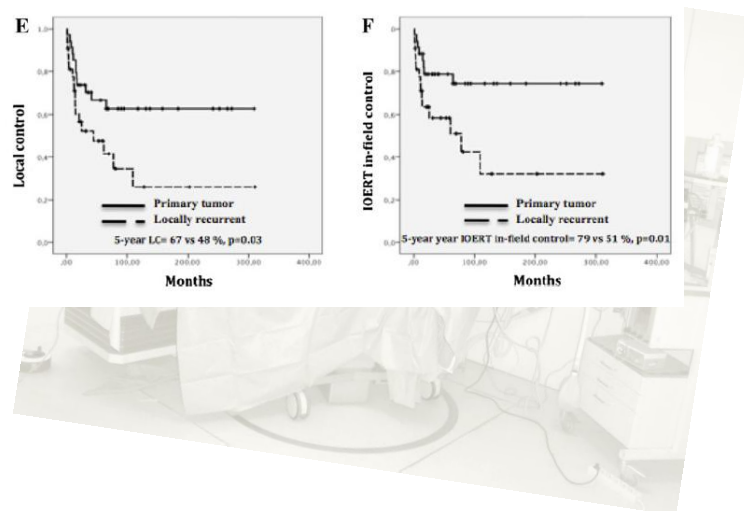
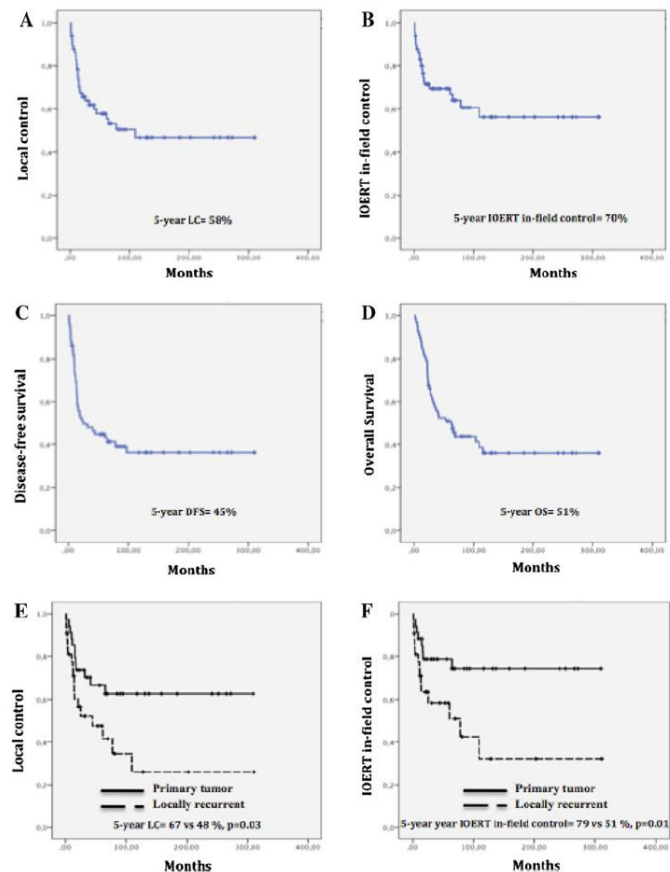
C. V. Sole · F. A. Calvo · M. Cambeiro · A. Polo ·  
A. Montero · R. Hernanz · C. Gonzalez · M. Cuervo ·  
D. Perez · M. S. Julian · R. Martinez-Monge

**Table 4** Factors associated with local control, IOERT in-field control, disease-free survival and overall survival in multivariate analyses

| Parameter                     | Variable  | Local control |           |                | IOERT in-field control |           |                | Disease-free survival |           |                | Overall survival |           |                |
|-------------------------------|-----------|---------------|-----------|----------------|------------------------|-----------|----------------|-----------------------|-----------|----------------|------------------|-----------|----------------|
|                               |           | HR            | 95 % CI   | <i>p</i> value | HR                     | 95 % CI   | <i>p</i> value | HR                    | 95 % CI   | <i>p</i> value | HR               | 95 % CI   | <i>p</i> value |
| Patients                      |           |               |           |                |                        |           |                |                       |           |                |                  |           |                |
| Age (years)                   | ≤50       | –             | –         | –              | –                      | –         | –              | –                     | –         | –              | 1.0              | 1.13–6.38 | <i>0.03</i>    |
|                               | >50       |               |           |                |                        |           |                |                       |           |                |                  | 2.68      |                |
| Pre-surgical variables        |           |               |           |                |                        |           |                |                       |           |                |                  |           |                |
| Tumor status                  | Primary   | –             | –         | –              | 1.0                    | 1.05–6.27 | <i>0.04</i>    | 1.0                   | 1.21–5.33 | <i>0.01</i>    | 1.0              | 1.08–3.26 | <i>0.04</i>    |
|                               | Recurrent |               |           |                |                        |           |                |                       |           |                |                  | 2.54      | 1.75           |
| Microscopic surgical specimen |           |               |           |                |                        |           |                |                       |           |                |                  |           |                |
| Histologic grade              | I–II      | –             | –         | –              | –                      | –         | –              | 1.0                   | 1.15–4.76 | <i>0.02</i>    | 1.0              | 1.03–4.76 | <i>0.04</i>    |
|                               | III–IV    |               |           |                |                        |           |                |                       |           |                |                  | 2.38      | 2.12           |
| Surgery                       |           |               |           |                |                        |           |                |                       |           |                |                  |           |                |
| Margin status                 | R0        | 1.0           | 1.90–8.30 | < <i>0.001</i> | 1.0                    | 1.36–7.67 | <i>0.008</i>   | 1.0                   | 1.15–4.88 | <i>0.01</i>    | 1.0              | 1.43–5.88 | <i>0.003</i>   |
|                               | R1        |               |           |                |                        |           |                |                       |           |                |                  | 3.97      | 2.90           |

