Meta-Analysis in Lymphomas

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Questions answered by meta-analysis in contemporary management of lymphomas

- ❑PET in Systemic Lymphomas
  - Staging (diagnostic performance of bone marrow involvement)
  - Response assessment
  - Surveillance
- ❑PET in Primary CNS Lymphomas
- ❑Role of Immunochemotherapy in Lymphomas
  - Rituximab in DLBCL
- ❑Role of consolidation RT in Lymphomas in rituximab era
  - Hodgkins Lymphomas
  - Non Hodgkins Lymphomas
- ❑Role of Radiation therapy in NK T cell Lymphomas
  - Optimal timing of radiotherapy

PET in Hodgkin Lymphomas-

Staging (diagnostic performance of bone marrow involvement)

Systematic review and meta-analysis on the diagnostic performance of FDG-PET/CT in detecting bone marrow involvement in newly diagnosed Hodgkin lymphoma: is bone marrow biopsy still necessary?

Annals of Oncology 25: 921–927, 2014

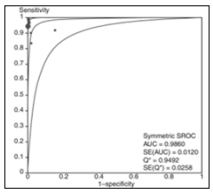
- N= 9 eligible studies
- N=955 pts
- Moderate methodological quality using QUADAS-2 scores

Study (year)	Country	Type of study	No. of patients	Age in years (range)	Sex (M/F)	Interval between FDG-PET/CT and BMB	Ann Arbor stage of included patients
Cortés-Romera et al. (2013) [17]	Spain	NR	63	37[a] (18–76)	42/21	<2 weeks	I-IV
Agrawal et al. (2013) [18]	India	Retrospective	31	NR	NR	<1 week	II-IV
Muzaffar et al. (2012) [19]	Pakistan	Retrospective	122	36[a] (6–78)	81/41	<2 weeks	I-IV
El-Galaly et al. (2012) [20]	Denmark	Retrospective	454	39[a] (15–87)	257/197	NR	I-IV
Pelosi et al. (2011) [21]	Italy	NR	130	NR	NR	<2 weeks	NR
Mittal et al. (2011) [22]	India	Retrospective	20	NR	NR	7–10 days	NR
Cheng et al. (2011) [23]	USA	Retrospective	31	15[a] (6–23)	11/20	<2 weeks	I-IV
Moulin-Romsee et al. (2010) [24]	France	Retrospective	83	31[a] (7–82)	45/38	'Few days'	I-IV
Ngeow et al. (2009) [25]	Singapore	Prospective	21	28[b] (17–71)	NR	NR	NR

[a]Mean.
[b]Median.
BMB, bone marrow biopsy; CT, computed tomography; FDG-PET, ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography; NR, not reported.

PET in Hodgkin Lymphomas-

Staging (diagnostic performance for bone marrow involvement)



Study (year)	Sensitivity (%)		Specificity (%)	
	Value	95% CI	Value	95% CI
Cortés-Romera et al. (2013) [17]	100	75.3–100	100	92.6–100
Agrawal et al. (2013) [18]	87.5	47.3–99.7	100	85.2–100
Muzahir et al. (2012) [19]	100	90.5–100	100	95.8–100
El-Galaly et al. (2012) [20]	94.9	87.4–98.6	100	99.0–100
Mittal et al. (2011) [22]	100	47.8–100	86.7	59.5–98.3
Cheng et al. (2011) [23]	100	39.8–100	100	87.2–100
Moulin-Romsee et al. (2010) [24]	100	81.5–100	100	94.5–100
Pooled estimate	96.9	93.0–99.0	99.7	98.9–100

- Pooled Sensitivity: **96.9% [95% CI 93.0% to 99.0%]**
- Pooled specificity :**99.7% (95% CI 98.9% to 100%)**
- The area under the ROC curve was **0.9860.**
- The proportion of FDG-PET/CT-negative patients with a positive BMB among all cases was **1.1% (95% CI 0.6% to 2.0%).**

PET in DLBCL Lymphomas-

Staging (diagnostic performance for bone marrow involvement)

