State of the Art in Early Hodgkin Lymphoma

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Disclosures

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Overview: What's New in Early Hodgkin Lymphoma?

- Evolution toward treatment de-intensification
  - Chemotherapy
  - Radiation
- PET-guided therapy
  - De-escalation for negative PET2
  - Escalation for positive PET2
- Modern Radiotherapy for Hodgkins

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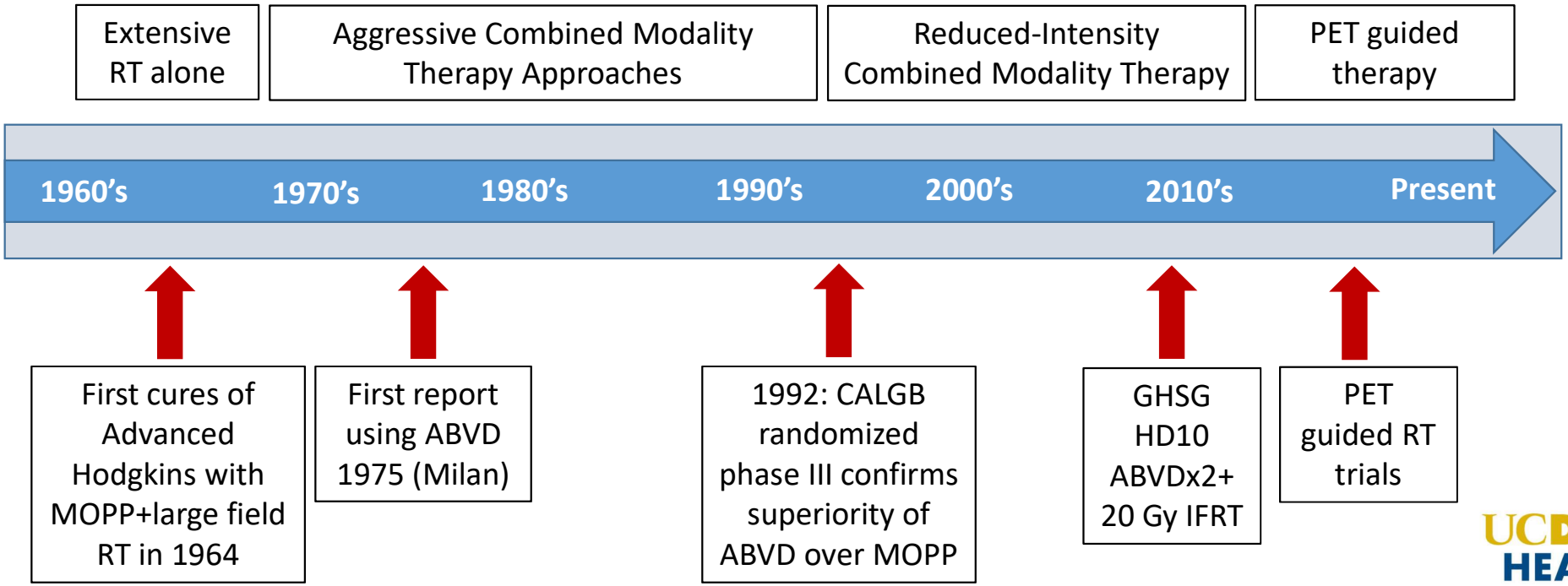
Treatment of Early Hodgkin Lymphoma over the Decades



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Definitions of Favorable/Unfavorable Hodgkins

	GHSG	EORTC	NCIC	NCCN
Age		≥ 50	≥ 40	
Histology			MC or LD	
ESR and B sx	> 50 if A > 30 if B	> 50 if A > 30 if B	> 50 or any B sx	> 50 or any B sx
Bulky	MMR > .33	MTR > .35	MMR > .33 or >10 cm	MMR > .33 or >10 cm
# Nodal sites	**> 2**	> 3	> 3	> 3
E-lesion	**any**			

Adapted from NCCN Guidelines Version 2.2019

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Definitions of Nodal Regions

	Ann Arbor	**EORTC**	**GHSG**
R cervical/SCV			
R ICL/Subpectoral			
R axillary			
L cervical/SCV			
L ICL/Subpectoral			
L axillary			
Mediastinum			
R hilum			
L hilum			
Total	9	5	5

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Adapted from NCCN Guidelines Version 2.2019

Treatment of Early Favorable-Risk Hodgkins

	Stage III/IV	Stage I/II	
		I/II Bulky Mediastinal	I/II No Bulk
North American	Advanced stage includes stage I/II bulky disease		**Early Stage**
GHSG	Advanced stage	Early stage unfavorable	**Early –stage favorable**

