

Radiotherapy For Primary Extra-Nodal Lymphomas: A brief overview

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No disclosures



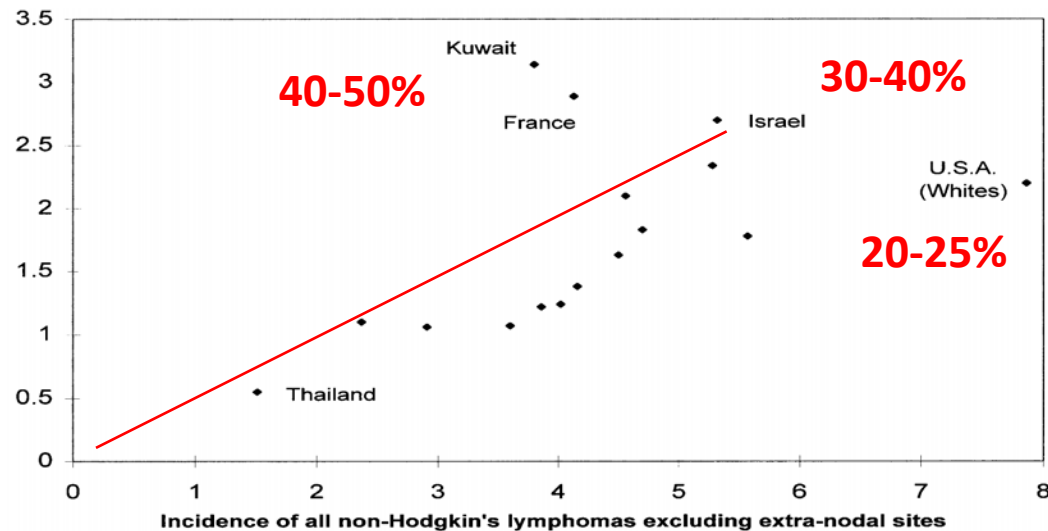
Background

Definition: Lymphomas confined to an extra-nodal organ +/- draining nodes

- Common- about 1/3 of all NHL
- Geographical variation (eg NKTCL in Asia)

Of great interest to lymphoma radiation oncologists!!

Usually localized (by definition)
Indolent cases highly radiosensitive
Clinically /anatomically diverse
Technically challenging



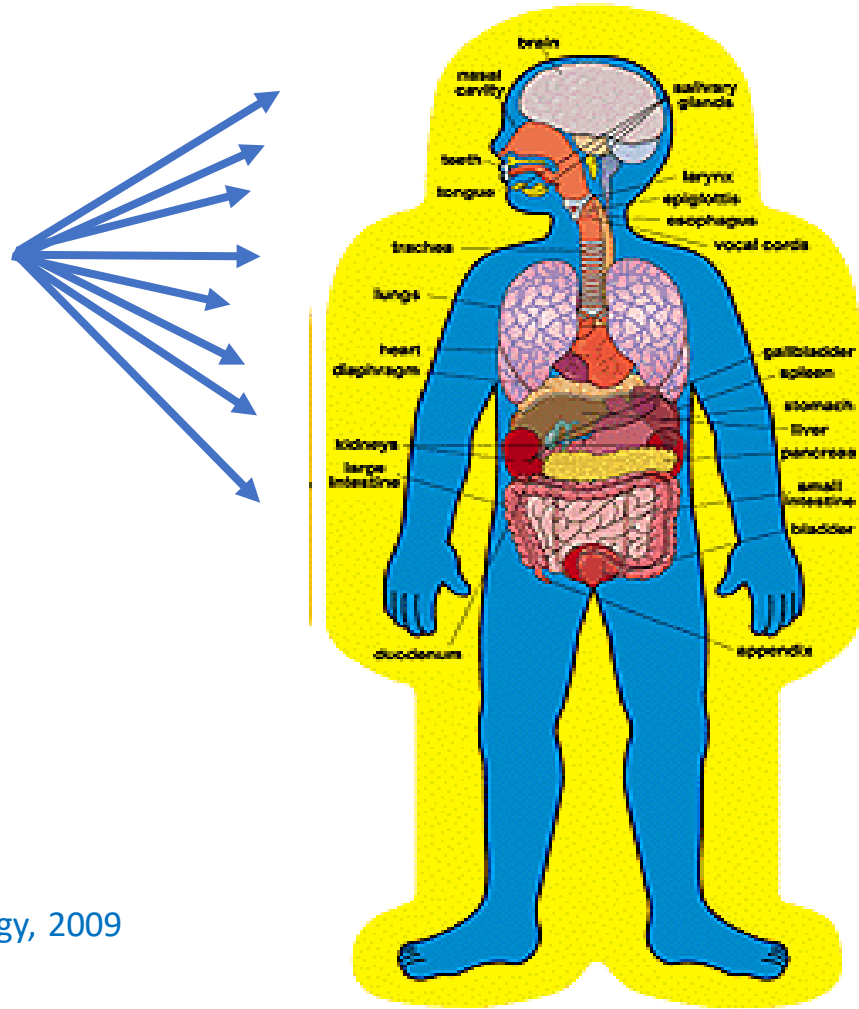
nearly half our sessions relate to PENL!