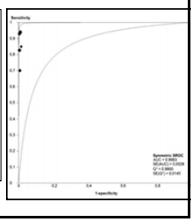
FDG PET/CT for the detection of bone marrow involvement in diffuse large B-cell lymphoma: systematic review and meta-analysis

Eur J Nucl Med Mol Imaging (2014)

- N= Seven studies, with a total of
- N =654 pts

Khan et al. [23]	2013	UK	Retrospective	130
Cortes-Romera et al. [24]	2013	Spain	Not reported	84
Bothat et al. [25]	2013	France	Retrospective	133
Hong et al. [26]	2012	Korea	Retrospective	89
Pelosi et al. [27]	2011	Italy	Not reported	120
Ngeow et al. [28]	2009	Singapore	Prospective	55
Ribrag et al. [29]	2008	France	Prospective	43

- Pooled Sensitivity : **88.7 %** (95 % CI, 82.5 – 93.3 %)
- Pooled Specificity: **99.8 %** (95 % CI 98.8 – 100 %).
- The area under the sROC curve was **0.9983**.
- Proportion of PET/CT-negative patients with positive BMB findings was **3.1 %** .
- Proportion of PET/CT-positive patients with negative BMB findings was **12.5 %**



PET in Systemic Lymphomas :Response assessment

Predictive Value of Interim PET/CT in DLBCL Treated with R-CHOP: Meta-Analysis Na Sun, Jinhua Zhao,Wenli Qiao et al, Biomed research int

Prognostic value of complete remission status at end-of-treatment FDG-PET in R-CHOP-treated diffuse large B-cell lymphoma: systematic review and meta-analysis.

Critical Reviews in Oncology/Hematology

Prognostic value of interim FDG-PET in R-CHOP-treated diffuse large B-cell lymphoma: Systematic review and meta-analysis

Hugo J.A. Adams (PhD) (MD)*, Thomas C. Kwee (PhD) (MD)

REVIEW ARTICLE

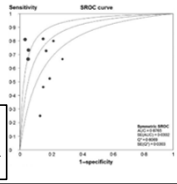
Systematic review and meta-analysis on the prognostic value of complete remission status at FDG-PET in Hodgkin lymphoma after completion of first-line therapy

PET in Systemic Lymphomas :Diagnostic performance of Interim PET

bjh research paper

Prognostic value of interim FDG-PET in Hodgkin lymphoma: systematic review and meta-analysis

N=10 STUDIES
N= 1389 patients
Question asked: Sensitivity, specificity, positive predictive value and negative predictive value of interim FDG-PET for predicting treatment failure.
Pooled sensitivity: 70.8% (95% CI:64%-77%)
Pooled Specificity:89.9% (95% CI: 88.0–91.6%)
PPV:0–86.0%
NPV: 84.4–98.6%



Take Home message:
- The overall prognostic value of interim PET is moderate for excluding and relatively high for identifying treatment failure in HL.
- Interim PET cannot yet be implemented in routine clinical practice due to moderate-quality evidence and inter-study heterogeneity that cannot be fully explained yet.

PET in Systemic Lymphomas-Role of Surveillance PET

Evidence-Based Focused Review ● blood

Evaluating surveillance imaging for diffuse large B-cell lymphoma and Hodgkin lymphoma

Jonathon B. Cohen,[1] Madhusmita Behera,[2] Carrie A. Thompson,[2] and Christopher R. Flowers[3]
[1]Winship Cancer Institute, Emory University, Atlanta, GA; and [2]Mayo Clinic, Rochester, MN

