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Systematic Review

Once daily (OD) versus twice-daily (BID) chemoradiation for limited stage small cell lung cancer (LS-SCLC): A meta-analysis of randomized clinical trials

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INTRODUCTION:

- Small-cell lung cancer : aggressive disease , represents 15% of all lung cancers.
- Only 30% of patients present with limited-stage disease (LS-SCLC) at diagnosis.
- Current standard of treatment for limited stage SCLC is Chemoradiation
- Several trials have examined the optimal radiotherapy schedule.

- Turrisi et al. (1999): Superior OS and DFS with hyperfractionated twice-daily radiotherapy (BID), compared to a conventionally fractionated once-daily (OD) schedule, both with a total dose of 45 Gy.

- CONVERT trial compared 45 Gy/30# BID with dose escalation of OD to 66 Gy, and dose escalation was not superior to the 45 Gy/30 BID schedule
- Despite the favorable outcomes with 45 Gy/30 BID, not universally adopted- a recent survey with 309 physicians in the US showed that 76% recognized that OD remains more common

- The main reason to limit the adoption of hyperfractionation involves the logistical complexity to execute the treatment ,concerns about toxicity, especially esophagitis.

OBJECTIVES

- To assess Once daily (OD) chemoradiation effectiveness for LS-SCLC compared with twice daily (BID) chemoradiation.

- The current meta-analysis aims to compare the data of LS-SCLC patients treated with OD (HYPO or CONV) versus BID.

MATERIALS & METHODS:

- Following the Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) guideline, eligible RCTs comparing OD and BID were identified on electronic databases from 1990 up to June 2021.

- Two reviewers individually performed the research using a standardized method, selected the articles initially by title and abstract, and then read the full article. A third reviewer settled discrepancies

- A meta-analysis was performed to compare OS, PFS and toxicity.

- A metaregression analysis was conducted to explore the influence of fractionation, BED, the proportion of patients treated with prophylactic cranial irradiation (PCI), elective nodal irradiation (ENI), and the start of radiotherapy (week 1 or week 4).

RESULTS

- Five RCTs with a total of 1941 patients : OD (965 patients) vs. BID (930 patients)
- Median follow-up: 45 months (range 24-60 months)

- RT techniques: one RCT used 3DRT (157patients),
  two IMRT/3DRT (1185 patients),
  one 2DRT (417patients), and
  one IMRT (182 patients).
- ENI was included in two RCTs.

- OD schedule: Conventional in 3RCTs (with median dose: 66 Gy range 45-70 Gy,)
  Hypofractionated in 2RCTs (with median dose:42-65 Gy in 15-25#
- BID schedule :45 Gy/30 fractions in all with BED of 51.75 Gy10.
- BED Gy10 in HYPO (range:53.7-81.25Gy10) and CONV studies (range 53.1-84Gy10)

Table 1
Characteristics of randomized clinical studies included in the meta-analysis.

