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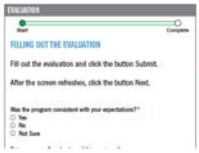

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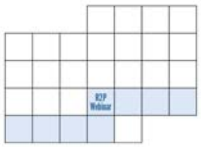

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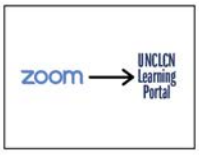

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7

Our Presenter

Kevin Pearlstein, MD

Kevin Pearlstein, MD, is an assistant professor in the Department of Radiation Oncology.

He is the primary radiation oncologist at our UNC Hillsborough campus where he is clinically active in multiple disease sites including breast and GI malignancies.

His research interests focus on identifying novel clinical strategies incorporating radiation for both malignant and benign diseases.

8

Our Presenter

9

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10

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11

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12

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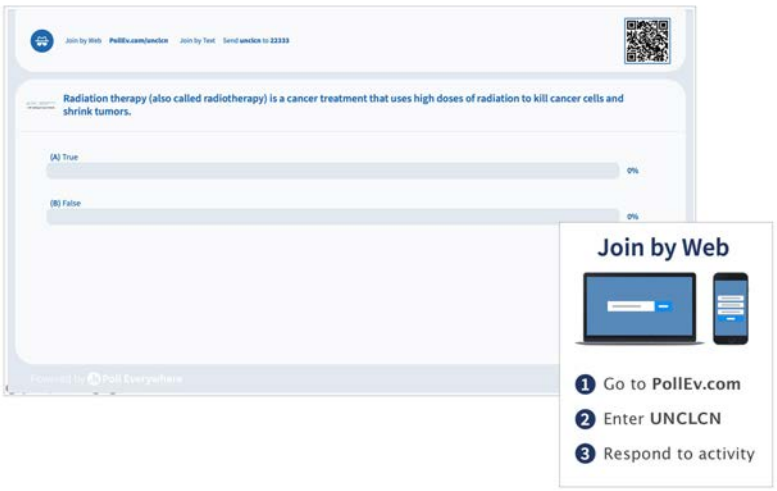
13

Sample Poll Everywhere Question



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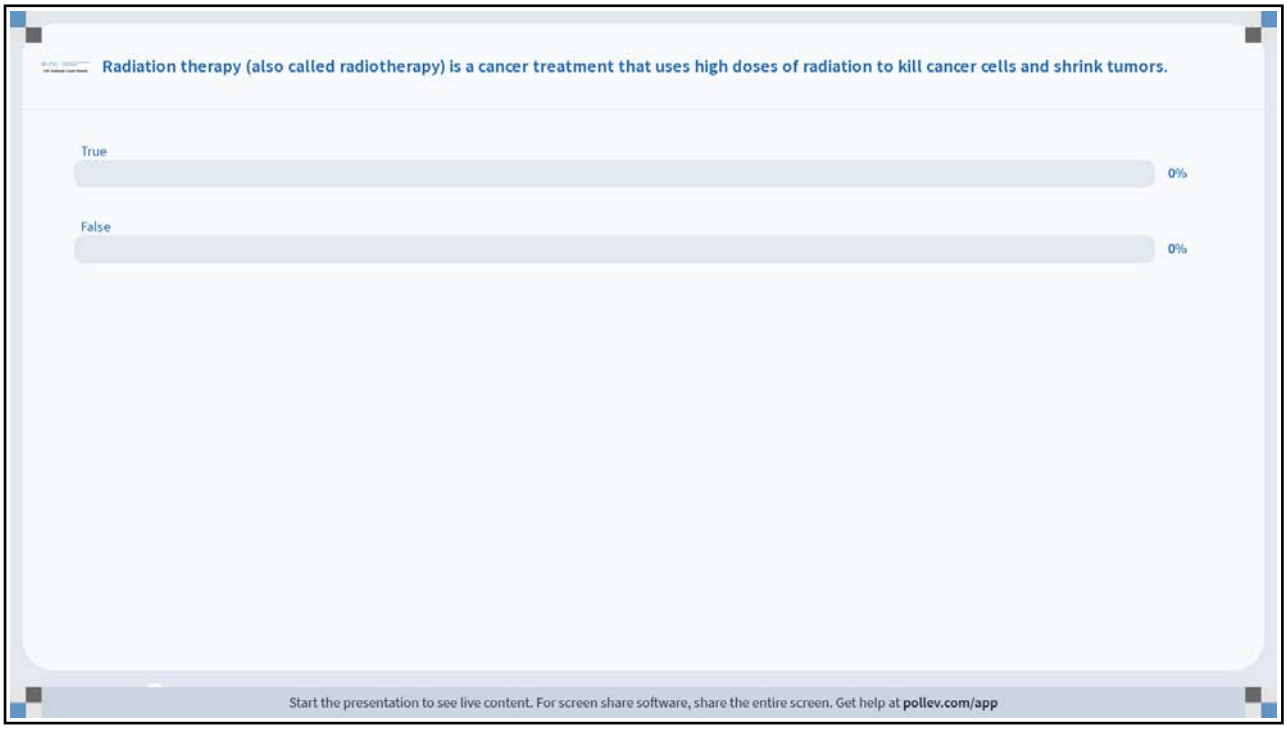

17

Selective Use of Radiation Therapy for Solid Tumors: Updates for 2024

Kevin Pearlstein, MD
Assistant Professor
Department of Radiation Oncology, University of North Carolina

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18

Disclosures: None

Learning Objectives

- Review basic radiobiologic principles and the general role for radiation in cancer care
- Discuss recent research evaluating omission of radiation and examine the impact on patient outcomes
    - Breast cancer
    - Rectal cancer
    - Sarcomas
- Identify technological advances in radiation oncology and explain how these can impact patient outcomes
- Discuss emerging treatment strategies incorporating radiation that omit surgery or systemic therapy

Radiation Background

Wilhelm Roentgen (1845-1923)

November 8, 1895: First xray

First documented patient treatment was 1896, 2 months after discovery of xray

Radiation Background

Radiation involves delivery of high energy x-rays or particles to tumors to destroy cancer cells

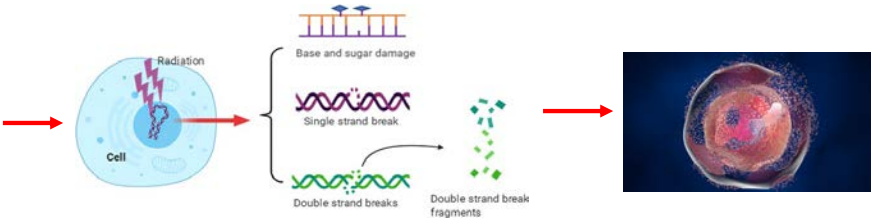
Radiation beams can be delivered from multiple angles and pass through patients to reach cancer

Radiation beams are focused at specific areas (locoregional treatment)