- N= 15 STUDIES (7 DLBCL, 6 HL, and 2 HL and DLBCL)
- N =3099 patients

Reference (study)	Disease	Modality	No. of patients	No. of relapses (%)	No. of relapses outside surveillance visit (% of relapses)	Asymptomatic relapse (% of relapses)
7 (Mayo)	DLBCL	CT or PET	552	112 (20)	69 (62)	13 (19)
8 (Lyon)	DLBCL	CT	222	55 (25)	34 (62)	6 (11)
9	DLBCL	CT	117	35 (30)	33 (94)	2 (6)
9	DLBCL	PET/CT	116	13 (12)	7 (54)	6 (46)
10	DLBCL	CT or PET	825	50 (6)	31 (62)	19 (38)
11	DLBCL	CT	341	113 (33)	88 (78)	25 (22)
12	DLBCL	PET	118	31 (26)	22 (71)	9 (29)
13	DLBCL	CT or PET	106	15 (14)	—	—
14	DLBCL	PET	75	23 (31)	20 (87)	3 (13)
15	HL/DLBCL	PET, CT, or gallium	—	125 (NA)	78 (62)	47 (38)
16	HL/DLBCL	PET/CT				
17	HL	PET/CT	161	22 (14)	12 (55)	10 (45)
18	HL	CT or PET	305	28 (9)	8 (29)	17 (61)
19	HL	CT or PET	174	6 (3)	—	—
20	HL	CT or PET	36	5 (14)	—	—
21	HL	PET/CT	150	40 (27)	15 (38)	25 (63)

PET in Systemic Lymphomas-Surveillance

Summary and recommendations

- No survival advantage with the use of surveillance imaging for patients with DLBCL or HL who achieved remission after first-line therapy.
- Surveillance imaging produces additional radiation exposure.
- Recommend that patients with HL and DLBCL who achieve CR should not receive routine surveillance imaging(Lugano2014)- **grade IB recommendation**

PET scan in Primary CNS Lymphomas

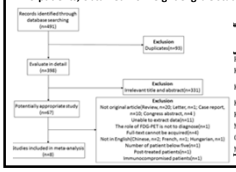
www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 25), pp: 41518-41528

Meta-Analysis

Diagnostic value of using ^{18}F-FDG PET and PET/CT in immunocompetent patients with primary central nervous system lymphoma: A systematic review and meta-analysis

Yaru Zou[1,*], Jianjing Tong[2,*], Haiyan Leng[3], Jingwei Jiang[4], Meng Pan[1,*] and Zi Chen[5,6,*]

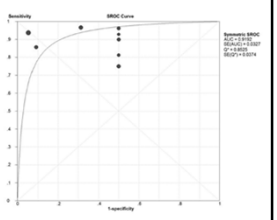
129 patients, obtained from eight eligible studies



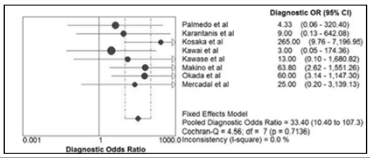
Study	Country	Year	Number of patients	Sex (M/F)	Mean age	Imaging	Immune system	Study design
Palmedo et al [17]	Germany	2005	7	4/3	66.4 ± 4.9	FDG-PET	Immunocompetent	retrospective
Karantanis et al [36]	America	2007	14	10/4	58.4 ± 12.2	FDG-PET/CT	Immunocompetent	retrospective
Kosaka et al [16]	Japan	2008	34	17/17	64.2	FDG-PET, FDG-PET/CT	Immunocompetent	retrospective
Kawai et al* [19, 32]	Japan	2010	17	9/8	65.1 ± 8.7	FDG-PET	Immunocompetent	retrospective
Kawase et al* [37]	Japan	2010	6	3/3	71.8 ± 8.9	FDG-PET	Immunocompetent	retrospective
Makino et al [18]	Japan	2011	21	13/8	67	FDG-PET/CT	Immunocompetent	retrospective
Okada et al [30]	Japan	2012	18	10/8	59.3 ± 14.9	FDG-PET	Immunocompetent	retrospective
Mercadal et al [28]	Spain	2015	12	6/6	61.4 ± 12.1	FDG-PET/CT	Immunocompetent	retrospective

PET scan in Primary CNS Lymphomas

- Pooled sensitivity in diagnosis :**0.88 (95% CI: 0.80–0.94)**
- Pooled specificity in the diagnosis:**0.86 (95% CI: 0.73–0.94).**
- Pooled positive likelihood ratio (PLR): **3.99** (95% CI: 2.31–6.90)
- Negative likelihood ratio (NLR): **0.11** (95% CI: 0.04–0.32)
- Pooled diagnostic odds ratio (DOR): **33.40** (95% CI: 10.40–107.3)
- (sROC) and the Q index : **0.9192** and the Q index :**0.8525**.