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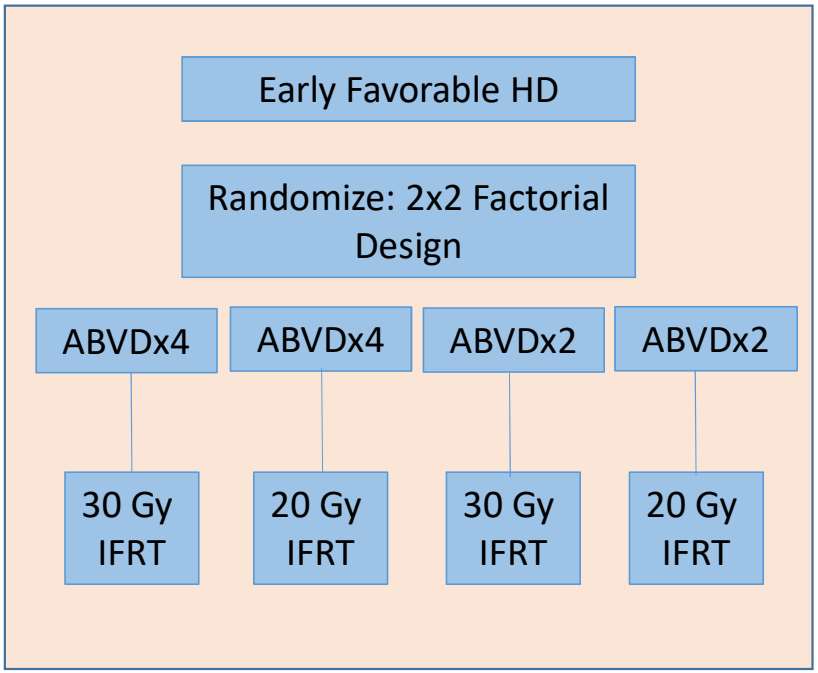
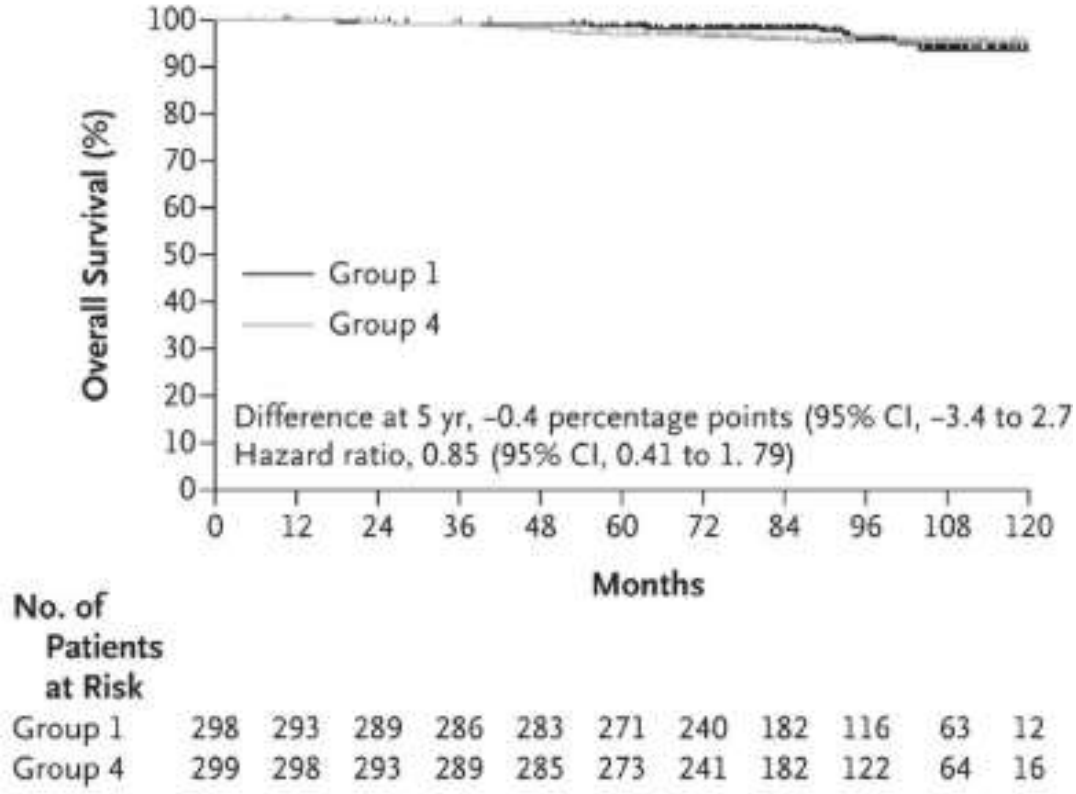
Adapted from: Younes A JCO 2012;30:895-896

German Hodgkin Study Group HD10



N=1131

Objective: To show non-inferiority (6%)



Engert A et al. Reducted Treatment Intensity in Patients with Early Stage Hodgkin's Lymphoma. NEJM 2010

GHSG HD10 Conclusions

- No significant difference in FFTF or OS between any of the four groups
- Established ABVDx2 followed by 20 Gy IFRT as a standard treatment option for early stage, favorable Hodgkin lymphoma patients meeting HD10 eligibility criteria
- No interim re-staging used after chemotherapy

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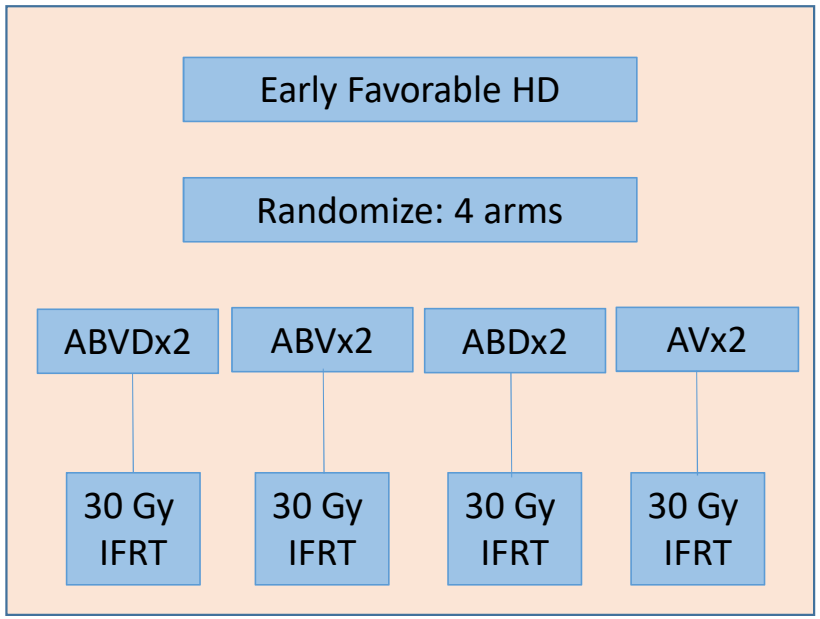
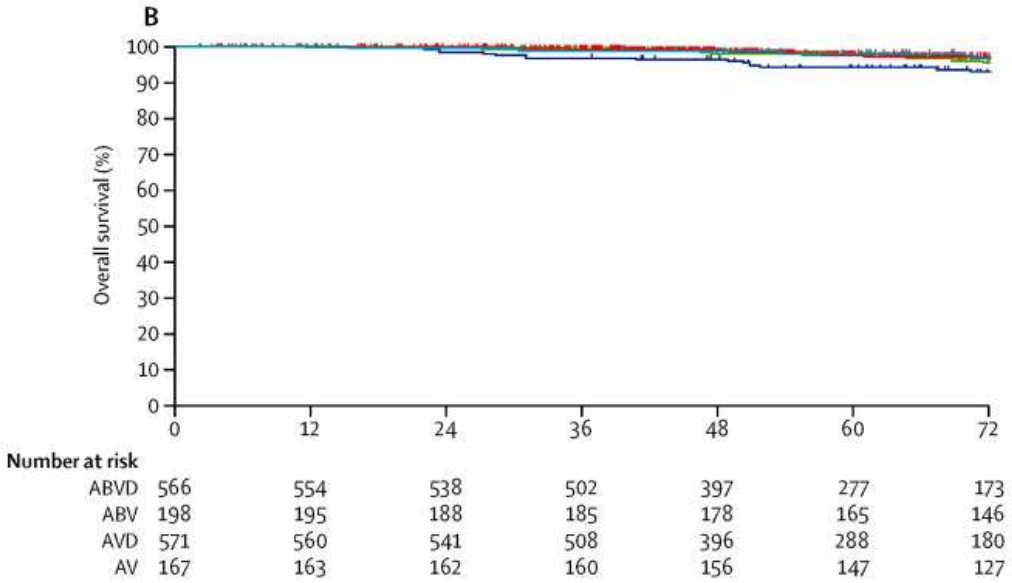
Engert A et al. Reducted Treatment Intensity in Patients with Early Stage Hodgkin's Lymphoma. NEJM 2010