Values in italic indicate *p* < 0.05

IOERT intraoperative electron-beam radiotherapy



# Van der Schueren 2011...



3 years after...

A synthesis of data, progress  
and opportunities





# IOeRT in resected primary cancer: 2014 update HGUGM published results

| Cancer                              | N   | Stage / treatment                      | In-field relapse | Survival  | Local adversity     | Local compensation    |
|-------------------------------------|-----|--|------------------|-----------|---------------------|-----------------------|
| <b>Esophago-gastric</b>             | 53  | IIA-IIIB<br>Neoadjuvant + CRT          | 5,4% vs 25%      | 48% (5y)  | No-IORT             | cN+, cT               |
| <b>Rectal</b>                       | 335 | cT3-4 or cN+<br>Neoadjuvant + CRT      | 5% (presacral)   | 72% (10y) | R1, ypN+            | Grade, distal margin  |
| <b>Pancreas</b>                     | 60  | IIA-IIIB<br>R + IOeRT +/- pre/post CRT | 4% vs 65%        | 20% (5y)  | No-IORT, R1         | pN+, R1 (+EBRT)       |
| <b>Gastric</b>                      | 32  | IIA-III<br>R + post CRT                | 0%               | 54% (5y)  | pN+ (non in-field)  | R1, pT3 stage         |
| <b>Extremity sarcoma</b>            | 159 | I-III 10cm<br>R + post RT              | 14%              | 72% (5y)  |                     |                       |
| <b>Pediatric extremity sarcomas</b> | 62  | R + post RT                            | 15%              | 81% (10y) | R1, >5cm            | Histology, grade deep |
| <b>Breast*</b>                      | 56  | T1-2Nx post-RT<br>T1-2N0 no-ERT        | 0% (3y)          | 96% (3y)  | Luminal B Marging + | With EBRT             |

CRT: chemo-radiation; R: resected; EBRT: external beam radiotherapy; \* under revision

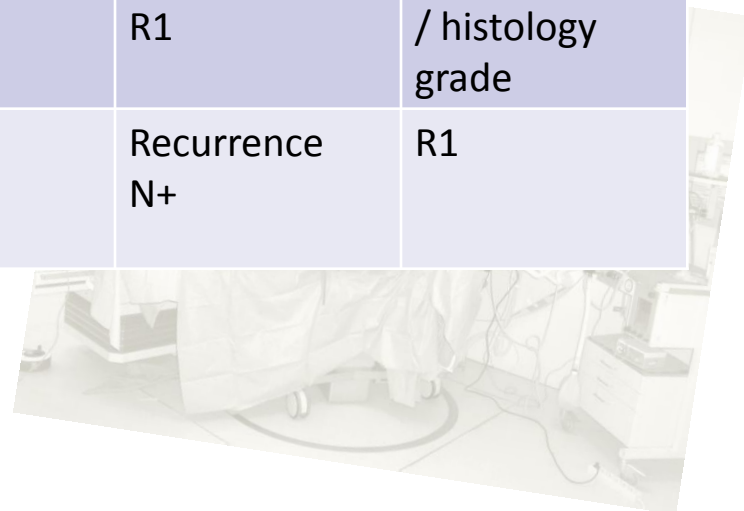
# IOeRT electrons: 2014 results update in oligorecurrence

| Cancer                     | N   | Local control | Survival | Adversity Local  | Compensation Local                    |
|----------------------------|-----|---------------|----------|------------------|---------------------------------------|
| Gynecological <sup>1</sup> | 61  | 69            | 42       | No EBRT          | Para-aortic                           |
| Rectal <sup>1</sup>        | 60  | 44            | 39       | No EBRT<br>R1    | Fragmentation                         |
| Sarcoma <sup>2</sup>       | 103 | 64            | 52       | No EBRT<br>R1    | Fragmentation<br>/ histology<br>grade |
| Renal <sup>3</sup>         | 98  | 72            | 43       | Recurrence<br>N+ | R1                                    |