A Modern linear accelerator

Radiation Background

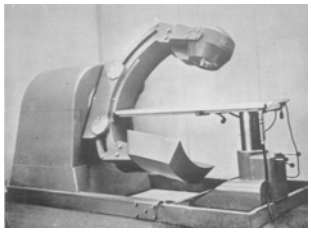
Ionizing radiation causes cell damage and induces cell death



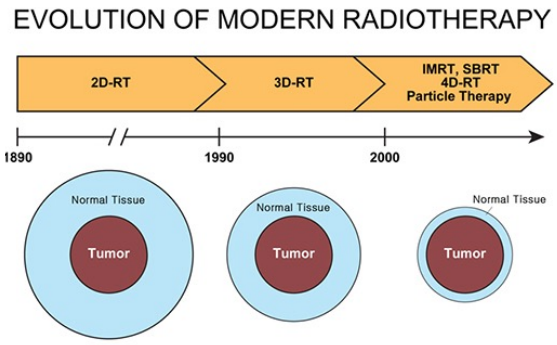
Evolution of radiation technologies

X-rays have been used to treat cancer patients since the 1890s

Advances in radiation technology allow safe delivery of more accurate, intensive treatments



Evolution of radiation technologies



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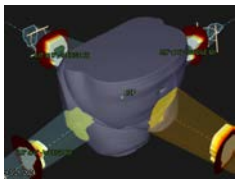
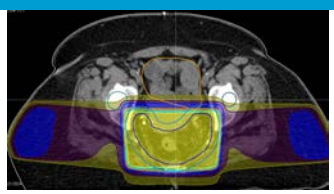
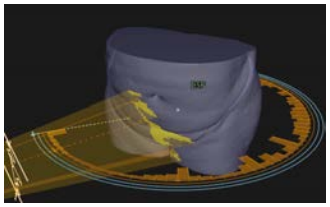
Radiation "alphabet soup"

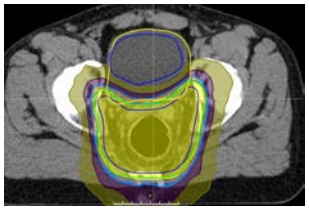
3DCRT- 3D conformal RT



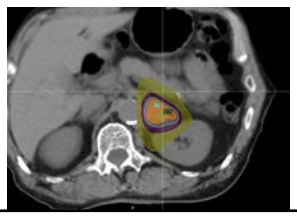


IMRT- Intensity Modulated RT





SBRT/SRS- Stereotactic Body RT



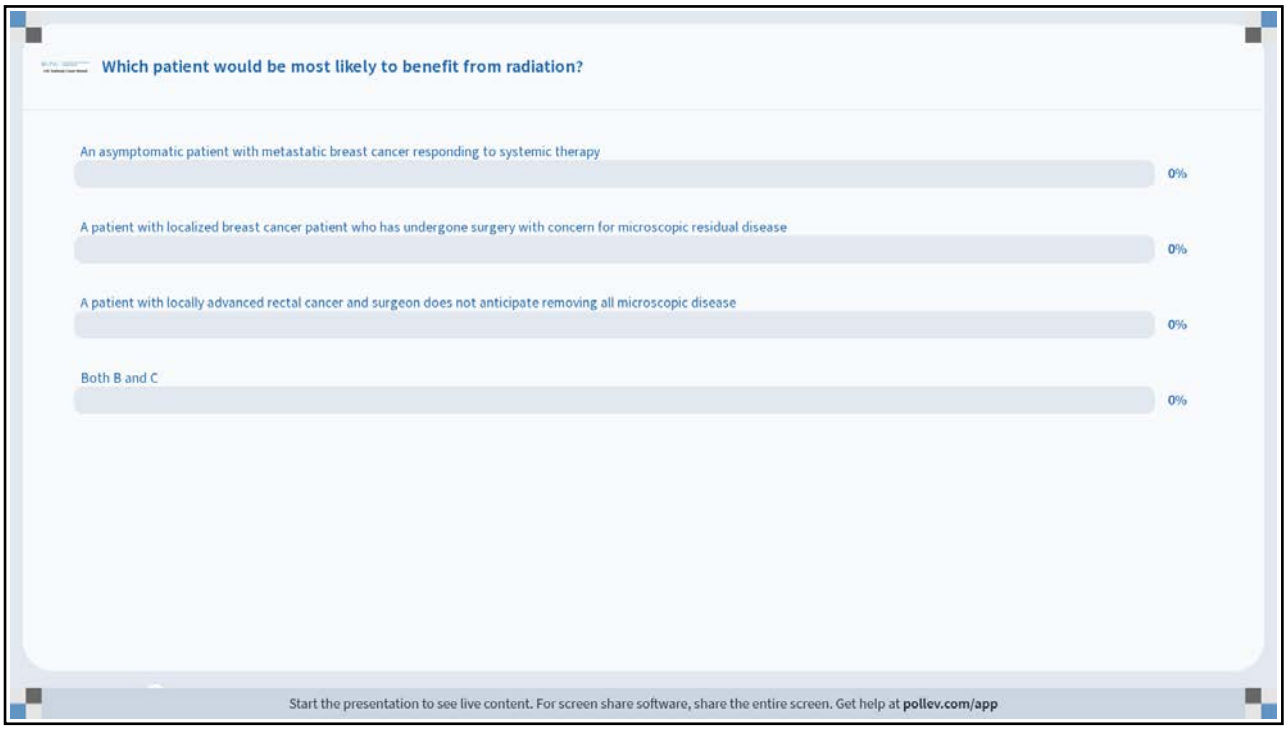
26

Poll

Which patient would be most likely to benefit from radiation?

A- An asymptomatic patient with metastatic breast cancer responding to systemic therapy
B- A patient with localized breast cancer patient who has undergone surgery with concern for microscopic residual disease
C- A patient with locally advanced rectal cancer and surgeon does not anticipate removing all microscopic disease
D- Both B and C

27



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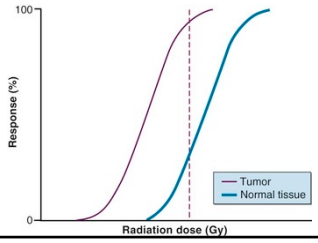
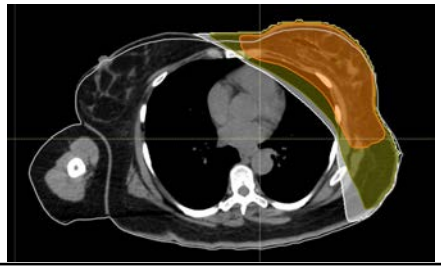
Decision making for radiation