Characteristics	Turrisi et al. [11]		Grønberg et al. [18]		CONVERT [12]		Bo Qiu et al. [19]		CALGB/RTOG [26]	
Design	Randomized phase III		Randomized phase II		Randomized phase III		Randomized phase II		Randomized phase III	
Follow-up (median)	60 months		59 months		45 months		24.3 months		33.6 months	
Sex % (male/female)	58/42%		49/51%		54/46%		82/18%		49/51%	
Total Sample (n)	417		157		638		182		638	
Clinical Stage Eligibility Criteria	Limited Stage (disease confined to one hemithorax, the ipsilateral supraclavicular fossa, or both)		Limited Stage (disease confined to one hemithorax and the mediastinum, contralateral hilus, and ipsilateral supraclavicular regions)		Limited Stage (Veterans Administration Lung Cancer Study Group definition; ie, patients whose disease can be encompassed within a radical radiation portal).		Limited Stage (Veterans Administration Lung Cancer Study Group definition; ie, acceptable radiotherapy target volume judged by the radiation oncologists).		Limited Stage (disease restricted to one hemithorax with regional lymph node metastases: ipsilateral hilar, ipsilateral supraclavicular, and ipsilateral and contralateral mediastinal lymph nodes).	
Staging Routine	CT or MRI of the chest, abdomen, and brain; bone scan; and bone marrow biopsy.		CT of the chest and abdomen, brain MRI, and bone scan.		Chest radiograph, CT scan of the thorax and upper abdomen, CT or MRI of the brain. PET/CT scans were allowed but not mandatory, with 57% of the patients in each arm using PET/CT for staging.		NR		CT scan of the thorax and upper abdomen, CT or MRI of the brain. Bone or PET/CT scans.	
Chemotherapy drugs	EP		EP		EP		EP		EP	
RT Timing	Week 1		Week 1		Week 4		Week 1		Week 1	
ENI (Yes/No)	No		Yes		No		No		Yes	
Data per arm	BID	CONV	BID	HYPO	BID	CONV	BID	HYPO	BID	HYPO
Sample (n)	211	206	73	84	274	273	94	88	313	325
Age (median)	61y	63y	63y	63y	62y	63y	58y	58y	64y	63y
RT total dose/fractions and BED Gy 10	45 Gy/30 fr 51.75 Gy10	45 Gy/25 fr 53.1 Gy10	45 Gy/30 fr 51.75 Gy10	42 Gy/15 fr 53.7 Gy10	45 Gy/30 fr 51.75 Gy10	66 Gy/33 fr 79.2 Gy10	45 Gy/30 fr 51.75 Gy10	65 Gy/25 fr 81.25 Gy10	45 Gy/30 fr 51.75 Gy10	70 Gy/35 fr 84 Gy10
RT technique	2DRT		3DRT		3DRT/IMRT 16%	3DRT/IMRT 17%	IMRT		3DRT/IMRT 60%	3DRT/IMRT 60%
% of patients treated with PCI	56*	49*	84	82	84	81	71.3	71.6	NR	NR
TNM Clinical Stage	NR		I 8 % II 12 % III 67 % X 12 %	I 8 % II 8 % III 76 % X 7%	I < 1 % II 12 % III 80 % X 7 %	I 1 % II 18 % III 76 % X 6 %	I - II 9 % III 91 %	I - II 5 % III 95 %	NR	

BED, biological effective dose; BID, twice daily radiotherapy; CONV, once daily conventional radiotherapy; (CT, computed tomography; ENI, elective nodal irradiation; EP, etoposide and cisplatin chemotherapy; HYPO, once daily hypofractionated radiotherapy; NR, data not reported; MRI, magnetic resonance imaging; PCI, prophylactic cranial irradiation; * Patients with complete response receiving PCI.