<sup>1</sup> HGUGM

<sup>2</sup> HGUGM, HRyC, CUN

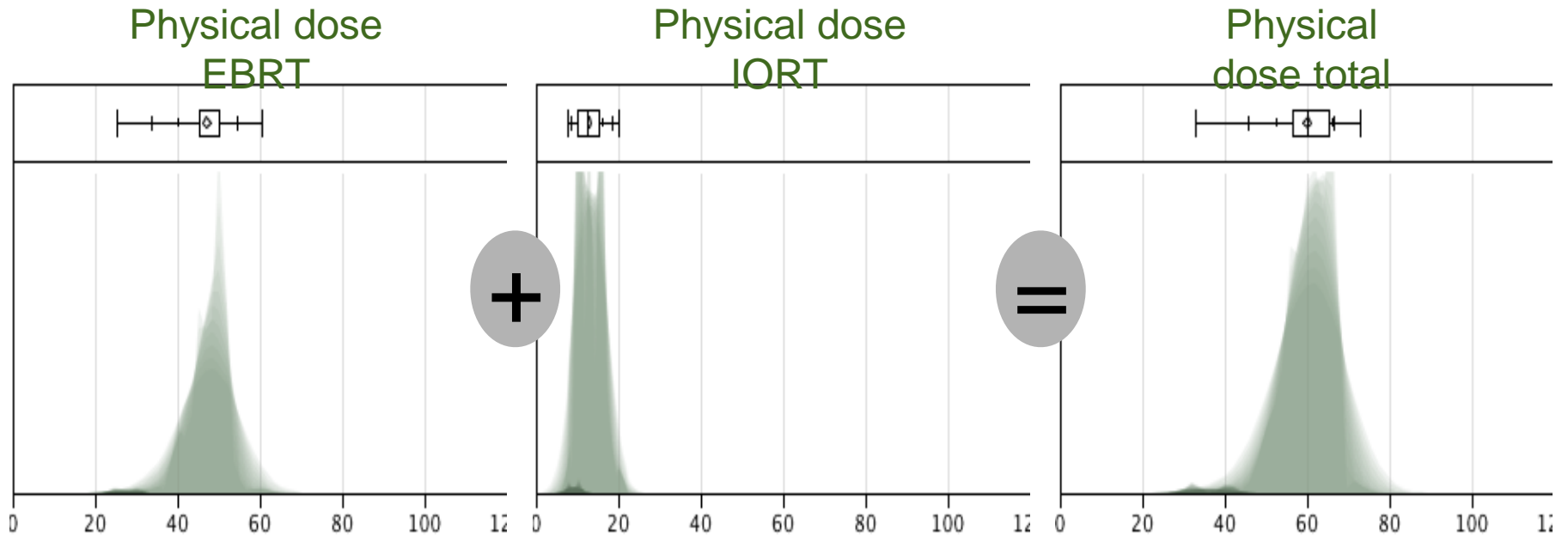
<sup>3</sup> HGUGM, CUN, MGH, Heidelberg



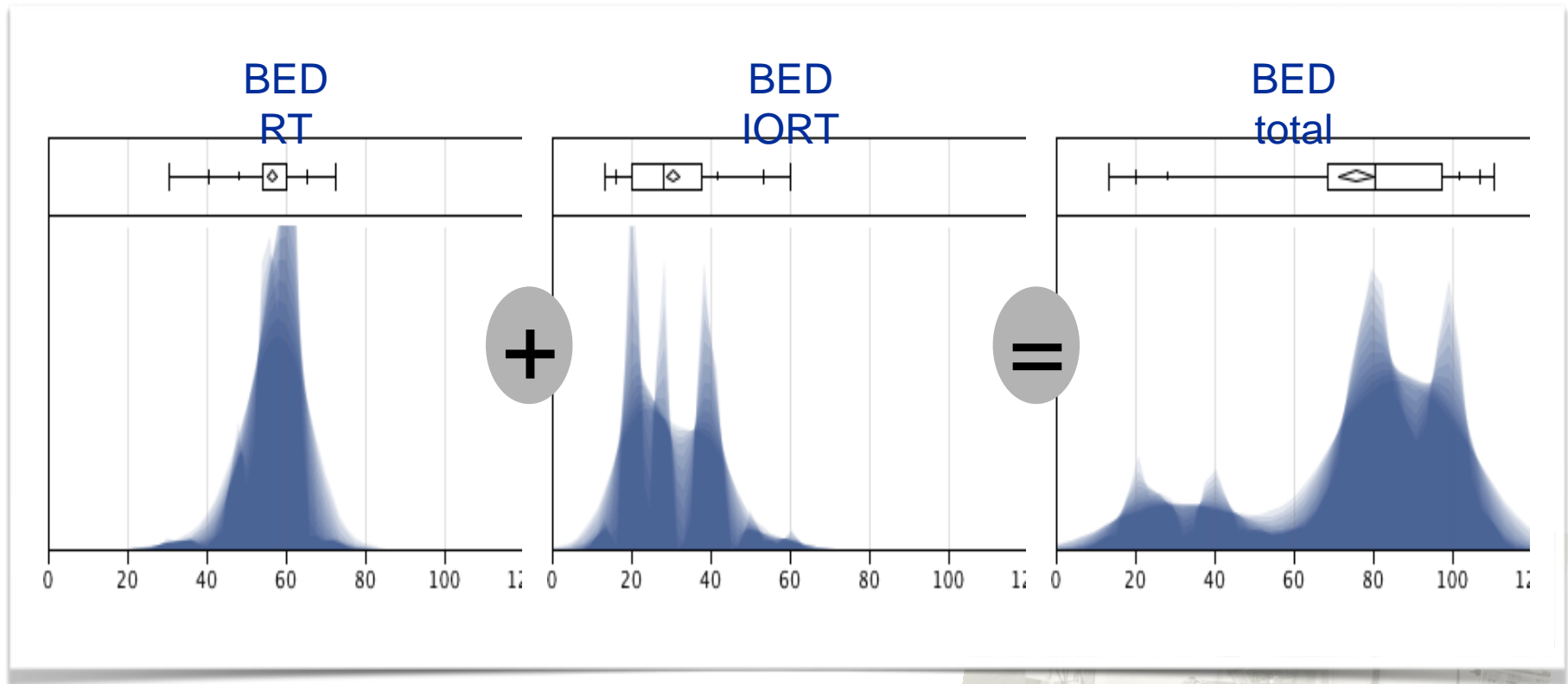
***Clinical opportunities...risk  
Bio-models + technology + outcome...***