- *PCNSL*
- *NKTCL*
- *PMBCL*
- *3 x CTCL*
- *Mediastinal RT*
- *MR linac*
- *Motion management*

A highly diverse group of conditions – can involve any organ/ any histology

Commonest organs

GI	25-30%
Skin	18%
H+N	15%



Histology

B-cell 80%:	DLBCL 40% MZL 12 %
T-cell 15-20%:	MF/SS 5%, NKTCL

Brain, testis - mainly DLBCL
GIT, skin - wide range of histologies

Prognosis varies widely

PCNSL rapidly fatal
Duodenal FL “innocuous”

Evaluation of PENL

Expert haemato-pathology review

- Low grade NHL v reactive

CT/PET/Marrow

Particular attention to:

- other EN sites/paired organ
- site specific clinical risks: airway, SVC, spinal cord compression, bony fracture
- Underlying infection/autoimmune disease

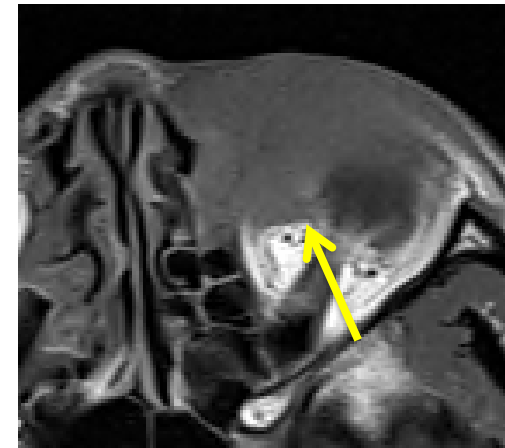
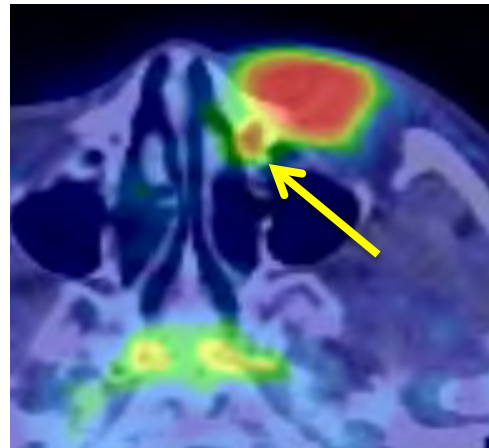
Whenever RT a possibility, meticulous delineation of tumour prior to initiation of systemic therapy!

GI: endoscopic US, pill cam

Skin: photographs and pre chemo sim

H+N: MRI, nasendoscopy, targeted biopsies

Orbital DLBCL with soft and lacrimal duct extension



Role of RT for EN lymphomas- consider four groups

Marginal zone/MALT lymphoma	curative as sole therapy
DLBCL	consolidation of systemic therapy
Nasal NKTCL	unique curative role - systemic therapy adjuvant *
Mycosis fungoides	key palliative role -integrated with systemic therapy*

* Discussed in separate sessions

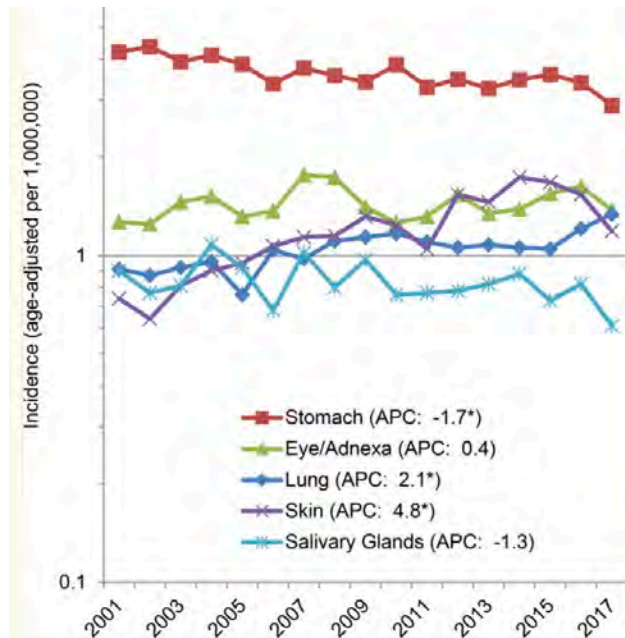
(Other: mantle cell, Burkitt, other T-cell)

Extra-Nodal MZL/MALT lymphoma

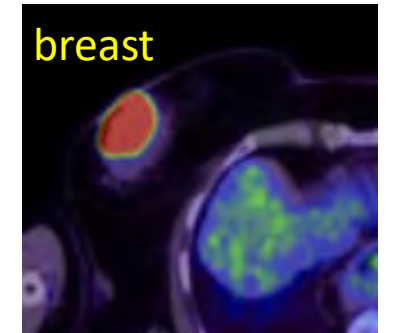
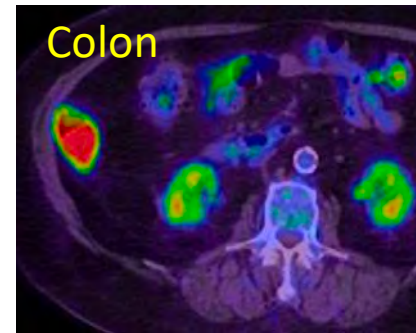
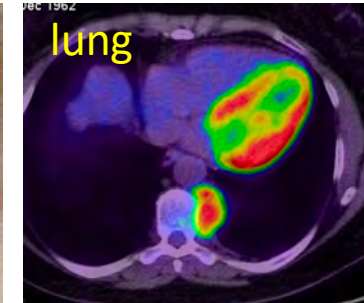
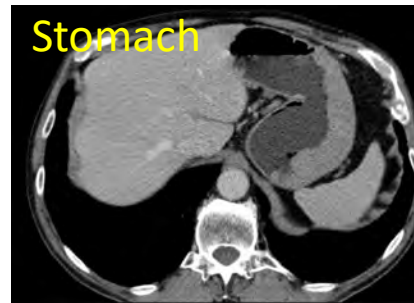
About 12% of EN lymphoma