OS: OD vs BID

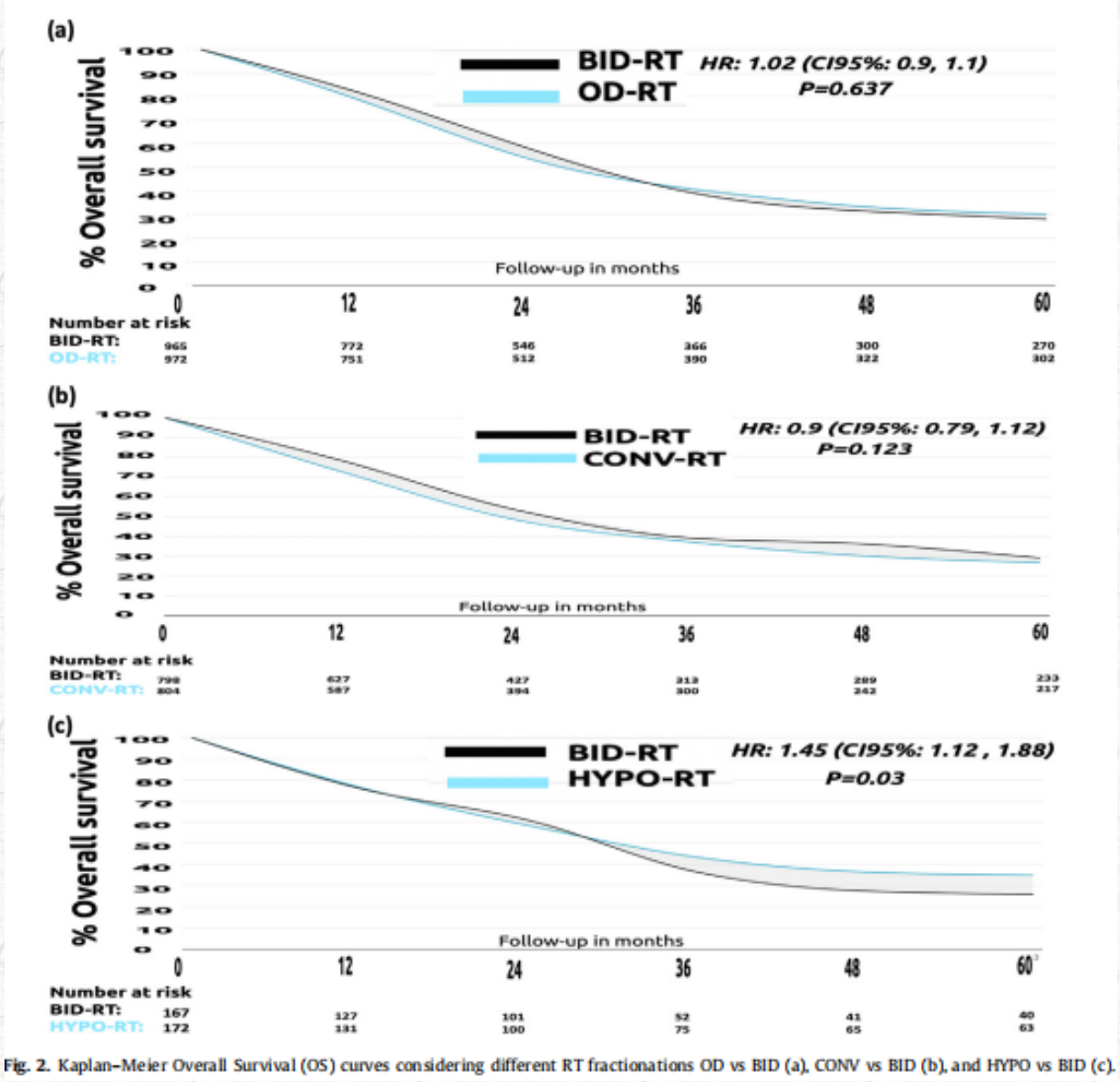

Fig. 2. Kaplan–Meier Overall Survival (OS) curves considering different RT fractionations OD vs BID (a), CONV vs BID (b), and HYPO vs BID (c).

OS	BID	OD	p
1 yr	80	77	0.637
3yr	38	40	
5yr	28	31	
RR for rate of OS at 3 yrs: 0.97 (CI95% 0.8–1.1, p =0.731			

OS		p
BID vs Conv	HR = 0.9 (CI95% 0.79–1.12)	0.123
BID vs HYPO	HR = 1.45 (CI95% 1.1–1.9)	0.03