# From physical dose outcome analysis...



# To biomodeling dose-dense IOERT containing results: pooled sarcoma data



Polo et al. ASTRO 2012





*Clinical opportunities...risk*  
**Bio-models + technology + outcome...**

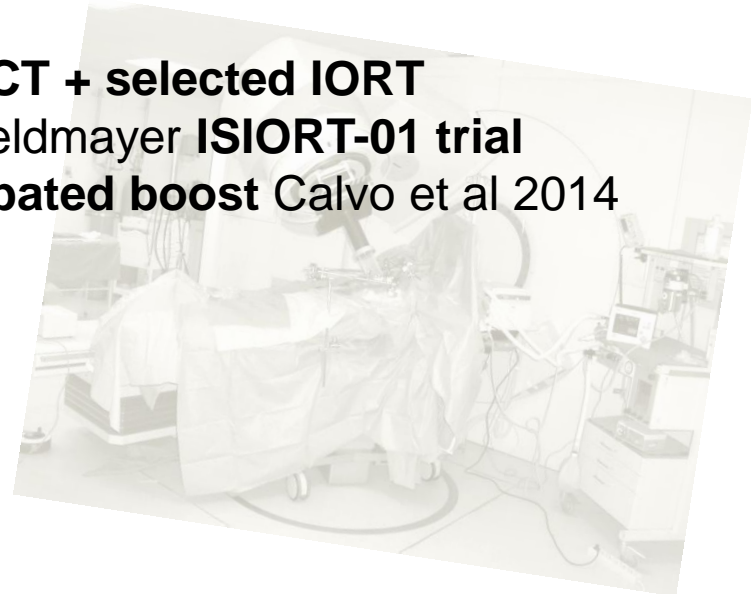


## **Dose-dense strategies: Hypofractionation**

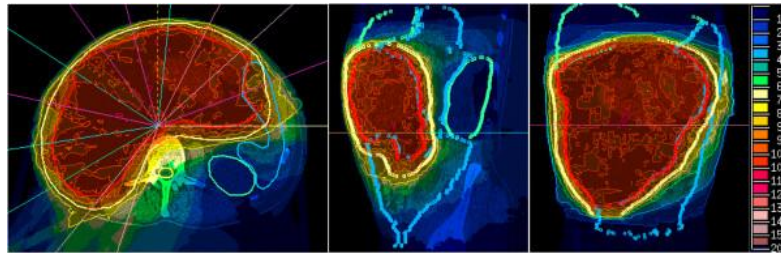
Rectal cancer: **5 x 5 Gy + CT + selected IORT**

Breast cancer: Fastner / Seldmayer **ISIORT-01 trial**

Pediatric sarcomas: **anticipated boost** Calvo et al 2014



## *Clinical opportunities...risk Bio-models + technology + outcome...*



### **Dose-dense-escalated strategies**

Extremity sarcomas: **IMRT vs 3D superior** Folkert / Alektiar J Clin Oncol 2014

Retroperitoneal sarcomas: **pre-IMRT + IORT** Roeder et al BMC Cancer 2014

Pancreatic cancer: **SBRT efficient** Trakul et al Sem Radiat Oncol 2014

Oligo-cancer: **SBRT curable** Corbin / Weichselbaum J Clin Oncol 2013

Rectal cancer: **laparoscopic resection + IORT**

Calvo / Sole (J Cancer Res Clin Oncol 2013)