Slow rise in incidence (except gastric)

Gastric about 30%, followed by orbit, lung and skin – about 10% each +wide range of other organs



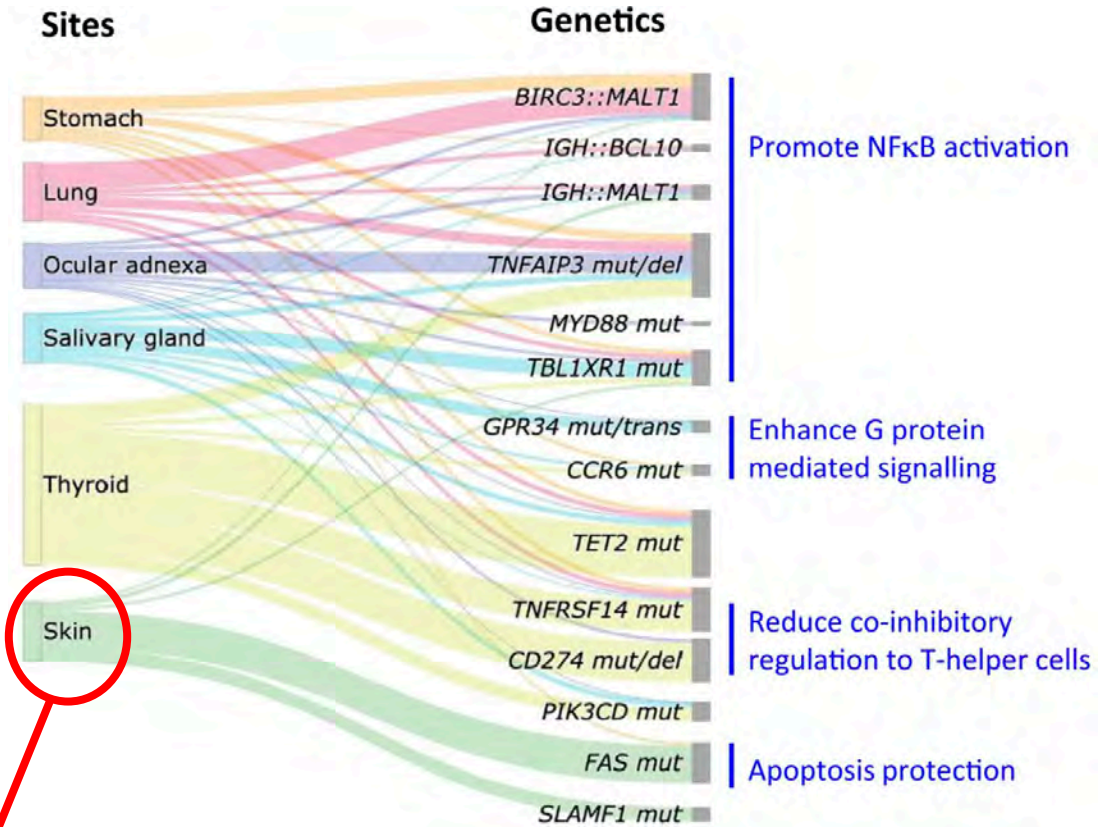
Cerhan Ann Lymphoma 2021



Extra-Nodal MZL

WHO lymphoma classification 5th edition
 Evolving classification - range of genetic/ pathogenetic features

Aetiology	
Underlying infection/autoimmunity	
Stomach:	<i>Helicobacter pylori</i>
Ocular adnexa:	<i>Chlamydia psittaci</i>
Small intestine:	<i>Campylobacter jejuni</i>
Skin:	<i>Borrelia burgdorferi</i>
Lung:	<i>Acromobacter xylosoxidans</i>
Hepatitis C	
Salivary gland:	Sjögren syndrome
Thyroid gland:	Hashimoto thyroiditis



Skin lymphoma separate from MALT in WHO 5
 International consensus classification: “primary cutaneous marginal zone lymphoproliferative disorder”

Treatment of localised MZL

Radiotherapy:

- Excellent local control, curative potential with limited morbidity
- Best documented long-term outcome data
- Standard of care for localised MALT lymphoma -no randomised trials, divergent views (Broccoli, ASH 2020)

Surgery:

- Diagnostic role, sometimes excisional biopsy is definitive

Antibiotics:

- Helicobacter pylori: 90% gastric MZL – eradication= first line therapy- 65-75% DFS
- Chlamydia psitacci: orbit – more variable incidence and use of antibiotics

Other

- Intralesional steroid, mabthera
- Systemic chemotherapy, mabthera
- Observation