GHSG HD13: Early Favorable Hodgkin Lymphoma



N=1502
Primary Objective: non-inferiority of the variant chemo regimens compared with ABVD in FFTF (6% at 5 years)



- Inferiority of dacarbazine-deleted varients detected with 5 year differences of -11.5% for ABV and -15.2% for AV.
- Non-inferiority of AVD could not be confirmed (5 year difference of -3.9% compared to ABVD)

Behringer K et al. Omission of dacarbazine or bleomycin, or both, from the ABVD regimen in treatment of early-stage favourable Hodgkin's lymphoma (GHSG HD13): an open-label, randomised, non-inferiority trial. The Lancet, April 2015

GHSG HD13 Results/Takeaways

- Dacarbazine cannot be omitted from ABVD without a substantial loss of efficacy
- With respect to the pre-defined non-inferiority margin, bleomycin also cannot be safely omitted
- The standard of care for patients with early stage, favorable HD should remain ABVD followed by IFRT

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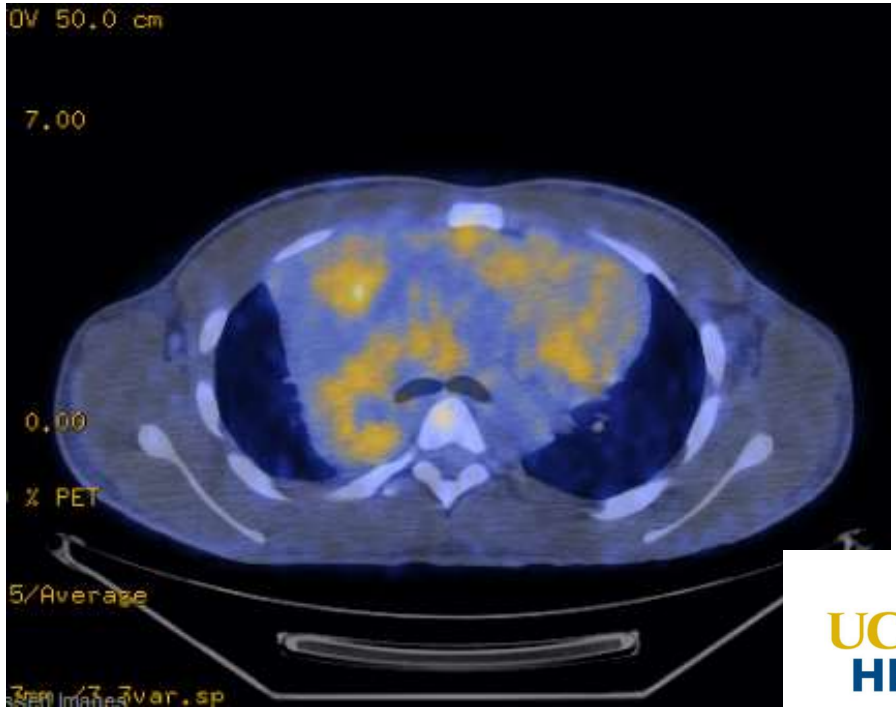
Deauville Criteria for Response Assessment

DEAUVILLE PET CRITERIA

Score	PET/CT scan result
1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately increased compared to the liver at any site
5	Uptake markedly increased compared to liver at any site
X	New areas of uptake unlikely to be related to lymphoma



Barrington et a, European Journal of Nuclear Medicine & Molecular Imaging 2010

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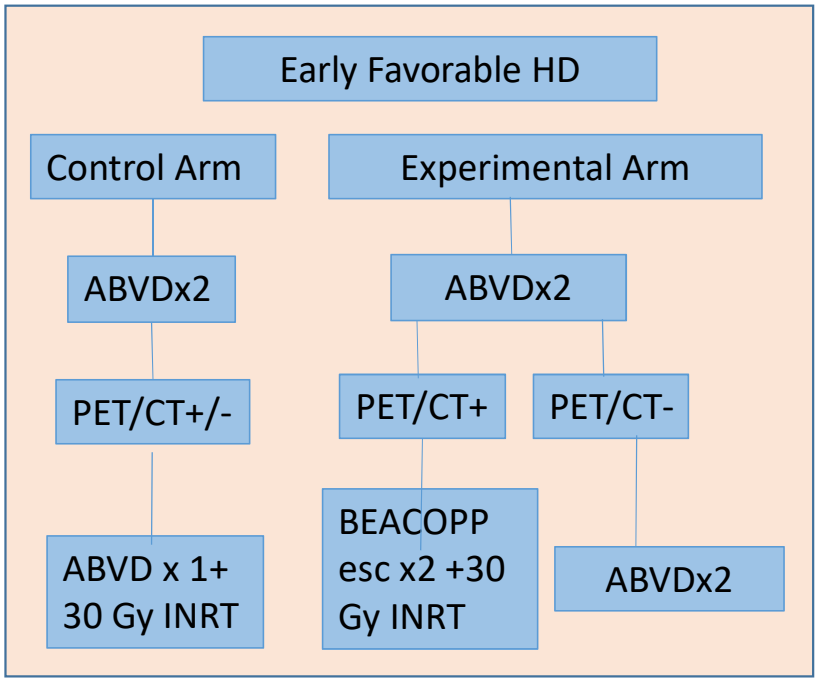
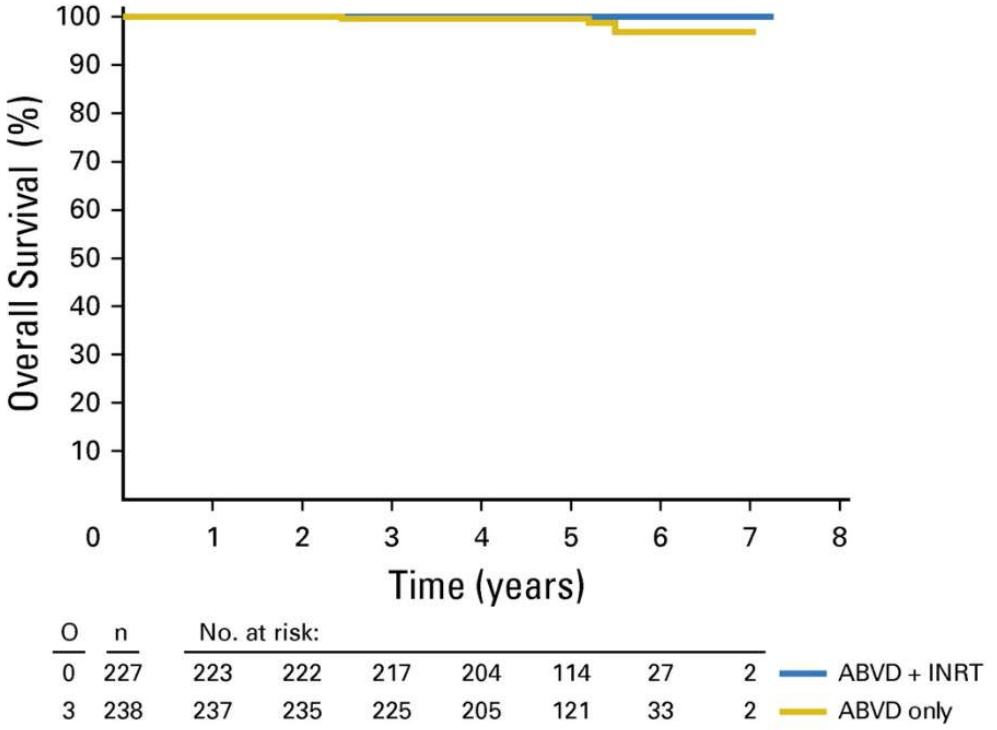
EORTC/LYSA H10F