*Clinical opportunities...risk  
Bio-models + technology + outcome...*



## Dose-dense-escalated-molecular-guided strategies

Breast cancer: **neoadjuvant CT + anticipated IORT**

*Fastner / Sedlmayer Int J Cancer 2014*

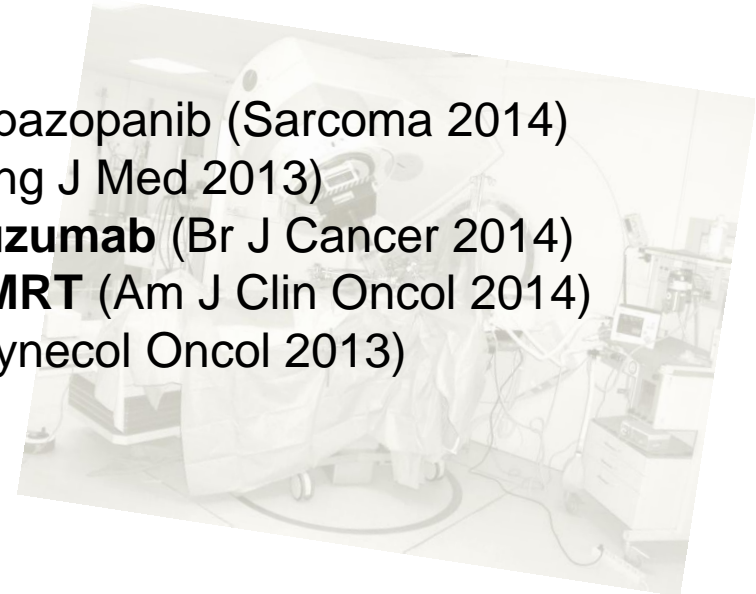
Sarcomas: **trabectedin** (Curr Oncol Rep 2014), pazopanib (Sarcoma 2014)

Pancreatic cancer: **stroma nab-paclitaxel** (N Eng J Med 2013)

Esophago-gastric cancer: **HER2 positive trastuzumab** (Br J Cancer 2014)

Rectal cancer: **K-RAS status personalized + IMRT** (Am J Clin Oncol 2014)

Gynecologic cancer: **EGFR mutations GOG** (Gynecol Oncol 2013)