"Benefit" of radiation
- Locoregional control
- Survival

"Risks" of radiation
- Toxicities
- Time
- Cost





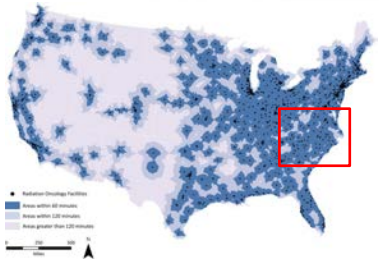
29

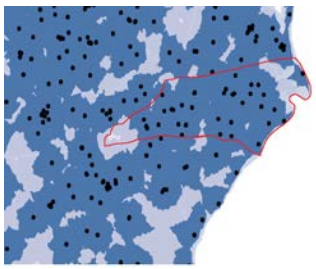
Decision making for radiation

"Benefit" of radiation
- Locoregional control
- Survival

"Risks" of radiation
- Toxicities
- Time
- Cost

Location of radiation oncology facilities in United States





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30

Decision making for radiation

"Benefit" of radiation
- Locoregional control
- Survival

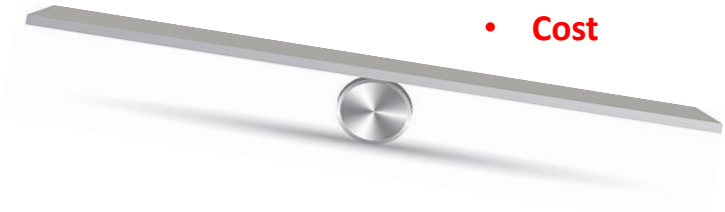
"Risks" of radiation
- Toxicities
- Time
- Cost

$$$$

De-escalating therapy

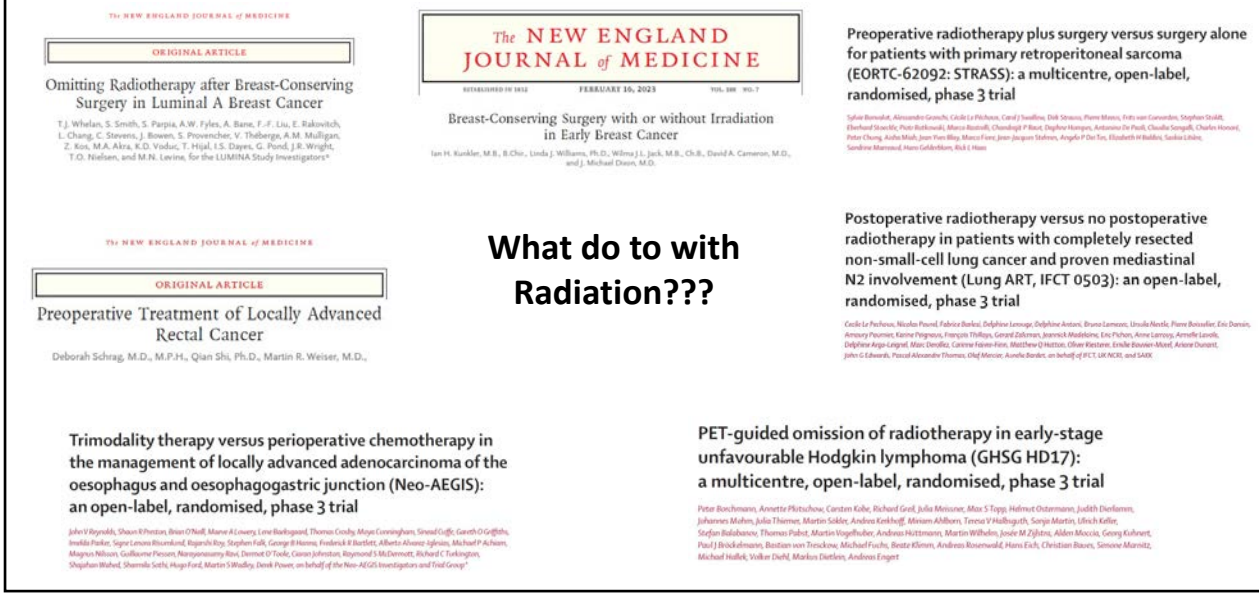
"Benefit" of radiation
- Locoregional control
- Survival

"Risks" of radiation
- Toxicities
- Time
- Cost



Are we able to identify patients at low risk for recurrence?

Can we safely de-escalate therapy in these patients?



33

Breast Cancer

34

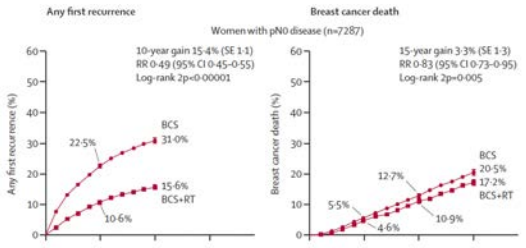
Lumpectomy followed by adjuvant radiation established as a standard of care through multiple randomized trials (1970s-1980s)

Early data suggested there was a low risk subgroup of women in whom RT could be safely eliminated

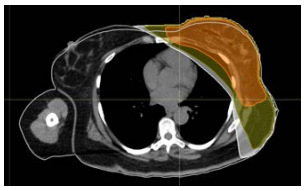
Side effects of RT

- Fatigue
- Skin irritation
- Fibrosis
- Edema
- Cardiac toxicity
- Pneumonitis
- Secondary malignancy

LR and BCM in women with breast cancer death with node-negative disease



EBCTCG Meta-analysis Lancet 2011



CALGB 9343

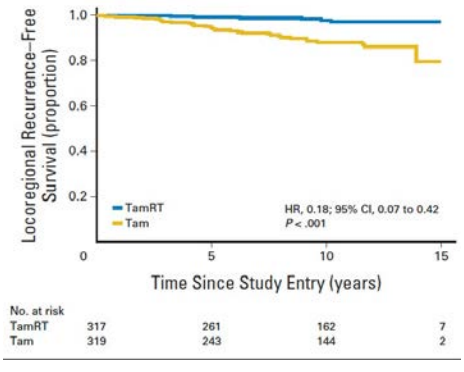
N=647 enrolled 1994-1999
Women ≥ 70 years old
pT1, cN0, ER pos tumors
55% >75 years old

Lumpectomy followed by Tamoxifen vs Tamoxifen + RT

10yr freedom from recurrence: 90% vs 98%

No difference in 10yr freedom from distant mets (95% vs 95%) or OS (67% vs 66%)

As of 2013 publication, only 6% died from breast cancer



Hughes JCO 2013

PRIME II (Kunkler NEJM 2023)

PRIME II

N=1326 enrolled 2003-2009
Women ≥ 65 years old
T1-2 (tumor <3cm)
Grade 3 or LVSI allowed (not both)