N=1137

Primary objective: Non-inferiority of PET-guided omission of RT (10% margin)

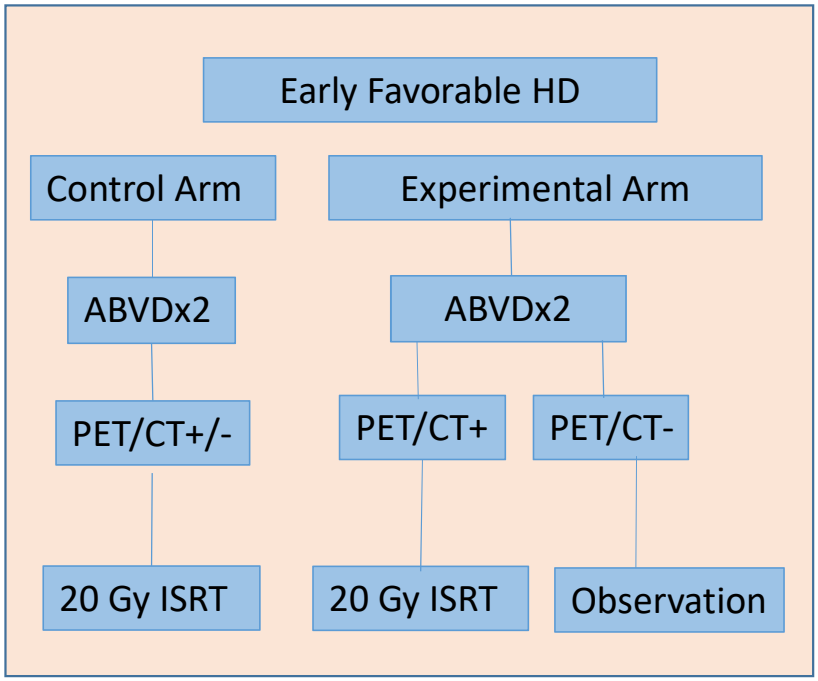
Raemaekers JM, JCO April 2014 and Andre MPE JCO 2017

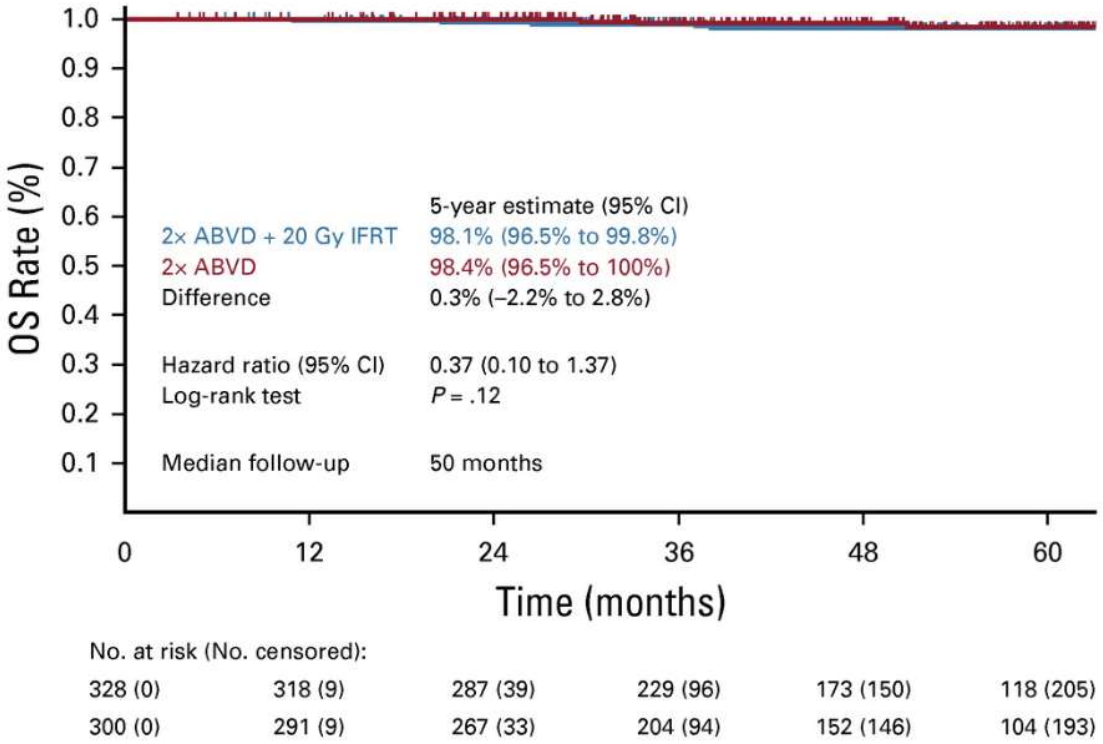
EORTC/LYSA H10F Conclusions

- Experimental arms for PET negative pts for both favorable and unfavorable cohorts closed early after interim safety analysis due to excess relapses
- Hazard ratio for failure of 9.36 for favorable arm, PET negative
- Long-term update:
  - Intensification to BEACOPP esc+INRT improved 5 year PFS from 77.4% to 90.6% in ePET+ patients (F+U combined)
  - For both favorable and unfavorable groups, non-inferiority of ABVD alone as compared to ABVD+RT could not be demonstrated (In favorable group, 5 year PFS 99.0% vs 87.1%)
  - No OS difference between arms