PET scan in Primary CNS Lymphomas



Take Home Message

- 18F-FDG PET and PET/CT are valuable radiological diagnostic tools in immunocompetent PCNSL patients.
- Complements MRI
- Helpful in narrowing down the differential diagnosis in pts suspected to have PCNSL
- Based on the High Diagnostic value of PET: Can be recommended in routine clinical practise

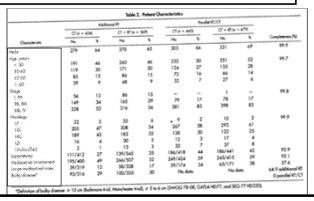
Role of consolidation therapy in hodgkin lymphomas

J Clin Oncol. 1998 Mar;16(3):810-29.

Meta-analysis of chemotherapy versus combined modality treatment trials in Hodgkin's disease. International Database on Hodgkin's Disease Overview Study Group.

Loeffler M[1], Brosteanu O, Hasenclever D, Sextro M, Assouline D, Bartolucci AA, Cassileth PA, Crowther D, Diehl V, Fisher RI, Hoppe RT, Jacobs P, Pater JL, Pavlovsky S, Thompson E, Wiernik P.

- **SCREENED 26 RANDOMIZED TRIALS**
- **TRIALS INCLUDED IN THE STUDY 14**
- **NO OF PATIENTS** 1740
- **QUESTION ASKED** : Role of consolidation RT in Hodgkin Lymphoma
- **End points questioned**
  - overall survival
  - disease control
  - Time to treatment related failure
  - time to leukemia related deaths

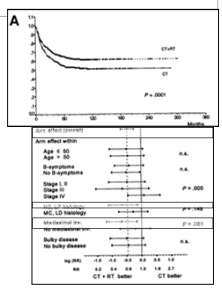


Role of consolidation therapy in Hodgkin lymphomas

Trials comparing addition of RT vs no RT

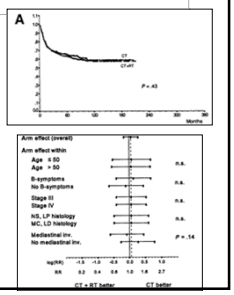
- N= 7 TRIALS
- N=918 PTS
- Conclusion

- 10 yr OS : 11% benefit in the additional RTarm(p=<0.001)
- multivariate analysis confirmed the results
-(HR reduced by 40%; relative risk:0.63 (95% CI:0.50-0.78)

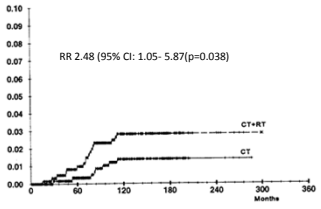


Role of consolidation therapy in hodgkin lymphomas

- **Trials comparing addition of RT vs addition of CT**
- N= 7 TRIALS
- N=837 PTS
- Conclusion
  - No improvement in overall survival by addition of CT after primary chemotherapy(p=0.43)
  - Multivariate analysis
    RR1.07(95% CI:0.85-1.34)



Role of consolidation therapy in hodgkin lymphomas: cumulative incidence of leukemia



RR 2.48 (95% CI: 1.05- 5.87(p=0.038)

Caveats

- Radiation doses were high :40-50Gy
- Large volumes were treated: EFRT was commonly employed

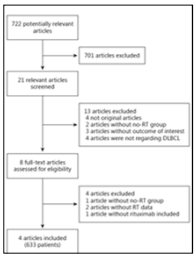
- **Contemporary era**
  - radiation doses have been deescalated to 20-30 Gy
  - Rt Volumes have been reduced to ISRT

Role of consolidation therapy in Non hodgkin lymphomas

The Role of Consolidative Radiotherapy after a Complete Response to Chemotherapy in the Treatment of Diffuse Large B-Cell Lymphoma in the Rituximab Era: Results from a Systematic Review with a Meta-Analysis

Chunhong Hu[a] Chao Deng[a] Wen Zou[a] Guangsen Zhang[b] Jingjing Wang[a]