Lumpectomy

Endocrine | **Endocrine + whole breast RT**

Characteristic	No Radiotherapy (N=668)	Radiotherapy (N=658)
Age — yr		
Mean	71.1±5.0	70.8±4.7
Median (IQR)	70 (67–74)	69 (67–73)
Tumor size — no. (%)		
0–1.0 cm	258 (38.6)	265 (40.3)
1.1–2.0 cm	326 (48.8)	319 (48.5)
2.1–3.0 cm	84 (12.6)	74 (11.2)
Excision margins — no. (%)		
<1 mm	10 (1.5)	9 (1.4)
1–5 mm	315 (47.2)	296 (45.0)
>5 mm	227 (34.0)	239 (36.3)
Reexcision†	112 (16.8)	110 (16.7)
Unknown	4 (0.6)	4 (0.6)
Tumor grade — no. (%)		
1	271 (40.6)	292 (44.4)
2	368 (55.1)	352 (53.5)
3	23 (3.4)	13 (2.0)
Unknown	6 (0.9)	1 (0.2)
Tumor location — no. (%)		
Left breast	359 (53.7)	345 (52.4)
Right breast	302 (45.2)	305 (46.4)
Side unknown	7 (1.0)	8 (1.2)
Lymphovascular invasion — no. (%)		
No	631 (94.5)	628 (95.4)
Yes	32 (4.8)	27 (4.1)
Unknown	5 (0.7)	3 (0.5)

Only a minority of patients with higher risk features

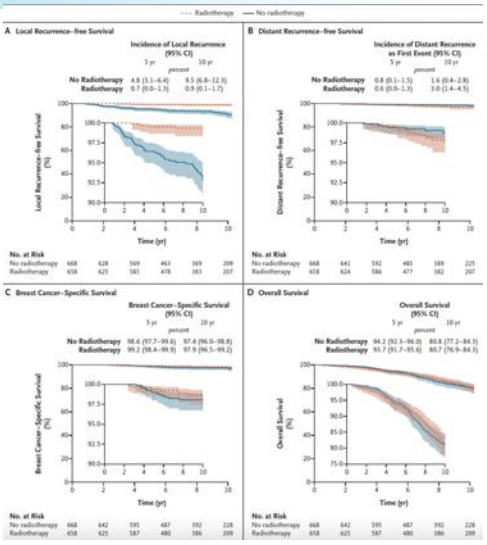
PRIME II

Improvement in local recurrence with radiation (10yr: 10% vs 1%)
- no clear plateau

No difference in breast cancer-specific survival (97% vs 98%) or OS (81% vs 81%)

Only 13% of deaths attributed to breast cancer

"Irradiation can be safely omitted in women 65 years of age or older who have grade 1 or 2, ER-high cancers treated by breast-conserving therapy, provided that they receive 5 years of adjuvant endocrine therapy."

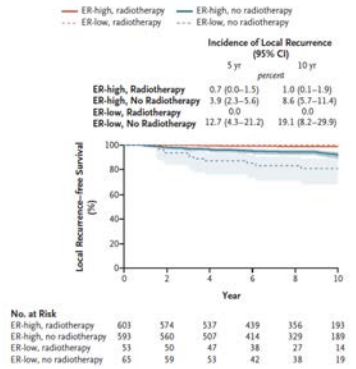


Higher Risk Populations

Some patients with early breast cancer have higher risk disease

- **Caution when considering omitting radiation in these patients**

ER-low populations



Kunkler NEJM 2023

Tumors >2cm

Grade 3 tumors

LVI

	No radiotherapy (n=668)	Radiotherapy (n=658)	p value
Tumour size (mm)			
0–10	10/258 (4%)	3/265 (1%)	0·04
10·1–20	10/326 (3%)	1/319 (<1%)	0·008
20·1–30	6/84 (7%)	1/74 (1%)	0·08
Grade			
1	8/271 (3%)	2/292 (<1%)	0·04
2	15/368 (4%)	3/352 (<1%)	0·006
3	3/23 (13%)	0/13 (0%)	0·21
Lymphovascular involvement			
No	24/631 (4%)	5/628 (<1%)	0·0004
Yes	2/32 (6%)	0/27 (0%)	0·29

Kunkler Lanc Onc 2015

LUMINA (Whelan NEJM 2023)

LUMINA

Prospective cohort study, N=500

- **Luminal A (ER pos, PR >20%, HER2 neg, Ki67<13.25%)**
- **Women>55**
- **pT1 (size <2cm)**
- **G1-2**
- **Ductal carcinomas**
- **Lumpectomy with margins >1mm, negative SLN/ALND**

Excluded

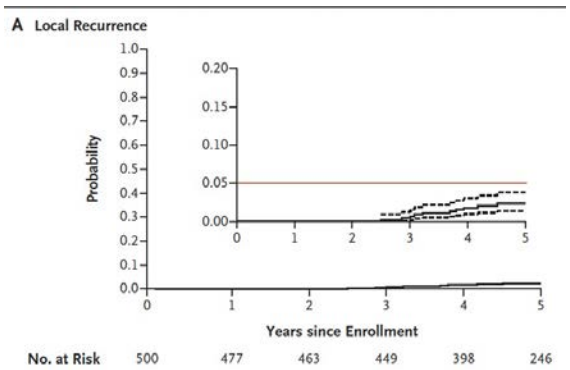
- **Lobular carcinomas**
- **Multifocal/centric disease**
- **LVI**

Eligible women received endocrine therapy alone

Characteristic	All Patients (N = 500)
Age	
Median (IQR) — yr	67.1 (62.9–71.6)
Distribution — no. (%)	
55 to <60 yr	61 (12)
60 to <65 yr	138 (28)
65 to <70 yr	136 (27)
70 to <75 yr	107 (21)
75 to <80 yr	42 (8)
≥80 yr	16 (3)
Tumor size	
Median (IQR) — cm	1.0 (0.7–1.4)
Distribution — no. (%)	
≤0.5 cm	39 (8)
0.5–1.0 cm	217 (43)
1.1–2.0 cm	244 (49)
Tumor grade — no. (%)	
1	330 (66)
2	170 (34)
Histologic cancer type — no. (%)	
Ductal	437 (87)
Tubular	25 (5)
Mucinous	26 (5)
Other	12 (2)

LUMINA

Local recurrences very low
5yr local recurrence 2.3%
5yr contralateral breast recurrence 1.9%