Raemaekers JM, JCO April 2014 and Andre MPE JCO 2017

GHSG HD16





N=1150

Primary objective: Non-inferiority at 10% level

Fuchs M et al. Positron Emission Tomography-Guided Treatment in Early-Stage Favorable Hodgkin Lymphoma: Final Results of the International, Randomized Phase III HD16 Trial by the German Hodgkin Study Group. JCO 2019

GHSG HD16 Conclusions

- Positive PET after two cycles ABVD indicates a high risk for treatment failure, particularly when a Deauville score of 4 is used as a cutoff
- In PET-2-negative patients, RT cannot be omitted without clinically relevant loss of tumor control
- Five-year OS was 98.1% (95% CI, 96.5% to 99.8%) with CMT and 98.4% (95% CI, 96.5% to 100.0%) with ABVD, with no significant difference

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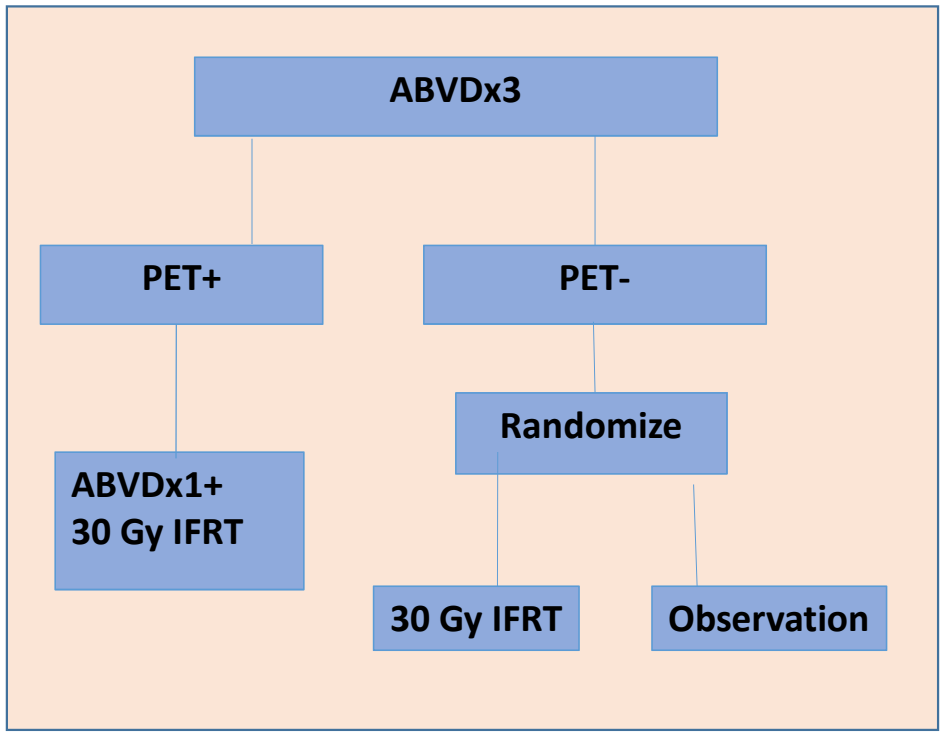
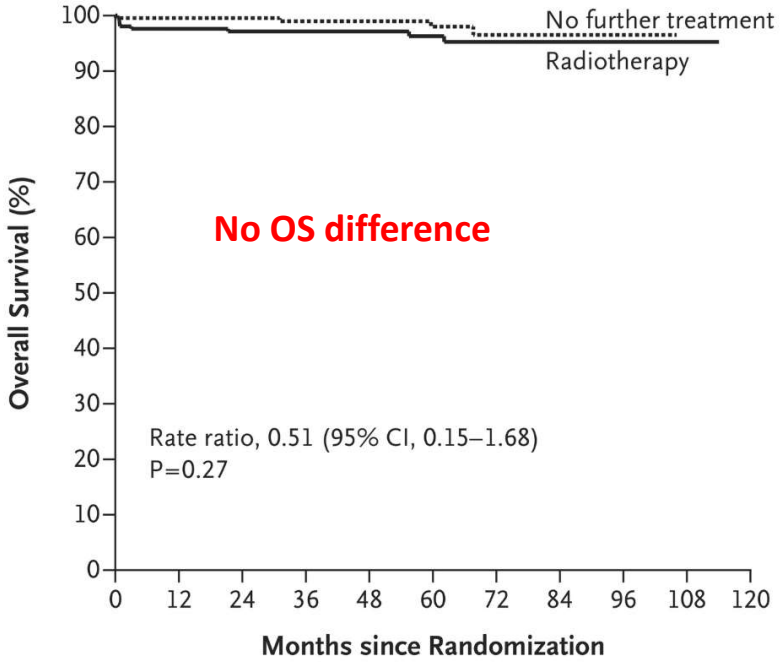
Fuchs M et al. Positron Emission Tomography-Guided Treatment in Early-Stage Favorable Hodgkin Lymphoma: Final Results of the International, Randomized Phase III HD16 Trial by the German Hodgkin Study Group. JCO 2019

UK RAPID





No. at Risk

Radiotherapy	209	200	191	175	139	103	60	34	13	2	0
No further treatment	211	204	196	167	140	97	56	18	6	0	0

Radford J et al. Results of a Trial of PET-Directed Therapy for Early-Stage Hodgkin's Lymphoma. NEJM 2015

UK RAPID Conclusions

- 3-year PFS improved with RT (3.8% in IIT and 6.3% per protocol)
- Did not meet pre-specified non-inferiority margin of 7% as 95% CI up to 8.8%
- Patients with negative PET after ABVDx3 had excellent outcomes with both approaches
- No OS difference between arms

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Treatment of Early Unfavorable-Risk Hodgkins

	Stage III/IV	Stage I/II	
		I/II Bulky Mediastinal	I/II No Bulk
North American	Advanced stage **includes stage I/II bulky disease**		Early Stage
GHSG	Advanced stage	**Early stage unfavorable**	Early –stage favorable