Acta Hematologica, 2015

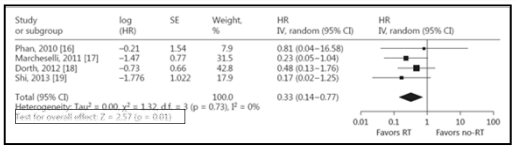


N= 4 studies
all retrospective studies
N= 633 pts
Question asked : Efficacy of consolidation RT after CR in DLBCL after R-CHOP therapy

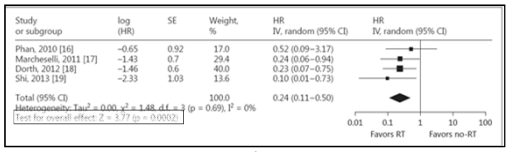
End points studied: Overall survival and progression free survival

Role of consolidation therapy in Non hodgkin lymphomas

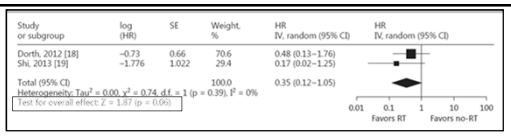
First author	Journal	Country of origin	Age, years (median)	Follow-up duration, months (median)	Stage	Patients, n (RT/no-RT)	CHOP regimen	Radiation dose, Gy	Definition of bulky disease	OS[a] HR (95% CI)	PFS[a] HR (95% CI)	EFS[a] HR (95% CI)
Phan [16]	J Clin Oncol	USA	20–92 (61)	4–85 (36)	I–IV	291 (84/207)	RCHOP* 6–8	30–39.6	>5 cm	0.813 (0.04–16.67)	0.52 (0.087–3.125)	
Marcheselli [17]	Leuk Lymphoma	Italy	>18 (69)	1–81 (30)	I–IV	153 (31/122)	RCHOP*6	34	>6 cm	0.23 (0.05–1.03)		0.24 (0.06–0.92)
Dorth [18]	Int J Radiat Oncol Biol Phys	USA	(62)	12–204 (56.4)	III–IV	79 (38/41)	RCHOP*6 (65%)	25	7 cm	0.48 (0.13–1.75)		0.23 (0.07–0.77)
Shi [19]	Int J Radiat Oncol Biol Phys	USA	20–81 (59.4)	1–151 (32.9)	III–IV	110 (14/96)	RCHOP*6	30.6	≥5 cm	0.169 (0.023–1.263)	0.098 (0.013–0.733)	



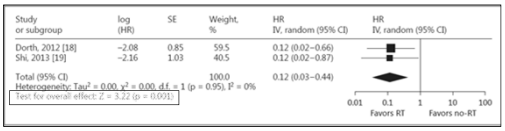
Forest plot of OS for all the patients



Forest plot of PFS/EFS for all the patients.



Forest plot of OS for patients with stage III–IV DLBCL.



Forest plot of LC for patients with stage III–IV DLBCL.

Take home Message

- RT has a clinically useful role in the rituximab era in DLBL pts treated with R-CHOP
- It should be considered as an option for DLBCL patients who achieve a CR to RCHOP, especially those with bulky disease.

Role of Immunochemotherapy in Lymphomas -----

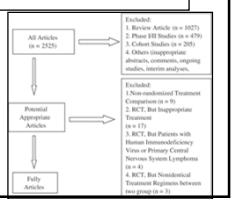
Rituximab in Lymphomas

A systematic review and meta-analysis of immunochemotherapy with rituximab for B-cell non-Hodgkin's lymphoma

Guanghui Gao, Xiaohua Liang, Jingwei Jiang, Xinli Zhou, Ruofan Huang,Zhaohui Chu & Qiong Zhan

Acta Oncologica,2010

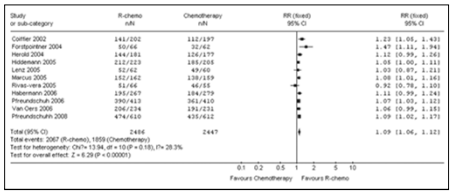
N= 12 studies
N= 4996 patients
Histology: diffuse large B cell Lymphomas & Follicular Lymphomas, mantle cell lymphomas.
Question asked: efficacy of rituximab with CHOP or CHOP like chemo
Endpoints: overall survival, overall response, disease control, and adverse events