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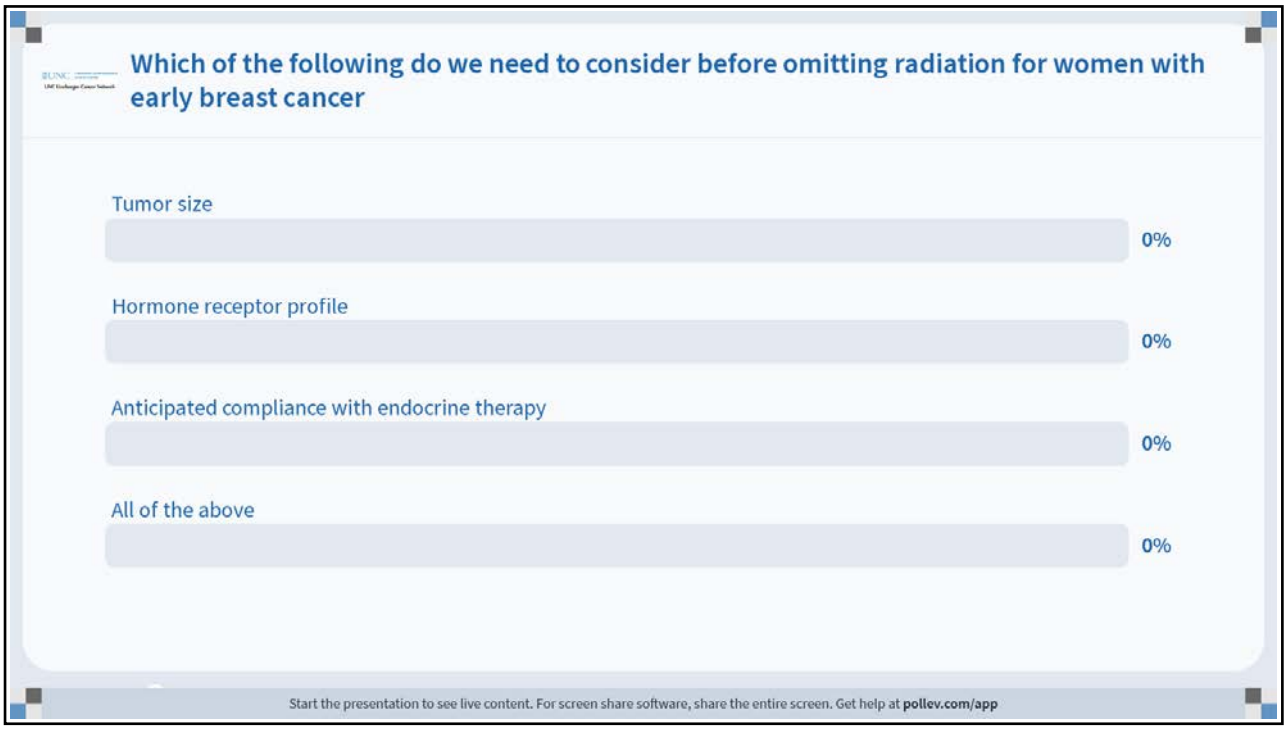

42

Endocrine therapy

Endocrine therapy +/- Radiation is standard of care treatment for HR-positive breast cancers

Compliance with full course of therapy can be limited
- LUMINA- 80%
- PRIME II- 60-70%
- "Real world"- as low as 50% in some studies

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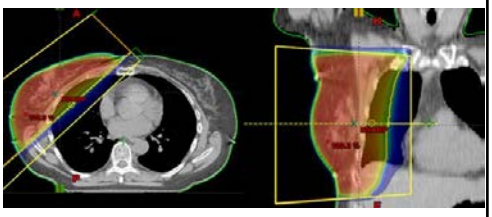
Evolution of radiation techniques

Traditional approach:
Whole breast radiation with conventional fractionation (5-6 weeks)
- time intensive
- whole breast skin irritation
- Late issues with fibrosis, cosmetic outcomes
- Lower risk of pneumonitis, cardiac toxicity

This is the technique used on CALGB 9343 and many patients on PRIME II



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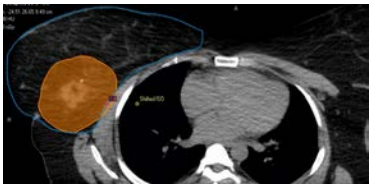
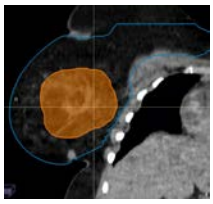
Modern Breast Radiation

Whole breast radiation with moderate hypofractionation (3-4 weeks)
- Less time intensive/resource utilization
- Improved cosmesis compared to conventional whole breast radiation (Shaitelman)

Whole breast radiation with extreme hypofractionation (1 week)
-FAST-Forward (Brunt Lancet 2020)
- Less time intensive/resource utilization
- current data suggests acceptable cosmesis, no increased risk of serious toxicity

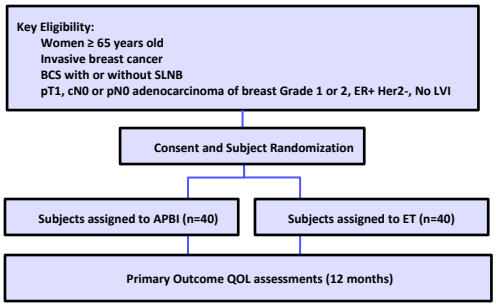
Partial breast radiation (1-3 weeks)
- Less time intensive/resource utilization
- Improved cosmesis





CAMERAN (LCCC 2104)

Comparison of Adjuvant Monotherapy With Endocrine Therapy or Accelerated Partial Breast Irradiation Following Lumpectomy for Low Risk Breast Cancer Patients Over 65 (CAMERAN)



Similar studies in progress:
EUROPA (women >70, Luminal A disease)
- N=1000, Primary endpoint HRQoL

Take home points: Breast Cancer

Radiation provides a local control benefit in many patients

There is a low risk population where this local control benefit is small

Need to weigh multiple factors to individualize decisions
- **Clinicopathologic features: size, grade, LVI, margins, etc**
- **Genetic features (aka luminal A intrinsic subtype)**
- **Life expectancy (age, comorbidities, etc)**
- **Anticipated adherence to endocrine therapy**

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Rectal Cancer

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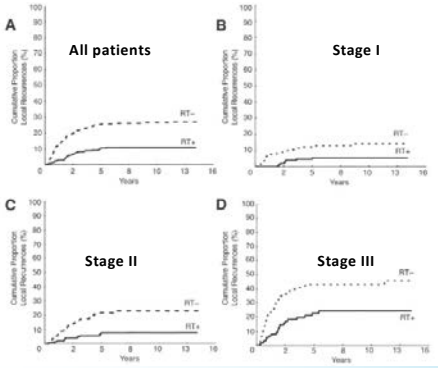
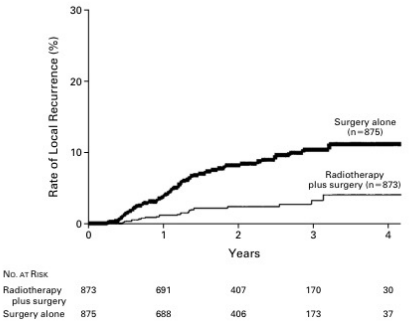
Role of radiation in rectal cancer

Neoadjuvant pelvic radiation followed by surgery has been a standard of care treatment for locally advanced rectal cancer since 1990s
- Reduces pelvic recurrence risk to <10%