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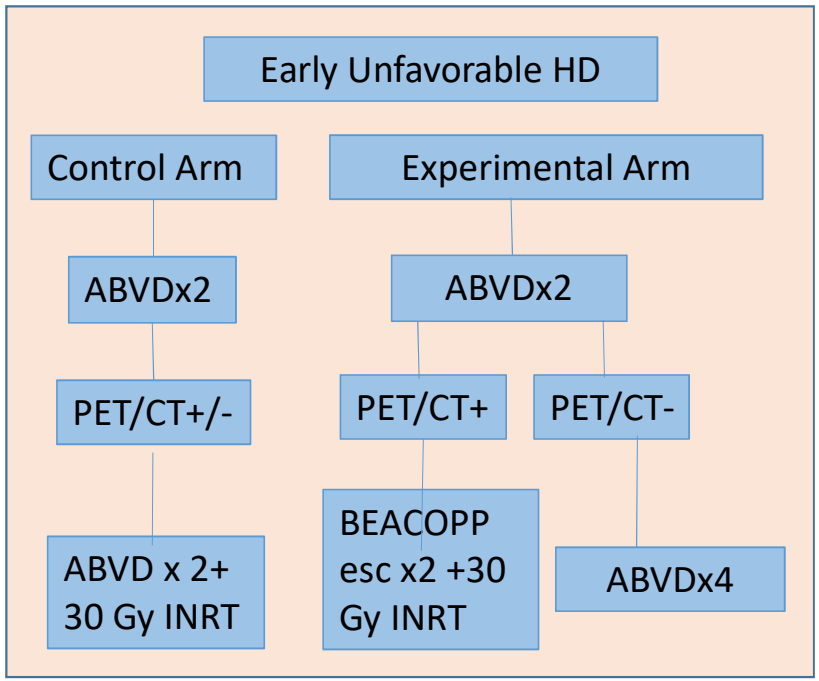
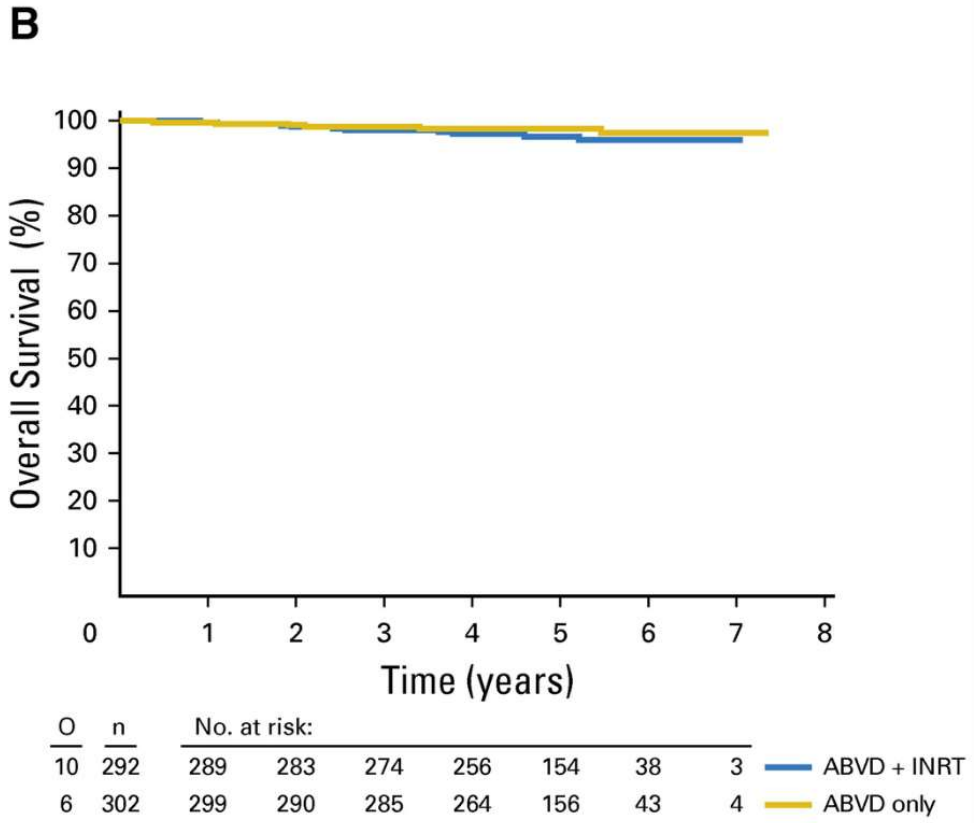
Adapted from: Younes A JCO 2012;30:895-896

EORTC H10U





Raemaekers JM, JCO April 2014 and Andre MPE JCO 2017

EORTC/LYSA H10U Conclusions

- Non-inferiority of chemotherapy alone for patients with negative PET2 could not be demonstrated
- No OS difference between arms
- A significant improvement (13.2%) of 5-year PFS was reached in the experimental BEACOPPesc + INRT arm (pooled F+U) compared with continuation with ABVD + INRT

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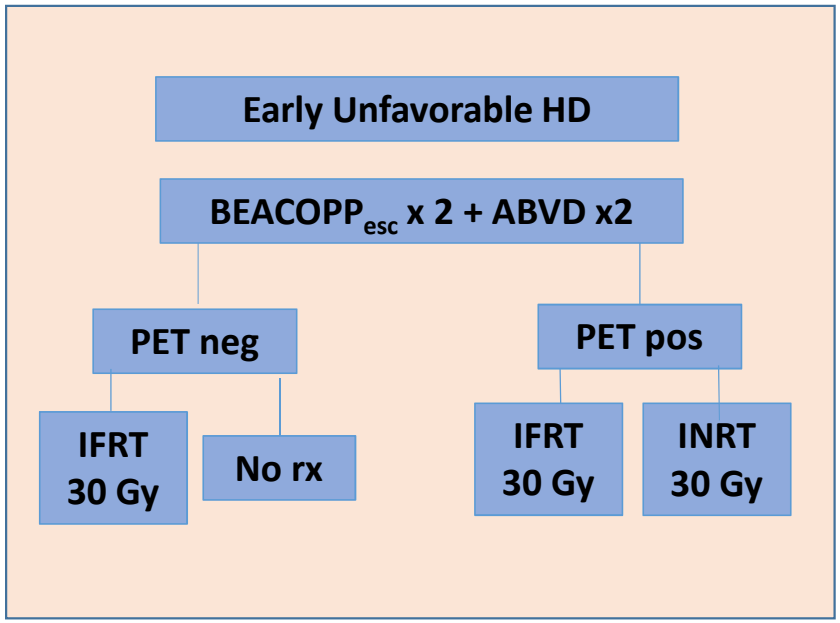
Raemaekers JM, JCO April 2014 and Andre MPE JCO 2017