Outcomes after RT

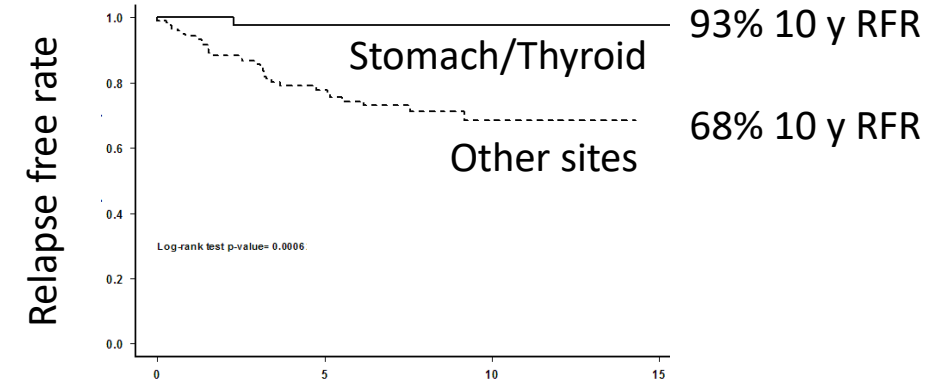
Durable local control >90%

5-10 yr freedom from relapse 65-85%*

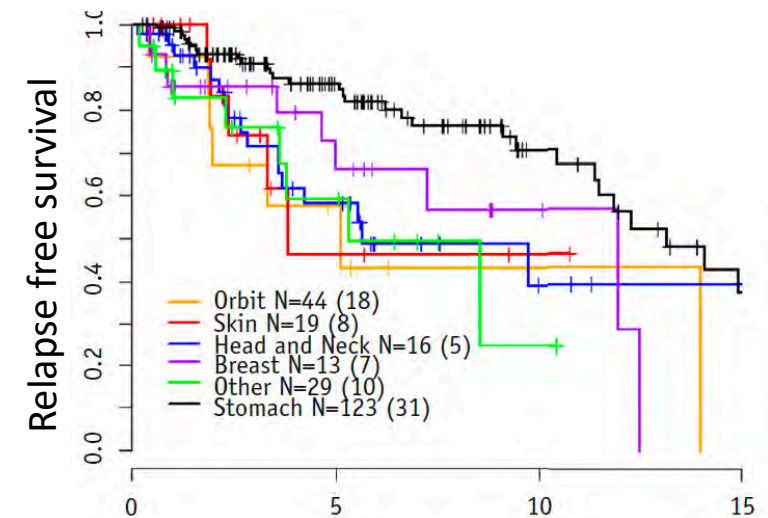
- Outcome varies by primary site
- Lowest relapse rate stomach and thyroid
- Relapses often in other MALT sites
- Skin – high relapse rate usually in skin

Cause specific mortality low (< 5-10%)

SMR not significantly elevated 1 for stage 1, cutaneous and gastric primary (Qi Blood Adv 2023)



Tsang JCO 2003, Goda Cancer 2010



Teckie IJROBP 2015

* Goda Cancer 2010, Teckie IJROBP 2015, Fang IJROBP 2021, MacManus EJC 2021, Conconi Ann Oncol 2015, Zucca Blood 2003, Qi Blood Adv 2023

Gastric MALT lymphoma

H Pylori eradication - 65-75% long-term remission

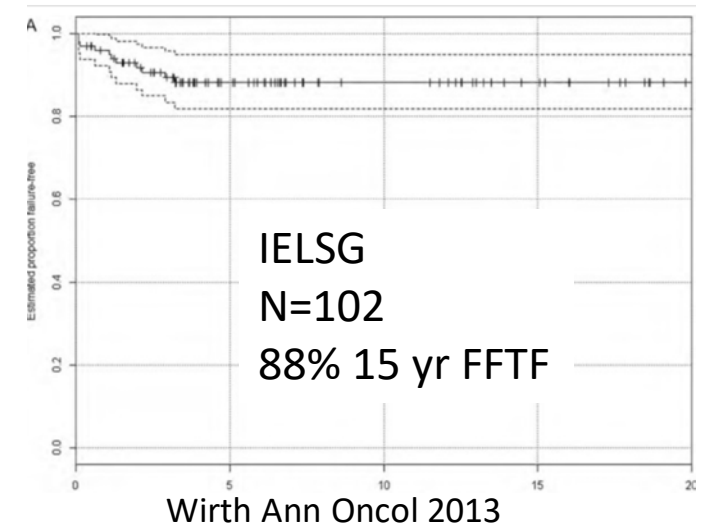
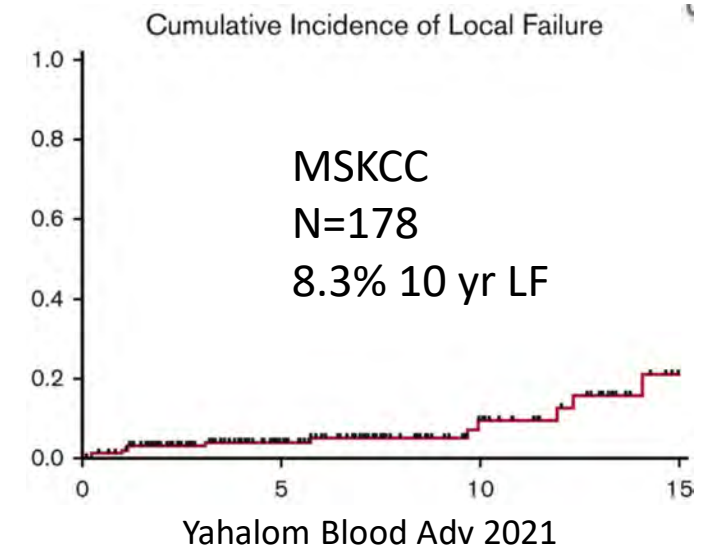
- responses can take >12-18 months (and be difficult to assess)
- consider observation for asymptomatic patients with ongoing improvement