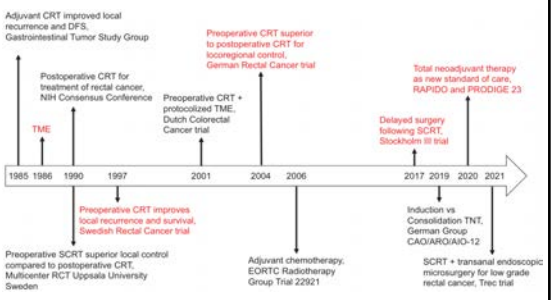
Folkesson JCO 2005



Dutch TME study, Kapiteijn NEJM 2001

Changes in Rectal Cancer Management

Surgical techniques have evolved
Total mesorectal excision (TME) is standard of care
Staging has improved
- MRI better able to identify high risk features, local extent of tumor
Timing of chemotherapy
Chemotherapy traditionally given in adjuvant setting
- Trend towards administering chemo and radiation prior to surgery (total neoadjuvant therapy)
- Early data demonstrated good response rates to chemo even before administering RT



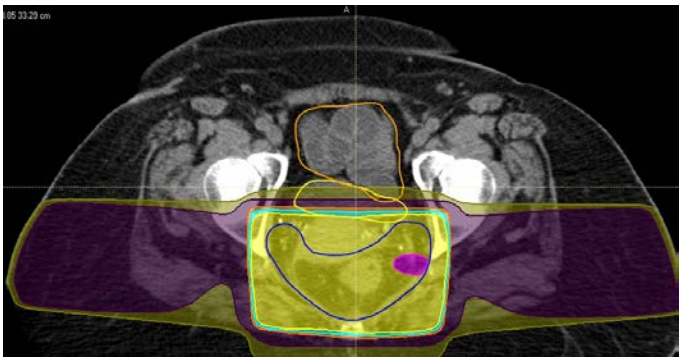
Affleck, Ann of GI 2022

Do all locally advanced rectal cancer patients need pelvic RT?

Conventional treatment is 5-6 weeks of daily treatment

Side effects

- **Diarrhea/bowel issues**
- **Urinary urgency/frequency**
- **Skin irritation**



PROSPECT Trial (Schrag, NEJM 2023)

PROSPECT Trial (2012-2018)

Neoadjuvant chemo vs chemoRT for locally advanced rectal cancer

N=1194

Included:

- **T2/3N+**
- **T3N0**
- **Sphincter sparing surgery**

Excluded:

- **T4**
- **≥4 LN**
- **Radial margin ≤3mm**

chemoRT → LAR → Optional FOLFOX x 8 (78% received)

FOLFOX x6* → LAR → Optional FOLFOX x 6 (75% received)**

***If <20% reduction in tumor size after chemo, then received chemoRT

Role of radiation in rectal cancer

Mid-high tumors

Characteristic	FOLFOX Group (N=585)	Chemoradiotherapy Group (N=543)
Primary rectal tumor on digital examination — no./total no. (%)		
Rectal tumor not palpable	290/580 (50.0)	259/536 (48.3)
Rectal tumor palpable	290/580 (50.0)	277/536 (51.7)
Rectal tumor location — cm from anal verge		
No. of patients with data	585	542
Mean	8.6±2.9	8.5±2.8
Median (range)	8 (2–25)	8 (2–18)
Rectal tumor location — no. (%)		
≤5 cm from anal verge	83 (14.2)	90 (16.6)
>5 to ≤10 cm from anal verge	375 (64.1)	344 (63.4)
>10 cm from anal verge	127 (21.7)	109 (20.1)
Clinical stage — no./total no. (%)		
T2 node positive	63/584 (10.8)	38/543 (7.0)
T3 node negative	232/584 (39.7)	198/543 (36.5)
T3 node positive	289/584 (49.5)	307/543 (56.5)
Staging performed with MRI — no. (%)		
Yes	494 (84.4)	458 (84.3)
No	91 (15.6)	85 (15.7)

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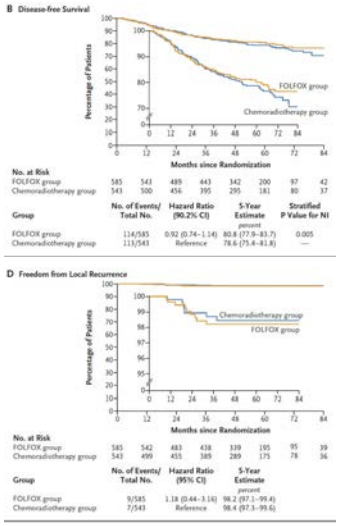
Role of radiation in rectal cancer

Neoadjuvant chemo with selective chemoRT non-inferior to chemoRT and adjuvant chemo
5yr DFS 81% vs 79%
5yr Local recurrence 1.8% vs 1.6%
R0 resection rate: 99% vs 97%

Only 7% of patients receiving neoadjuvant chemo required chemoRT for poor response



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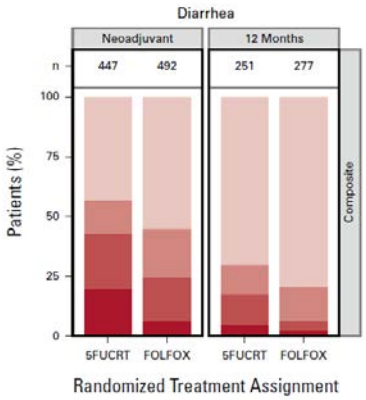
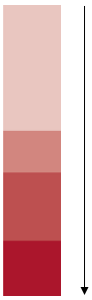
Patient reported outcomes (Basch JCO 2023)

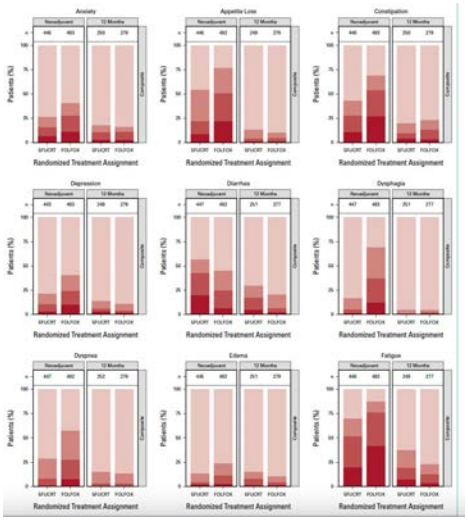
Patient reported outcomes collected as part of study protocol
- PRO-CTCAE (all patients)
- additional PRO regarding bowel, bladder, sexual health, health-related QOL (subset of patients)

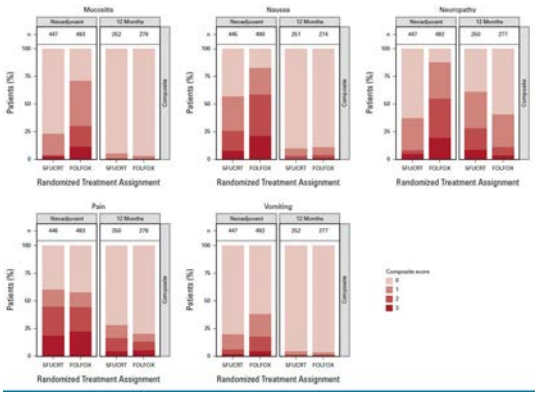




Severity increasing

Patient reported outcomes (Basch JCO 2023)





Patient reported outcomes (Basch JCO 2023)