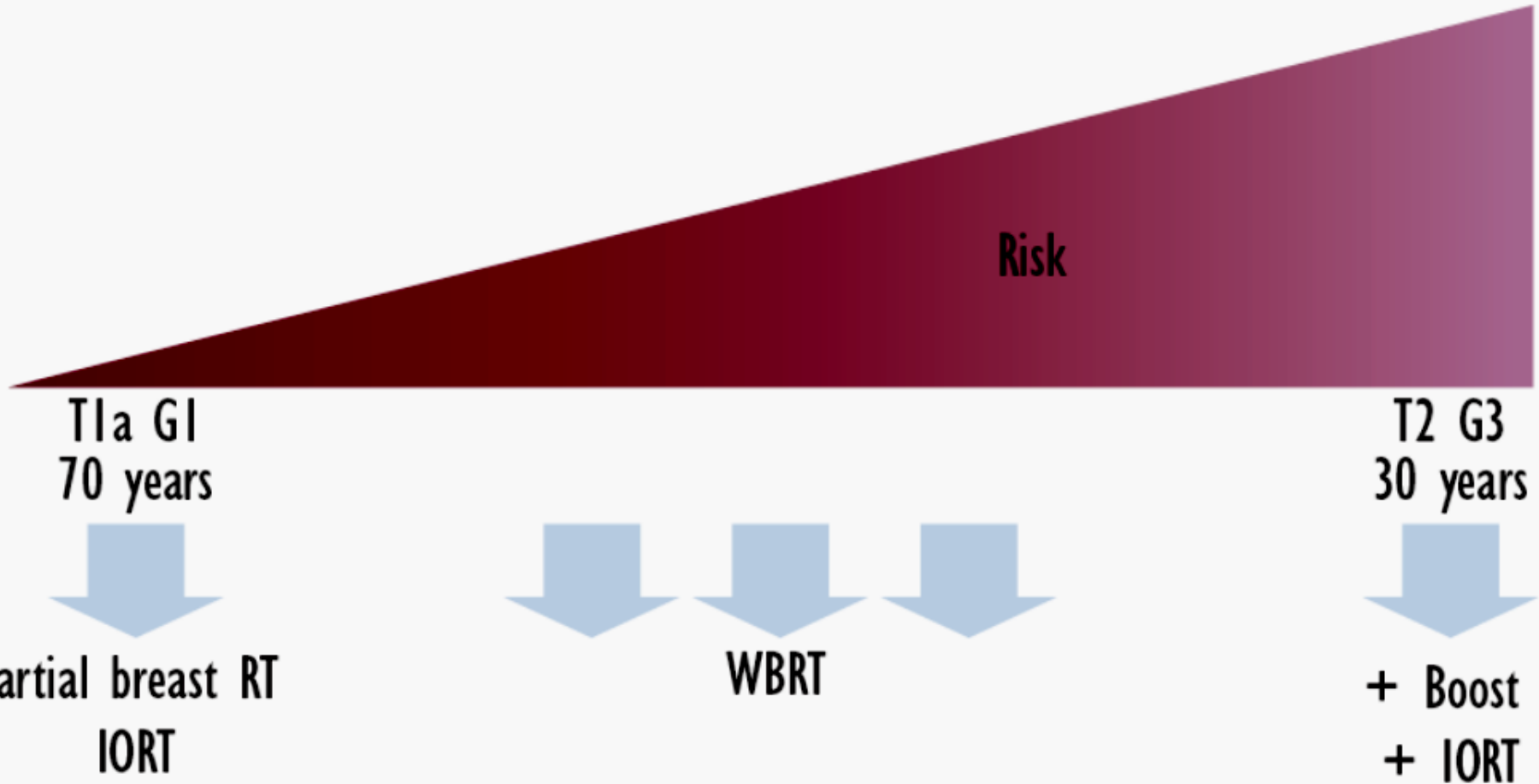




From **ISIORT** 2012 to 2014



## Personalized RT? Risk adapted RT?



*IORT = intra-operative radiotherapy, WBRT = whole breast radiotherapy.*

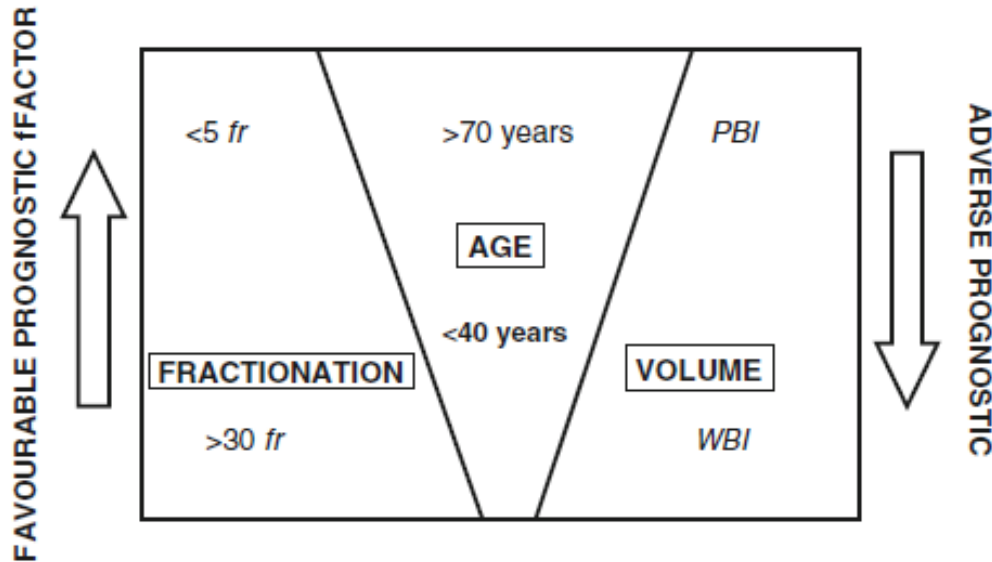


NEW TRENDS IN CLINICAL ONCOLOGY

## The use of radiotherapy for early breast cancer in woman at different ages

F. A. Calvo · C. V. Sole · S. Rivera · R. Meiriño · S. Lizarraga · M. A. Infante · E. Boldo · C. Ferrer · H. Marsiglia · E. Deutsch

Received: 3 January 2014 / Accepted: 12 February 2014  
© Federación de Sociedades Españolas de Oncología (FESEO) 2014



**Fig. 1** Evidence-based idealized representation of radiotherapy treatment technical factors (volume and fractionation) in relation to age and prognostic risk for early breast cancer *WBI* whole-breast irradiation, *PBI* partial-breast irradiation, *fr* fractions

**Table 2** Practice-oriented technological options adapted to prognostic risk

| Technological alternatives  | Favourable prognosis | Unfavourable prognosis |
|-----------------------------|----------------------|------------------------|
| IMRT                        | +++ PBI              | ++ WBI                 |
| 3D conformal radiotherapy   | +++ PBI              | +++ WBI                |
| HDR brachytherapy           | +++ PBI              | + Boost                |
| Intraoperative radiotherapy | +++ PBI              | + Boost                |