Role of Immunochemotherapy in Lymphomas
Rituximab in Lymphomas

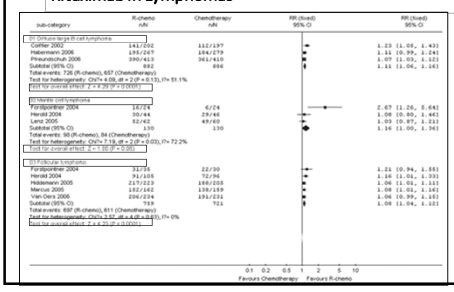
First author	Lymphoma subtype	Quality scores	Study arms	Total patients	Eligible patients	Previous therapy	Stage
Coiffier[16]	DLBCL	3	R-CHOP CHOP	399	399	No	III/IV
Forstpo intner[17]	FL/MCL	3	R-FCM FCM	147	128	Yes	III/IV
Habermann[18]	DLBCL	3	R-CHOP CHOP	632	546	No	III/IV
Herold[19]	FL/MCL	3	R-MCP MCP	358	358	No	III/IV
Hiddemann[20]	FL	3	R-CHOP CHOP	428	428	No	III/IV
Lenz[21]	MCL	3	R-CHOP CHOP	128	122	No	III/IV
Lin[14]	DLBCL	2	R-CHOP CHOP	63	63	No	II/III/IV
Marcus[23]	FL	3	R-CVP CVP	362	361	No	III/IV
Pfreundschuh[24]	DLBCL	3	R-CHOP like CHOP like	824	823	No	II/III/IV
Rivas-vera[25]	FL	3	R-CNOP CNOP	121	121	No	III/IV
Van Oers[26]	FL	3	R-CHOP CHOP	474	464	Yes	III/IV
Pfreundschuh[27]	NS	3	R-CHOP CHOP	1242	1222	No	II/III/IV

Role of Immunochemotherapy in Lymphomas -----
Rituximab in Lymphomas



overall survival among patients receiving rituximab with chemotherapy (R-chemo) or chemotherapy alone

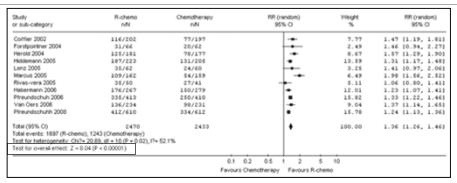
Role of Immunochemotherapy in Lymphomas -----
Rituximab in Lymphomas



Overall survival for the subgroups with **diffuse large B-cell lymphoma, mantle cell lymphoma or follicular lymphoma** receiving **rituximab** with chemotherapy (R-chemo) or **chemotherapy alone**

Role of Immunochemotherapy in Lymphomas

Rituximab in Lymphomas



Meta-analysis of disease control for all patients receiving rituximab with chemotherapy (R-chemo) or chemotherapy alone. **Disease control is shown as the relative risks (RR) for a disease event (progression, relapse, death)**.

Take Home Message.

- Addition of Rituximab improves overall and progression free survival in all lymphomas.
- It should be recommended in all CD 20 positive lymphomas

Role of radiation therapy in the contemporary management of NK T cell Lymphomas

Meta Analysis of Treatment for Stage IE~IIE Extranodal Natural Killer /T Cell Lymphomas in China

Hui Li*, Chun-Sen Wang, Xiao-Dong Wang

Asian Pacific Journal of Cancer Prevention, Vol 15, 2014

- No of trials included:11
- No of patients:871
- Type of studies: randomized controlled trials
- Subjects: Stage IE-IIE
- Heterogeneity across studies: I^2=0- 55%

Question :

1. sequencing of RT and chemotherapy
2. RT alone vs combined modality therapy
3. combined modality therapy VS chemotherapy