GHSG HD17: Completed Accrual



Evaluates omission of RT following BEACOPPesc x 2 + ABVD x2 with negative PET/CT for early unfavorable HD

Evaluates INRT in place of IFRT following BEACOPPesc x 2 + ABVD x2 with negative PET/CT for early unfavorable HD

Primary Objective: To Compare PFS at 3 years between arms

Secondary Outcomes: OS, CR rate

N=1100

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Risks of Radiation

- Secondary cancers
  - Breast, lung, thyroid, other
- Heart injury
  - Related to volume of heart within field and delivered dose
- Hypothyroidism
- Muscle wasting
  - Avoid radiating cervical chains unless involved

However, risk of radiation is related to volume of irradiated normal tissue and dose

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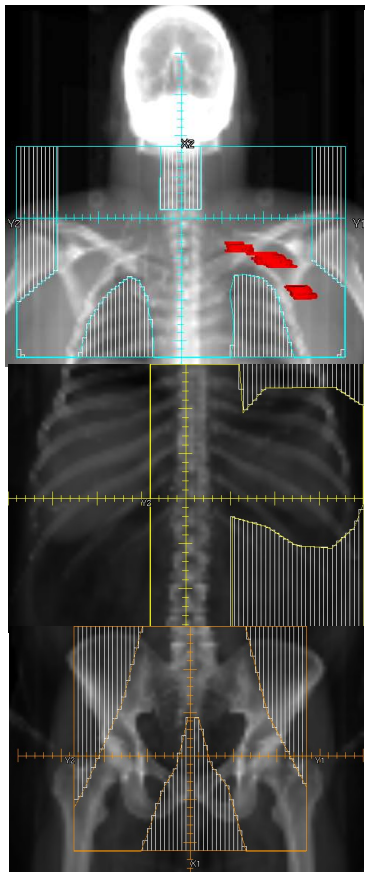
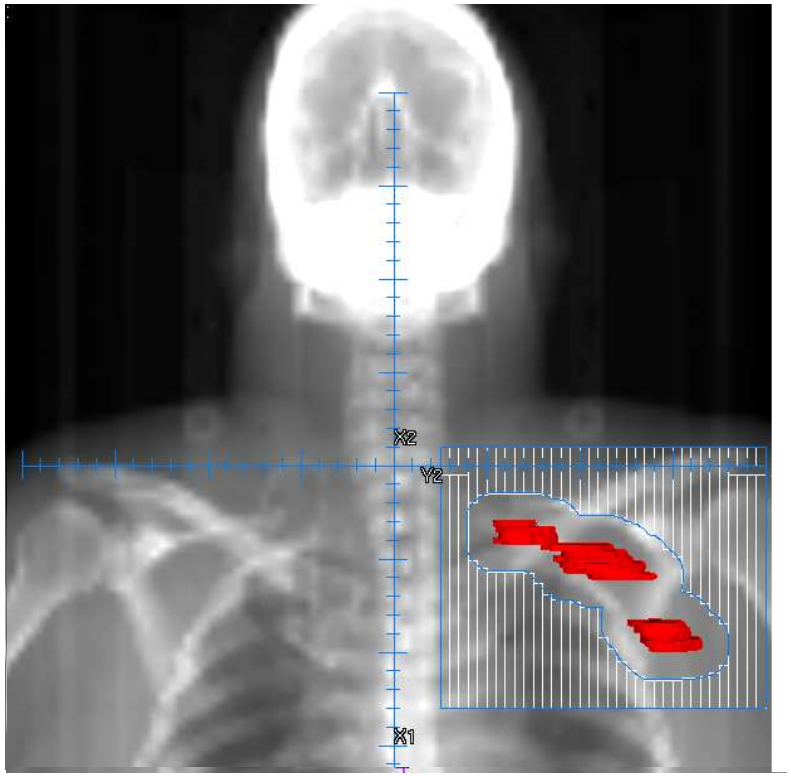
Evolution of Radiation For Hodgkin Lymphoma





Involved Node

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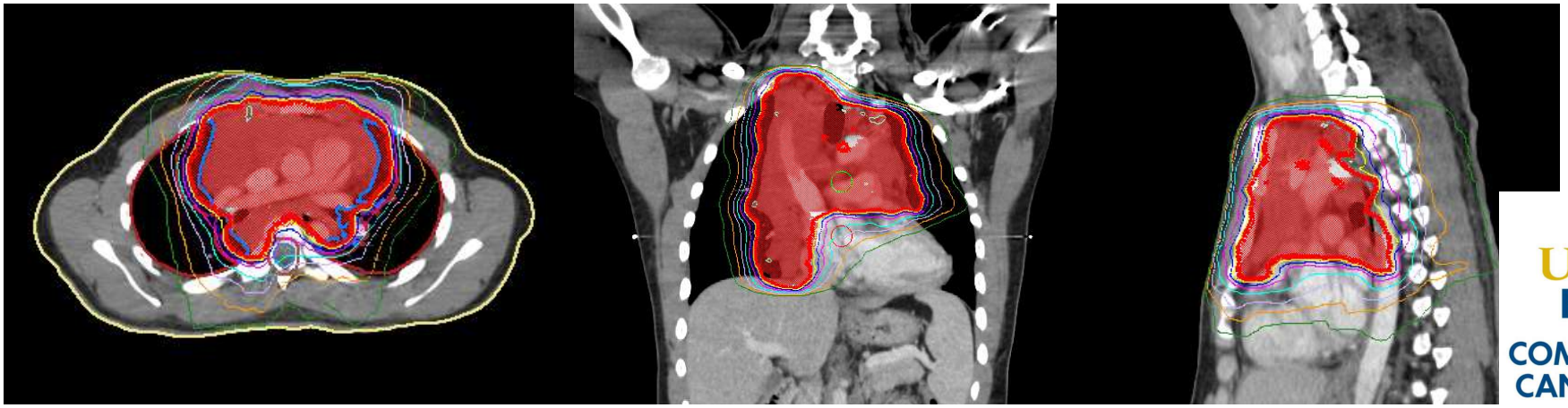
Modern Radiotherapy Techniques to Reduce Risk

- Intensity Modulated Radiation (IMRT)
- In well selected patients can reduce cardiac and lung dose with mediastinal disease, depending on disease distribution
- Limits parotid and oral cavity dose for cervical disease