Indications for RT

- no response, progressive disease or relapse (confirmed HP eradication)
- residual disease > 6-12 months with
 - Symptoms and/or predictors of poor response
 - HP -ve, deep invasion, node +ve, T11-18 (BIRC3:MALT1)

RT results in CR in 90% and long-term FFP 80-90%

GELA criteria Copie-Bergman BJH 2013, Zullo Clin Gastroenterol Hepatol 2010, Kuo Cancers 2022, Liu Gastroenterology 2002, Zullo J Clin Gastr 2013



Orbital adnexal MZL

C Psittaci positivity varies greatly: < 5% USA to 50-70% Korea, Italy

Travaglino AJCP 2019

IELSG 27 Doxycycline x 3 weeks Response 50-65%, 2-year PFS 60%

better outcomes with 6 months treatment IELSG 39

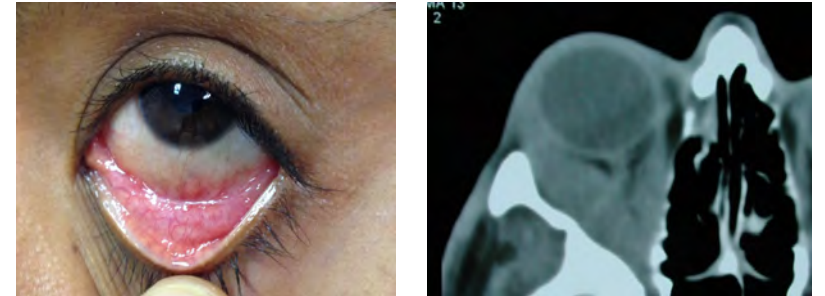
Ferreri JCO 2012, Blood 2022

TNM staging prognostic – conjunctival (=T1) best outcome

Kwon Br J Ophthal 2020

Bilateral disease 10-20% -comparable outcome to unilateral disease

ILROG Tran IJROBP 2021



- T1 Lymphoma involving the conjunctiva alone without eyelid or orbital involvement
- T2 Lymphoma with orbital involvement with or without conjunctival involvement
- T3 Lymphoma with preseptal eyelid involvement with or without orbital involvement and with or without conjunctival involvement
- T4 Orbital adnexal lymphoma and extraorbital lymphoma extending beyond the orbit to adjacent structures, such as bone, maxillofacial sinuses, and brain.

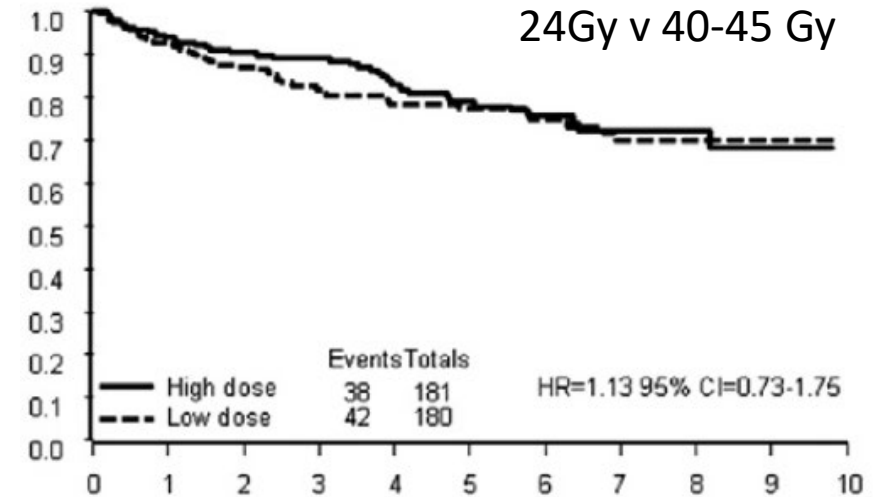
RT dose for indolent PENL

Historically 30-40Gy

24 Gy equivalent to higher doses in randomised trial

Standard initially for orbit lymphoma: excellent local control + less morbidity*

Increasingly used for gastric and other sites #



Lowry Radiother Oncol 2011

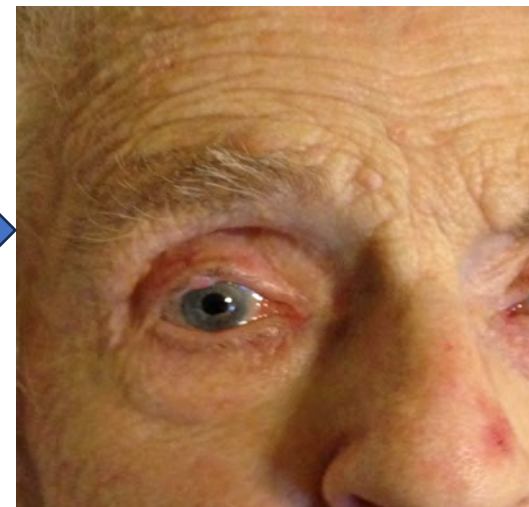
*Fung 2003, Uno 2003, Zhou 2005, Nam 2009, Bayraktar 2010, Goda 2011, Tran 2013