During neoadjuvant therapy…

Worse with neoadjuvant chemoRT

- **Diarrhea**

Worse with neoadjuvant chemo

- **Anxiety**
- **Appetite loss**
- **Constipation**
- **Depression**
- **Dysphagia**
- **Dyspnea**
- **Edema**
- **Fatigue**
- **Mucositis**
- **Nausea**
- **Neuropathy**

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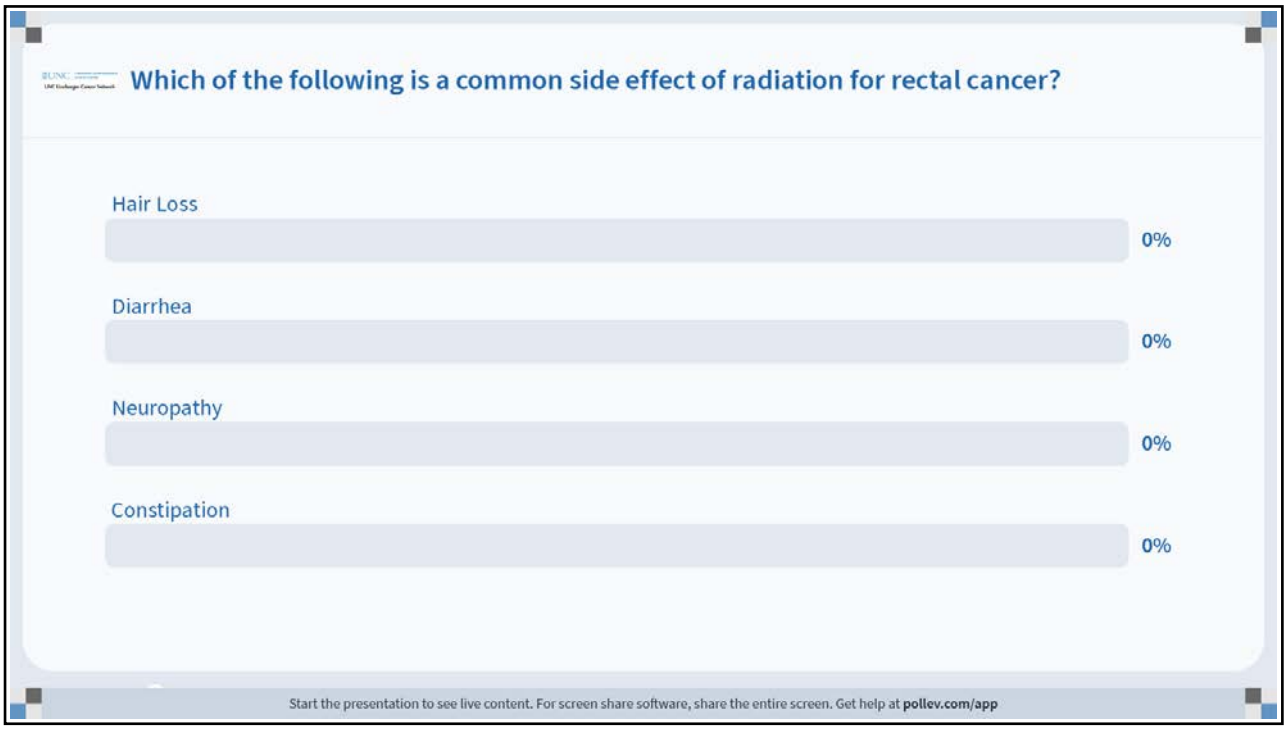


58

Patient reported outcomes (Basch JCO 2023)

12 months following surgery…

Worse with neoadjuvant chemoRT

- Fatigue
- Neuropathy
- Overall bowel function
- Overall sexual function

Worse with neoadjuvant chemo

- None

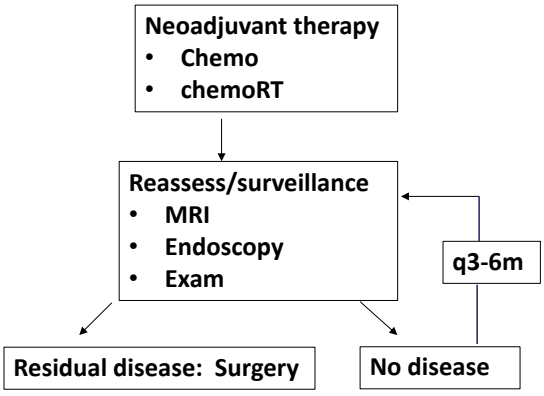
<15% of patients had severe issues with individual symptoms regardless of treatment
Patients reported similar health-related QOL in both groups

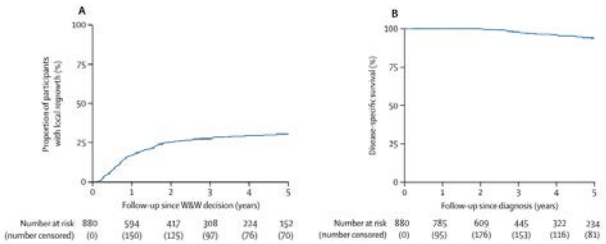
Other strategies for de-escalating rectal cancer treatment

<u>Non-operative management</u>

- surgery associated with morbidity

- Responders to neoadjuvant therapy (chemo, chemoRT) who have a clinical complete response may have smaller benefit from surgery





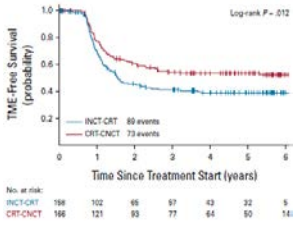
Analysis of International Watch & Wait Database, N=1009
Van der Valk Lancet 2018

Role of radiation in rectal cancer

OPRA Trial (Organ Preservation in Rectal Adenocarcinoma)
N=324 stage II/III rectal cancer (80% cT3, 70% cN+)
Phase II trial evaluated sequencing of chemo and chemoRT

- **Arm 1: chemo → chemoRT**
- **Arm 2: chemoRT → chemo**

Those with a clinical CR (via DRE, imaging, endoscopy) underwent watchful waiting
Those with incomplete response/recurrence underwent surgery



5 year surgery-free survival ~50% for patients receiving chemoRT → chemo

Verheij JCO 2023

Take Home Points: Rectal Cancer

- **Many treatment options for locally advanced rectal cancer**
  - **Traditional: chemoRT → surgery → chemo**
  - **Total Neoadjuvant Therapy: chemoRT →chemo →surgery**
  - **PROSPECT: chemo → surgery**
  - **Non-Operative: chemoRT → chemo**
- **Treatment approach requires consideration of:**
  - **Clinical staging**
  - **surgical options/complexity (LAR, APR)**
  - **Patient preferences**