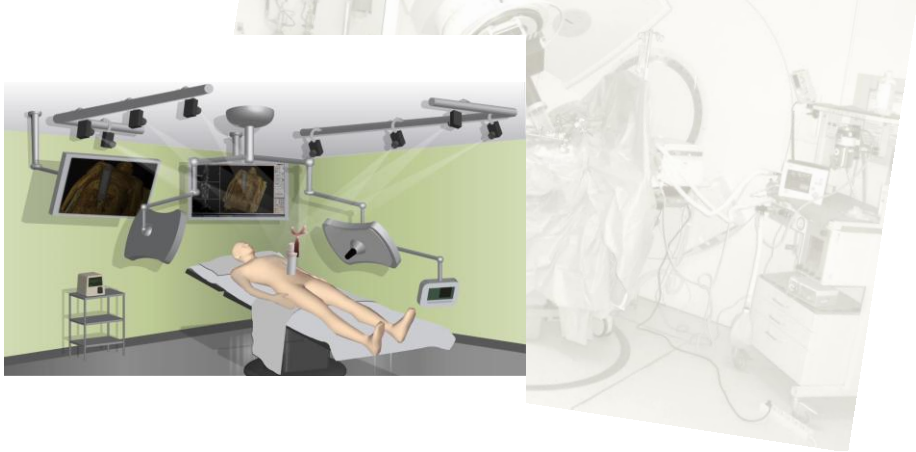
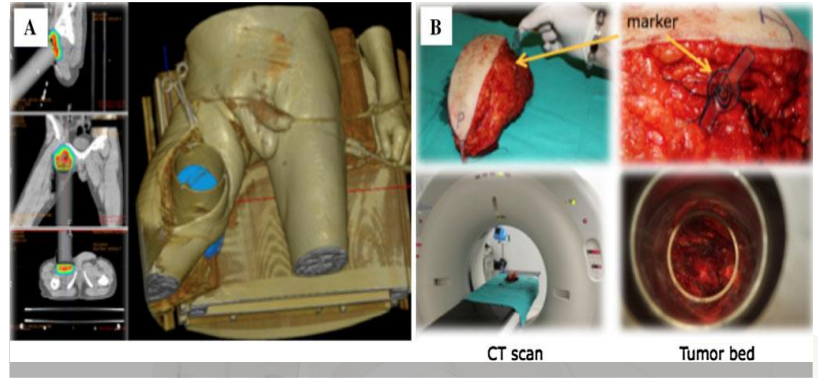
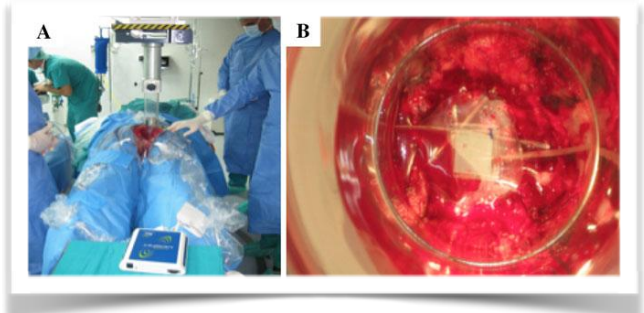
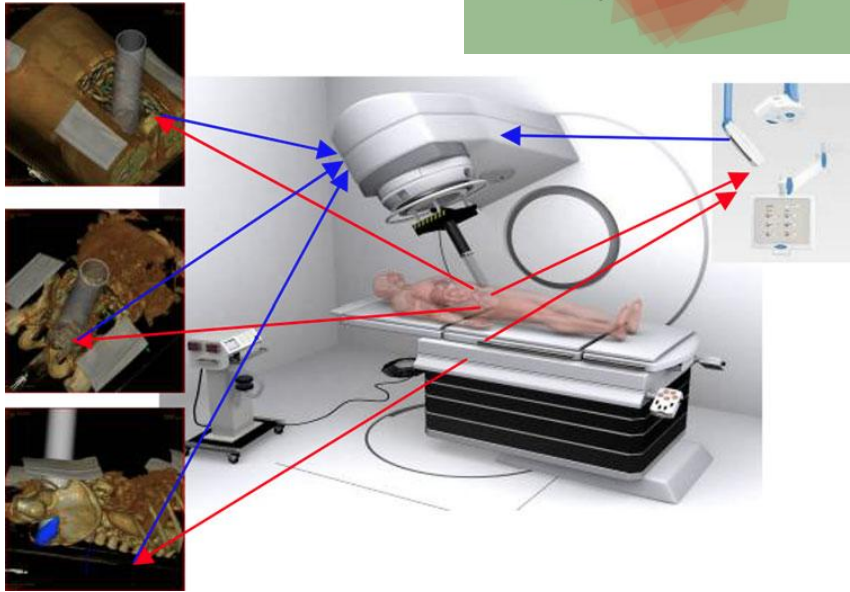
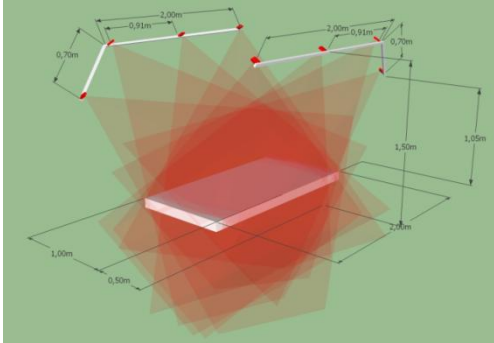
*IMRT* intensity-modulated radiation therapy, *HDR* high dose rate, *PBI* partial-breast irradiation, *WBI* whole-breast irradiation



NEW TRENDS IN CLINICAL ONCOLOGY

Research opportunities in intraoperative radiation therapy:  
the next decade 2013–2023

F. A. Calvo · C. V. Sole · M. E. González · E. D. Tangco ·  
J. López-Tarjuelo · I. Koubychine · J. A. Santos ·  
J. Pascau · R. Herranz · C. Ferrer



## IORT...

Is radiotherapy... *feasible and tolerable* **Practice expanded by technology**

Is precise radiotherapy... *able to be planned and registered* **TPS + IMRT/IGRT/SBRT**

**Is a precise component of RT for dose-escalation...**

*50Gy + 10/15Gy IORT LC >90%* **R0**

**Hypofractionation (EBRT)**

*50Gy + 10/15Gy IORT LC >50%* **R+, fragmentation, ypN+**

**Hypofractionation (EBRT) + further escalation**

Is an efficient alternative for RT dose-de-escalation...