Pinnix IJROBP 2019, Shmelz 2019, Saifi 2021

2 x 2 Gy has been an effective, non-toxic palliative option for 3 decades

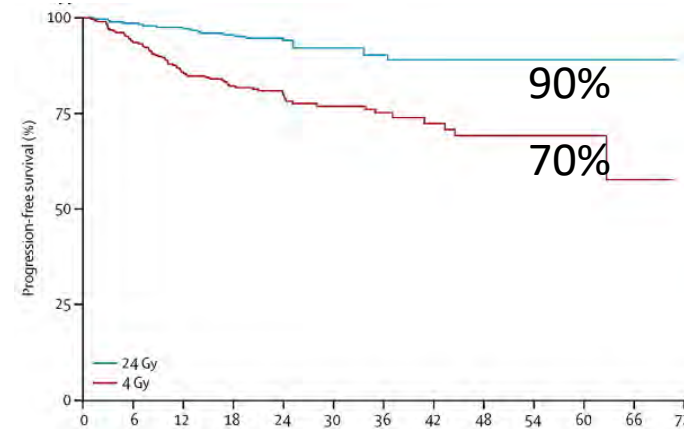
Ganem Hematol Oncol 1994, Girinsky IJROBP 2001, Haas JCO 2003

...and still seems like magic!

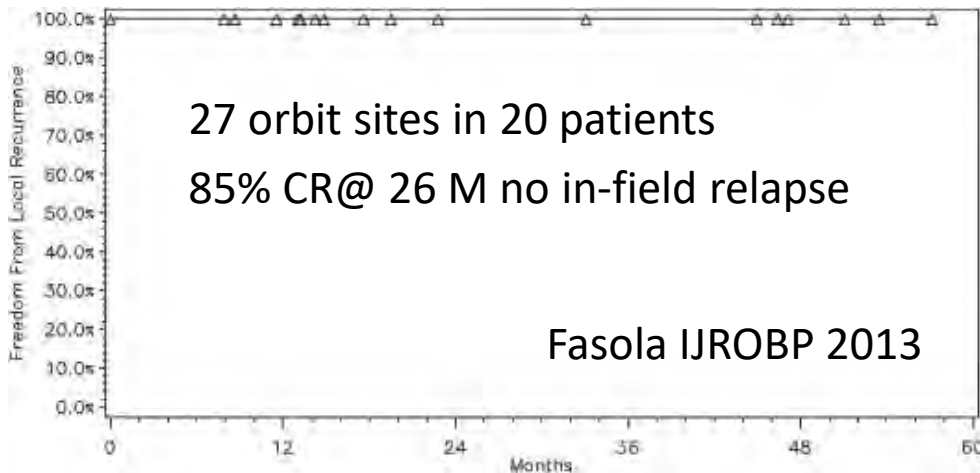


Interest in 4Gy (“ultra low-dose” or “boom-boom”) is ...booming

4 Gy inferior to 24 Gy but still very effective
UK randomised trial Hoskin Lancet Oncol 2021



Multiple series with encouraging results of 4 Gy in range of clinical settings for MZL



Fasola IJROBP 2013
Pinnix Head and Neck 2017
König Strahlenther Onkol 2018
Goyal J Am Acad Dermatol 2018
Gunther Leuk Lymph 2020
Baron Radiation Oncol 2021

Cerrato BJR 2021
Imber IJROBP 2021
Wijetunga IJROBP 2021
Yang Radiat Oncol 2022
Chelius Hematol oncol 2022
Park Cancers (Basel) 2022

Response adapted therapy

 International Journal of Radiation
Oncology*Biography*Physics
Volume 114, Issue 3, Supplement, 1 November 2022, Pages S2-S3

3
Response Adapted Ultra Low Dose Radiation Therapy for the Definitive Management of Orbital Indolent B-Cell Lymphoma

C.C. Pinnix¹, B. Dabaja¹, J.R. Gunther¹, P. Fang², S.Y. Wu¹, L. Nastoupil², P. Strati², R. Nair², S. Ahmed², R. Steiner², J. Westin², S.S. Neelapu², M.A. Rodriguez², H. Lee², M.L. Wang³, N. Fowler², C. Flowers², L. Feng⁴, L. Chi³, B. Esmali²

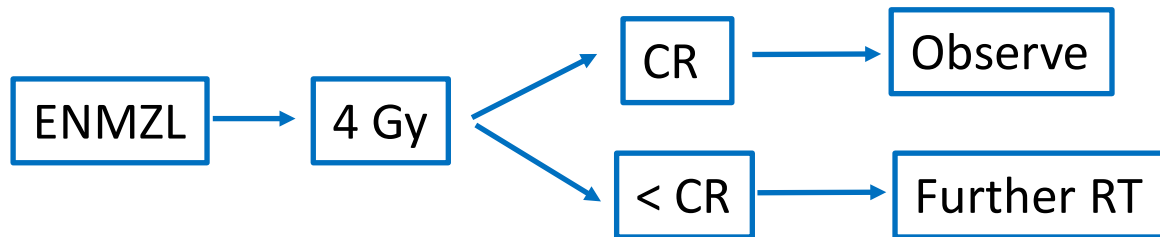
blood advances ISSUES ▾ LATEST ARTICLES ▾ GUIDELINES COLLECTIONS ▾

LYMPHOID NEOPLASIA | OCTOBER 22, 2021

Excellent response to very-low-dose radiation (4 Gy) for indolent B-cell lymphomas: is 4 Gy suitable for curable patients?