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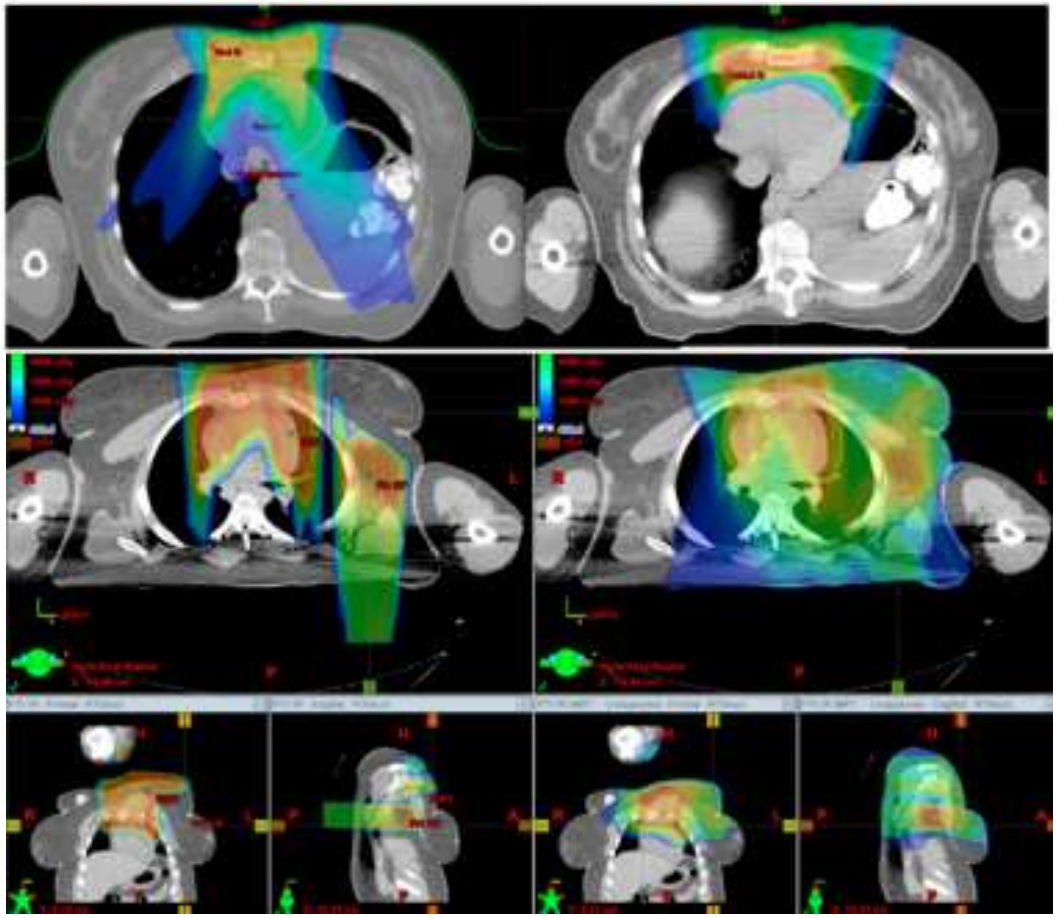
Proton Therapy

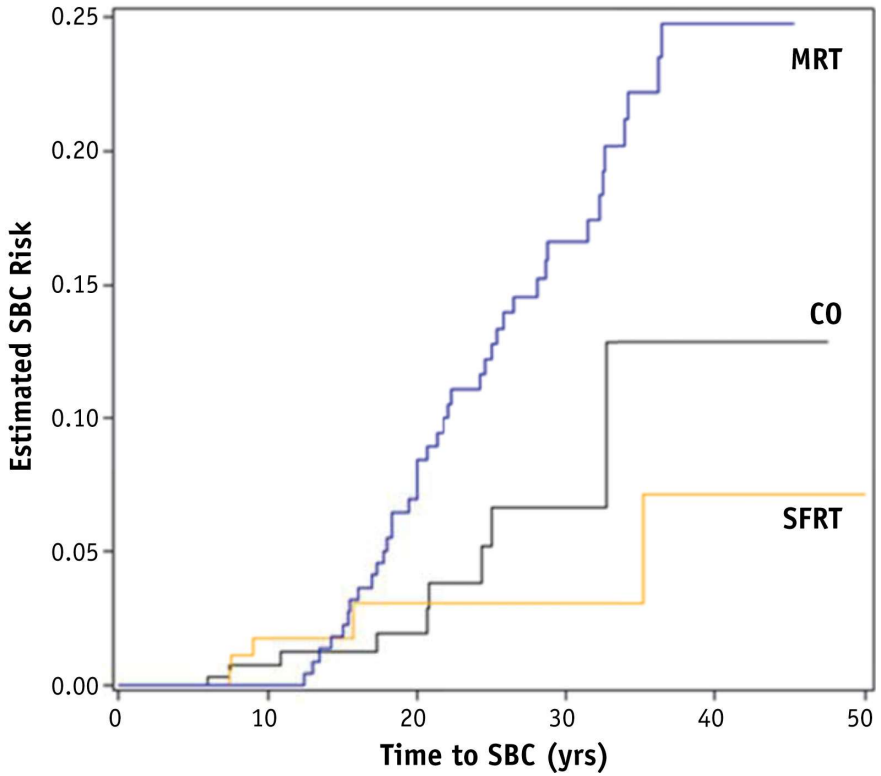
- For well-selected cases, proton therapy may reduce dose to heart, lungs, and breasts, among other structures
- Must be balanced against significant increased costs and travel burden to patients



Dabaja BS et al. Proton therapy for adults with mediastinal lymphomas: the International Lymphoma Radiation Oncology Group guidelines, Blood, 2018

Secondary Breast Cancer Risk with Modern Radiation

- Analysis of the BC Cancer Agency database of 734 female patients <age 50 with supradiaphragmatic HD treated 1961-2009.
- Categorized as mantle fields, “smaller” RT fields (IFRT, ISRT, INRT), or chemo alone
- 7% overall developed a breast cancer, at a median time of 20 years
- 20 year cumulative incidence of secondary breast cancer:
  - Mantle field: 7.5%
  - Smaller RT field: 3.1%
  - Chemotherapy only: 2.0%



Conway JL et al. Secondary Breast Cancer Risk by Radiation Volume in Women With Hodgkin Lymphoma. IJROBP 2017 97, 35-41DOI: (10.1016/j.ijrobp.2016.10.004)

Conclusions

- Modern approaches to Hodgkins focus on reduced treatment intensity while maintaining excellent cure rates
- De-intensification of both chemotherapy and radiation have been successful
- Interim PET based selection of patients for omission for radiation results in modestly reduced PFS without an OS difference
- Individual patients and disease-related risk factors should be taken into account when selecting patients for RT-omission

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Thank you!

Questions?