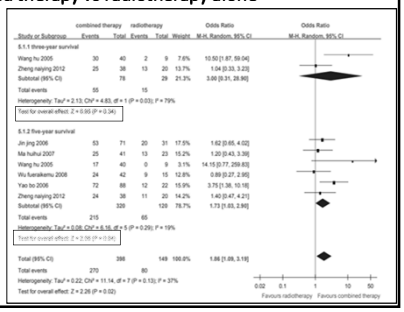
End points

1. Complete response rates
2. Overall survival

Overall survival- combined therapy vs radiotherapy alone

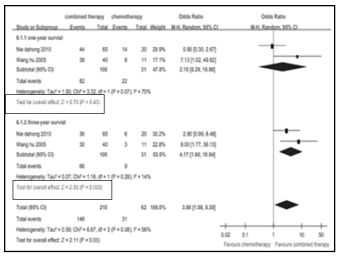
N= 6 RCT's
N=547 patients

- 2RCT'S compared 3 years survival and
- 6 RCT'S compared 5 year survival rates



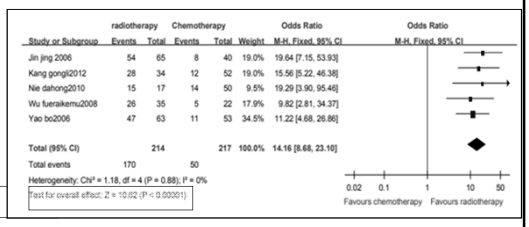
Overall survival- combined therapy vs chemotherapy alone

N= 2 RCT's
N =272 patients



Overall survival- timing of radiotherapy

N= 5 RCT'S
N=516 patients



The optimal timing of radiotherapy in the combined modality therapy for limited-stage extranodal NK/T cell lymphoma (ENKTL): a systematic review and meta-analysis

Annals of Hematology,2018

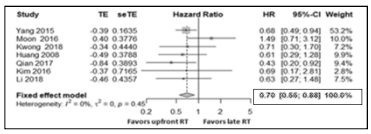
- No of trials included:7
- No of patients:1593
- Type of studies: retrospective cohort studies
- Subjects: Stage IE-IIE
- Heterogeinity across studies: I^2=0.
- Quality of trials: Jadad scale for randomized controlled trials and the Newcastle-Ottawa quality assessment scale (NOS) for non-randomized controlled studies

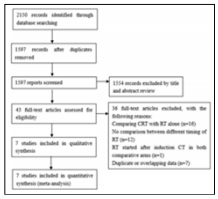
Question : sequencing of radiotherapy with chemotherapy

RT followed by chemotherapy
OR
Chemotherapy followed BY Radiotherapy

Overall survival- Timing of radiotherapy

- N=7 studies
- N=1489 pts
- I^2 = 0%

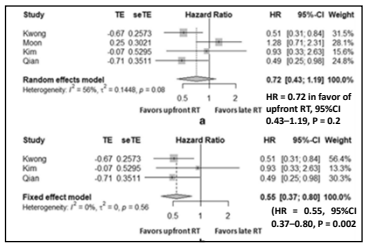




(HR = 0.70, 95%CI 0.55–0.88, P = 0.002)

Progression-free survival –timing of radiotherapy

- N=4 studies
- N= 454 pts

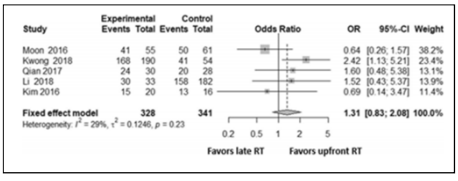


HR = 0.72 in favor of upfront RT, 95%CI 0.43–1.19, P = 0.2

(HR = 0.55, 95%CI 0.37–0.80, P = 0.002

Complete remission rate- Timing of radiotherapy

- N= 5 Studies
- N=669 pts



There was no significant difference in CR rate between upfront RT and late RT (OR = 1.31 in favor of upfront RT; 95% CI 0.83 to 2.08; P = 0.25)

Meta-Analysis –NK T cell Lymphomas
(Take Home message)

- Upfront RT confers survival advantage over late RT in the combined modality therapy.
- upfront RT may not have any advantage in complete response rates over late RT in the combined modality.
- Combination therapy has better clinical outcomes as compared to single modality (RT or chemotherapy alone)

Thank you!