Ψ Clinical Trials & Observations

Brandon S. Imber, Karen W. Chau, Jasme Lee, Jisun Lee, Dana L. Casey, Joanna C. Yang, N. Ari Wijentunga, Annemarie Shepherd, Carla Hajj, Shunan Qi, Monica R. Chelius, Paul A. Hamlin, M. Lia Palomba, Erel Joffe, Zhigang Zhang, Andrew D. Zelenetz, Gilles A. Salles, Joachim Yahalom



Interest in moving 4 gy into curative setting

Frail, elderly, toxicity averse

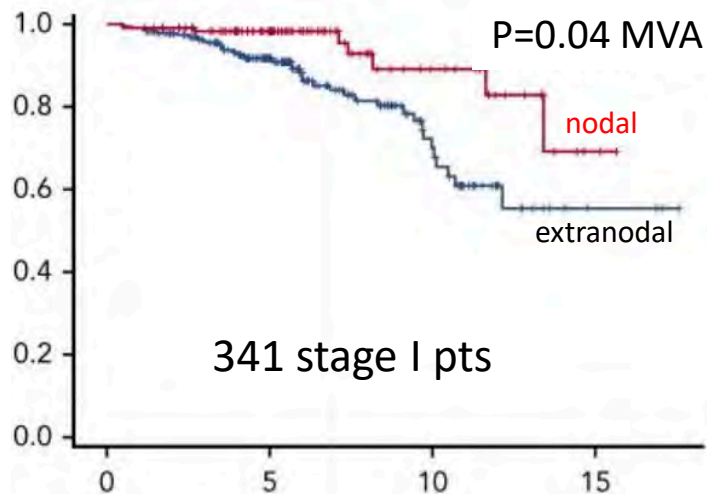
Selected, well informed younger patients?
Especially orbit, salivary

Extra nodal DLBCL

30-40% of PENL

Common sites: GI, H+N, CNS

Poorer prognosis than nodal



MSKCC Bobillo, Blood 2021

Primary sites vary in prognosis

Poor prognosis- widespread dissemination + CNS

testis, CNS, vitreo-retinal - immune privileged sites
breast, Leg type skin, adrenal, uterus

- MYD88, CD79B mutations, ABC

Better prognosis

H+N, uni focal bone, gastric, thyroid

- GCB, no MYD88 mutations

Castillo Am J Hematol 2013, Gupta J Hematol 2022, Ollila, Curr Treatment Opt Oncol 2018, Takahara Cancers (Basel) 2023

Indications for RT for EN DLBCL

PCNSL, PMBCL- discussed in separate lectures

- RT historically integral to management
- toxicity concerns have led to reduction in the use of RT in favour of intensified systemic therapy
- Question: Will new RT techniques and lower doses lead to reevaluation of the role of RT?

Other primary sites

- Data predominantly retrospective
- CHOP data of uncertain relevance
- RCHOP studies -small and heterogeneous

Consequently, expert opinion varies on which primary sites require RT

Organ specific recommendations for RT

RT always recommended:

Testis

RT often recommended:

Breast, bone, thyroid, cutaneous leg-type

Less agreement

Stomach, H+N

Limited data:

Lung, liver, pancreas, adrenal

Also consider

- **General indications** as for nodal DLBCL – bulk, poor response to systemic therapy
- **Critical sites-** spine, airway
- **Difficulty assessing response** – eg residual PET changes in bone after RCHOP

Testicular DLBCL

Poor prognosis

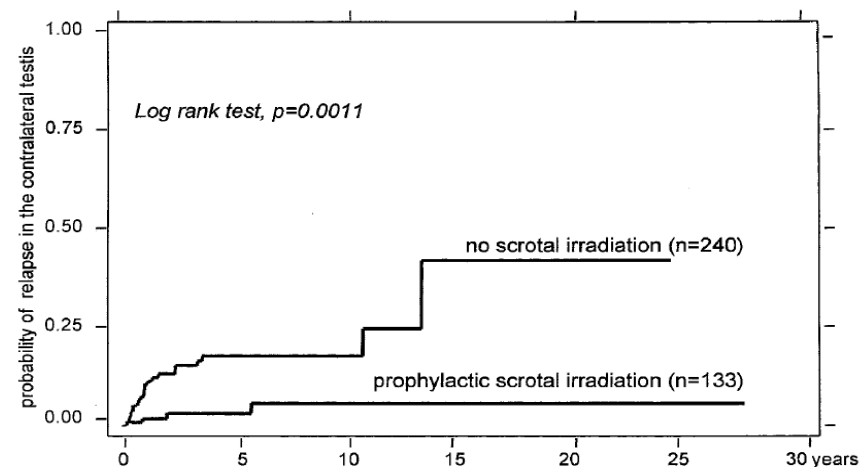
CNS relapse 20-30% - CNS proylaxis

C/L testis relapse 15-40% (blood testis barrier)

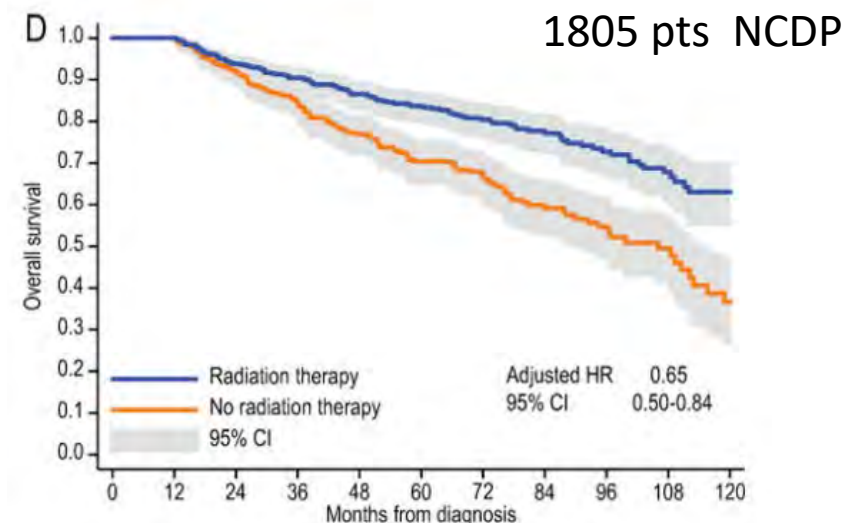
Role of radiotherapy to c/l testis established by IELSG studies and remains standard of care