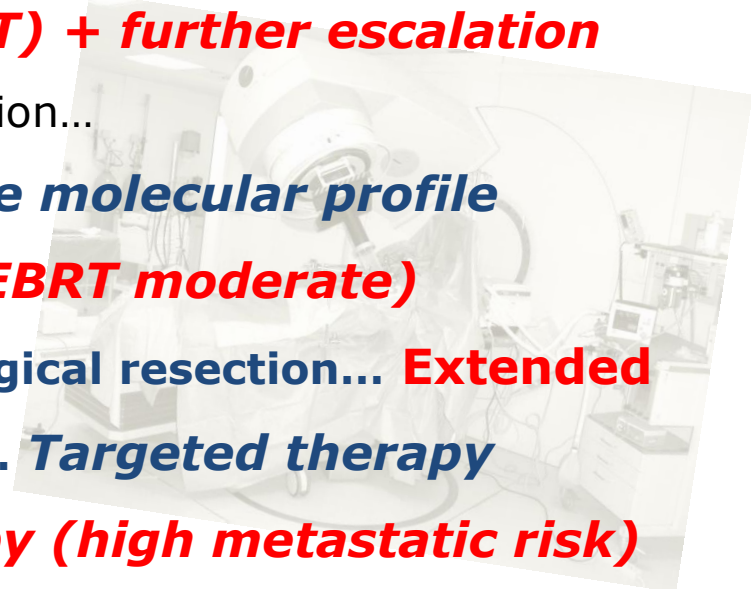
*20-21Gy LC >95%* **R0 favourable molecular profile**

**Hypofractionation (EBRT moderate)**

**Adds a radiobiological safety margin to surgical resection... Extended**

**Does not interfere with systemic therapy... Targeted therapy**

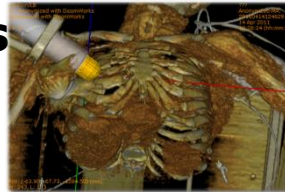
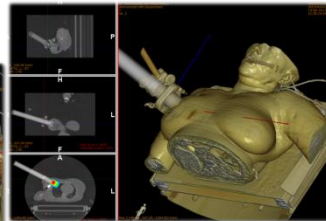
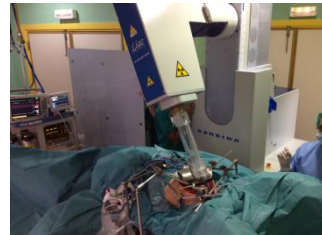
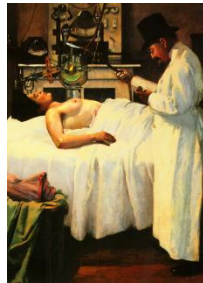
**Neo-adjuvant systemic therapy (high metastatic risk)**



# Cancer RT & Individualized Medicine

**Technology & future...Cycle of innovated practice  
Personalized RT / IORT in to Personalized Oncology**

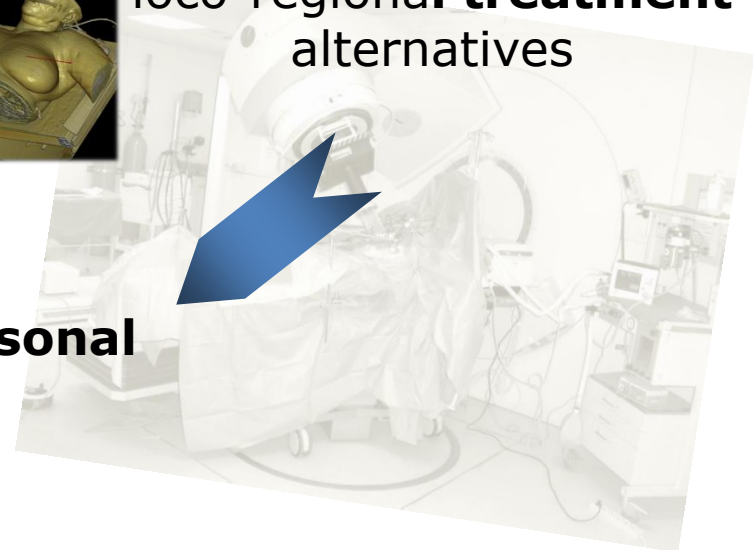
Technological development  
**Diversity & innovation**



Understanding  
**heterogeneous**  
loco-regional **risks**

**Adapting**  
loco-regional **treatment**  
alternatives

**Cost-efficient**  
RT strategies  
**Social/Medical/Personal**  
**profit**



Peter P. Yu ASCO President 51th... Messages

## **“The State of Cancer in America: 2014”**

- 1/4 uninsured individuals
- annual cost rise projected \$104 billion in 2006 to \$173 billion in 2020
- Excess economic burden of survivorship:
  - recently diagnosed \$16,000 per survivor, per year
  - previously diagnosed \$4,000 per survivor , per year
- 25% of personal bankruptcies are precipitated by health care crisis

ASCO 2014 “Science and Society”





# The Museum, 1983...