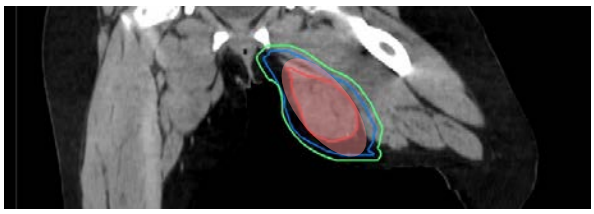
Sarcoma

Role of radiation in sarcomas

Pre-operative radiation has a well-established role in extremity sarcomas as part of a limb-sparing approach

Sarcomas tend to have significant microscopic extension

Surgical excision can "miss" microscopic disease



Pre-op RT targeting a larger area (green) can treat microscopic disease

Improvement in local control demonstrated in multiple trials

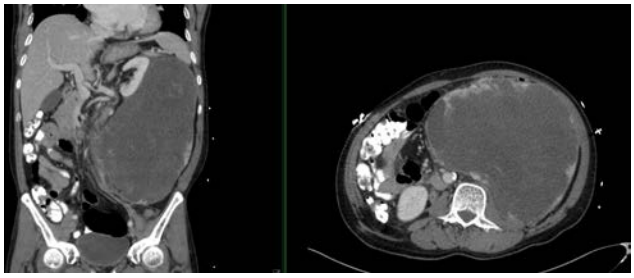
Role of radiation in sarcomas

Retroperitoneal sarcomas are less common than extremity sarcomas and present unique challenges

- **Complex anatomy and critical structures limit ability to get wide margins**

Data for extremity sarcomas has often been extrapolated to RP sarcomas

- **Many radiation sensitive organs in the abdomen/pelvis can lead to higher toxicity risks**
  - **Bowel**
  - **Stomach**
  - **Kidney**
  - **Liver**
  - **Spinal cord**



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Role of radiation in sarcomas

<u>"Benefit" of radiation</u>

- **Locoregional control?**

<u>"Risks" of radiation</u>

- **Toxicities**

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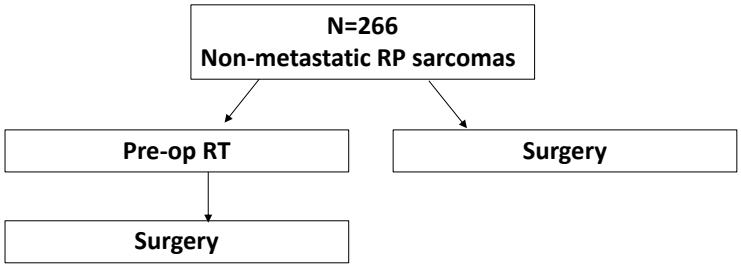
STRASS (Bonvalot Lancet Onc 2020)

First (completed) randomized trial of pre-op radiation in retroperitoneal sarcomas

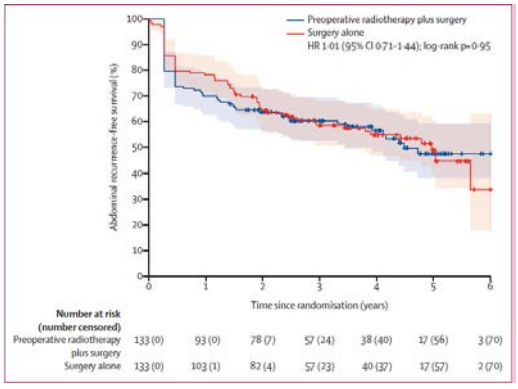


STRASS (Bonvalot Lancet Onc 2020)

Primary endpoint: Abdominal recurrence-free survival
No improvement with Radiation

Conclusion: "Preoperative radiotherapy should not be considered as standard of care treatment for retroperitoneal sarcoma"

Does this mean that there are no indications for radiation for RP sarcomas?



STRASS (Bonvalot Lancet Onc 2020)

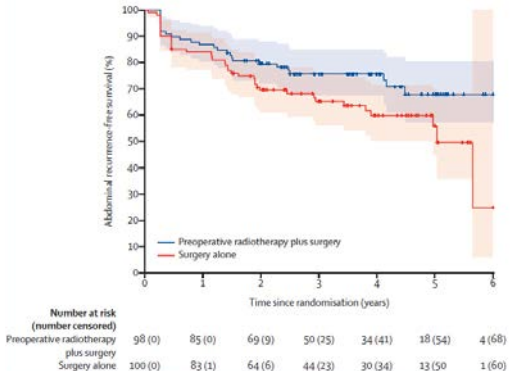
RP sarcomas encompass multiple histologic subtypes

- **Different subtypes have different patterns of recurrence**

RP liposarcomas tend to have a locoregional recurrence pattern

- **These patient did benefit from RT on subgroup analysis**

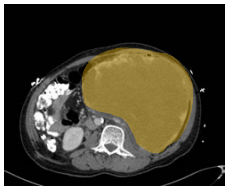
Other types of RP sarcomas tend to metastasize- RT probably less beneficial for these patients!



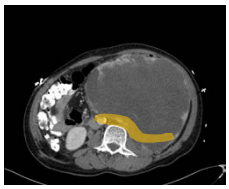
STRASS (Bonvalot Lancet Onc 2020)

Other potential issues with the trial design/interpretation:

- **Abdominal RFS is an unusual composite endpoint- should we expect RT to impact all of these?**
  - **Tumor becomes inoperable**
  - **Patient becomes non-operative candidate**
  - **peritoneal mets at time of surgery**
  - **macroscopic disease left at surgery**
- **Among patients who had an R0 resection, there was a significant improvement with radiation (Local recurrence 37% vs 20%)**
- **There may be RT techniques to mitigate the toxicity of RT**



Treating the entire tumor
More side effects



Focusing on the area where surgeons likely to have difficulty
Fewer side effects

RP Sarcoma Take home points

- Treatment decisions for RP sarcoma are complex and require multidisciplinary decision making
- Selective use of radiation for retroperitoneal sarcomas is appropriate
  - There are likely patients who still benefit from pre-op radiation
- Identification of patients who benefit from RT depends on
  - Clinical findings (imaging, histologic subtype, etc)
  - Surgical approach and expectation for residual disease
  - Expected toxicity of treatment

Overall Summary

- Radiation is an important part of curative-intent treatment for many cancer patients
  - Provides a locoregional control benefit across many cancer types
- Omission of radiation can be considered for patients with low locoregional recurrence risk
- Ideal candidate for omission of RT depends on a number of factors
  - Clinical/pathologic features of cancer
  - Expected compliance with surgery, systemic therapy, etc
  - Patient preferences
- Advances in radiation technologies→ less toxicity, shorter treatment courses, etc
  - Radiation can facilitate omission of other therapies (surgery, systemic therapy)
- "Best" treatment approach is not always clear- requires joint decision making with patient and the multidisciplinary team

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75

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The song ***Back Rhodes*** written and performed by **Don Poe**

76

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Ricardo Padilla, DDS

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Nancy Vogler, RN, MSN, AGPCNP

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June 26
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Kristalyn Gallagher, DO, FACOS, FACS

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Frances Collichio, MD

78

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