- largely eliminates testicular relapse
- appears to improve survival (Zucca 2003, Ollila 2019)

Role of RT to involved regional nodes- less clear



IELSG Zucca JCO 2003, Vitolo JCO 2011



Ollila Leuk and Lymphoma 2019

Breast DLBCL

Poor prognosis

Relapse in ipsi- and contralat breast and CNS

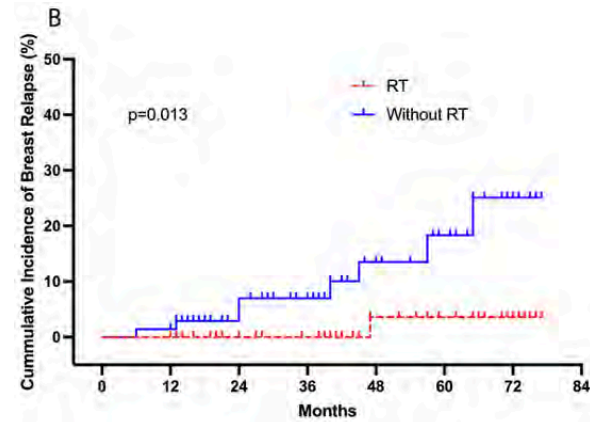
Benefit of RT consistent across studies:

CHOP

- IELSG Ryan Ann Oncol 2008

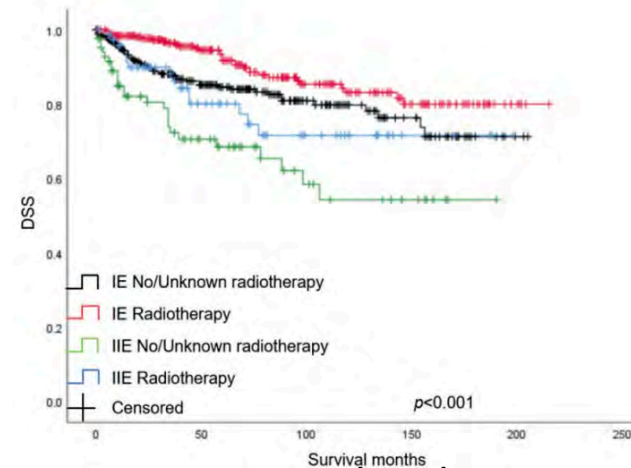
RCHOP

- Hosein, BJH 2014
- Hu, Cancer Sci 2018
- Weng, Research Square 2023
- Zhang, Eur Rev Med Pharm Sci 2022



135 pts multicentre, retrospective study
RT reduced breast relapse improved OS.

Weng 2023



956 pts in SEER data base 1998 – 2015
MVA/ propensity score matched

Zhang 2022

Bone DLBCL- data less consistent

RT beneficial

Beal Cancer 2006 (MSKCC n=101)

Tao ILROBP 2015 (MDACC n=102)

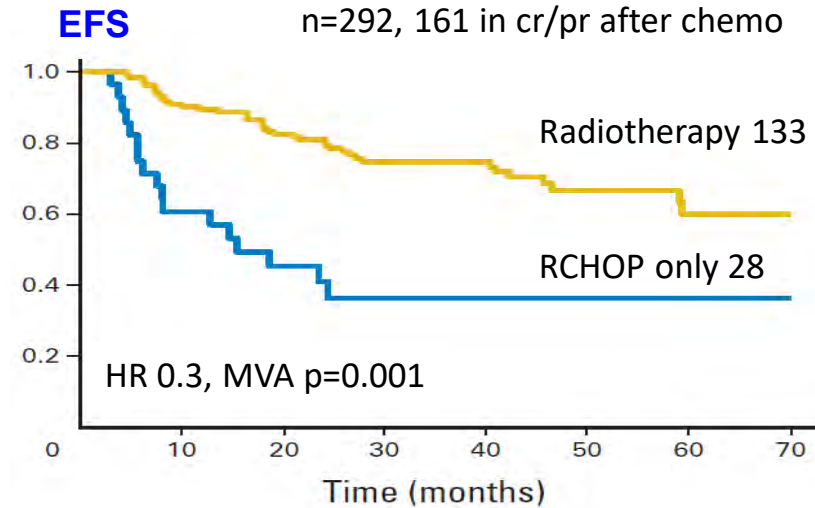
Held JCO 2013 (GLSG prospective n=292)

RT not beneficial

Ramadan Ann Oncol 2007 (BC n= 131)

Freeman Blood 2021 (BC 103 PET -ve)

Ventre Oncologist 2014 (IELSG 14 n=161)



Consider case by case: unifocal, bulky, soft tissue, uncertain response

Conclusion

- RT plays key role in PENL
- Central, curative role for indolent ENL
 - Use of low dose RT rapidly expanding (potential in combination with immunotherapy)
- Role for DLBCL more selective with new, intensive systemic therapies
- T cell lymphomas
 - Unique role for NKTCL
 - Key role for CTCL

Thank you