HYPO improved OS

PFS: OD vs BID

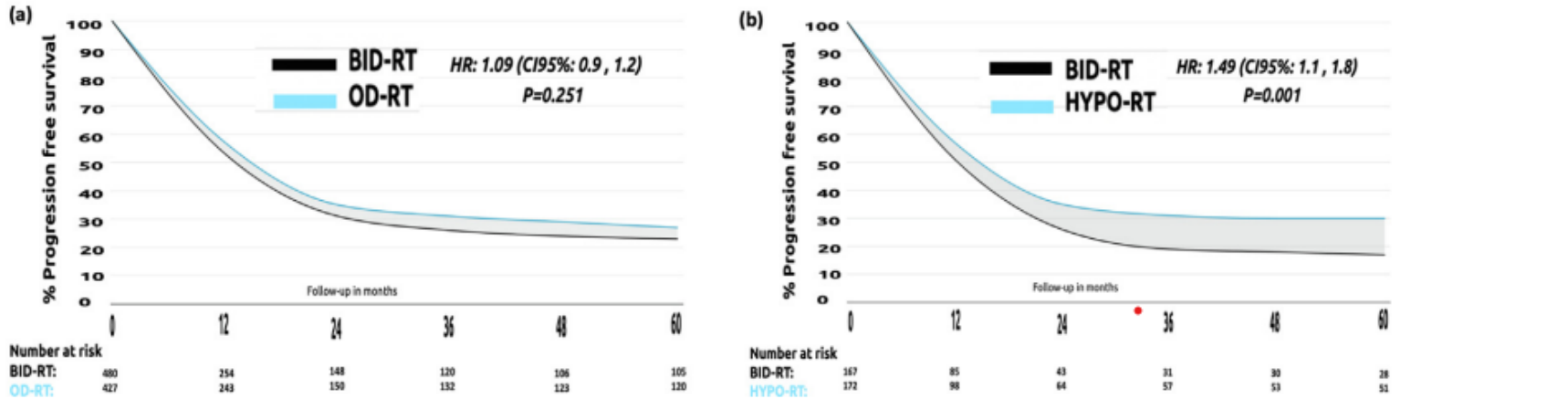

Fig. 3. Kaplan–Meier curves considering different RT fractionations OD vs BID (a) and HYPO vs BID (b) for Progression-free Survival (PFS).

PFS	BID	OD	p
1 yr	53	57	0.251
3yr	31	36	
5yr	25	32	
Rate of PFS at 3yrs : 0.9 (CI95% 0.7–1.1, p = 0.20)			

BID vs HYPO	HR = 1.49 (CI95% 1.1–1.8)	0.01

HYPO : improved PFS

	OD	BID	p
Three trials with 756 patients reported response rate			
Complete Response	33%	40%	0.97
Partial Response	57%	50%	0.94
Overall response	93%	89%	0.99
Rate of completed planned RT	96%	94%	0.66
% of 4 chemo cycles received	74%	74%	0.99
Four trials with 1303 patients reported the sites of failure.			
Local failure	40%	33%	0.88
Distant failure	36%	36%	0.99

Toxicity: OD vs BID

Toxicity Rate (Four studies)	OD	BID	p
Esophagitis:			
Grade 2	37%	41%	0.99
Grade 3	31	33	0.33
Pneumonitis:			
Grade 2	21	21	0.99
Grade 3	2	3	0.99
The rate of second-line chemo beyond progression	41	41	0.97

No difference in response rate, failure rates, completion of RT and toxicity

Table 2

Metaregression analysis of treatment details impact on overall and progression free survival.

Variable	β	P
3y- Overall survival		
% PCI (49–84% continuous)	−0.473	0.279
BED Gy10 (53.1–84 Gy10 continuous)	−0.005	0.294
CONV-RT	0.03	0.543
HYPO-RT	−0.3	0.038
ENI (yes vs. No)	−0.03	0.709
Timing RT -W1	0.06	0.829
Timing RT - W4	0.15	0.21
3y Progression free survival		
% PCI (49–84% continuous)	0.03	0.510
BED Gy10 (53.1–84 Gy10 continuous)	0.0007	0.215
CONV-RT	0.003	0.950
HYPO-RT	−0.46	0.020
ENI (yes vs. No)	−0.03	0.772
Timing RT- W1	−0.13	0.110
Timing RT-W4	0.16	0.140

PCI: prophilatic cranial irradiation, CONV-RT: conventional fractionation, HYPO-RT: hypofractionation, BED: biological effective dose, ENI: elective nodal irradiation, CHT: chemotherapy, W: week.

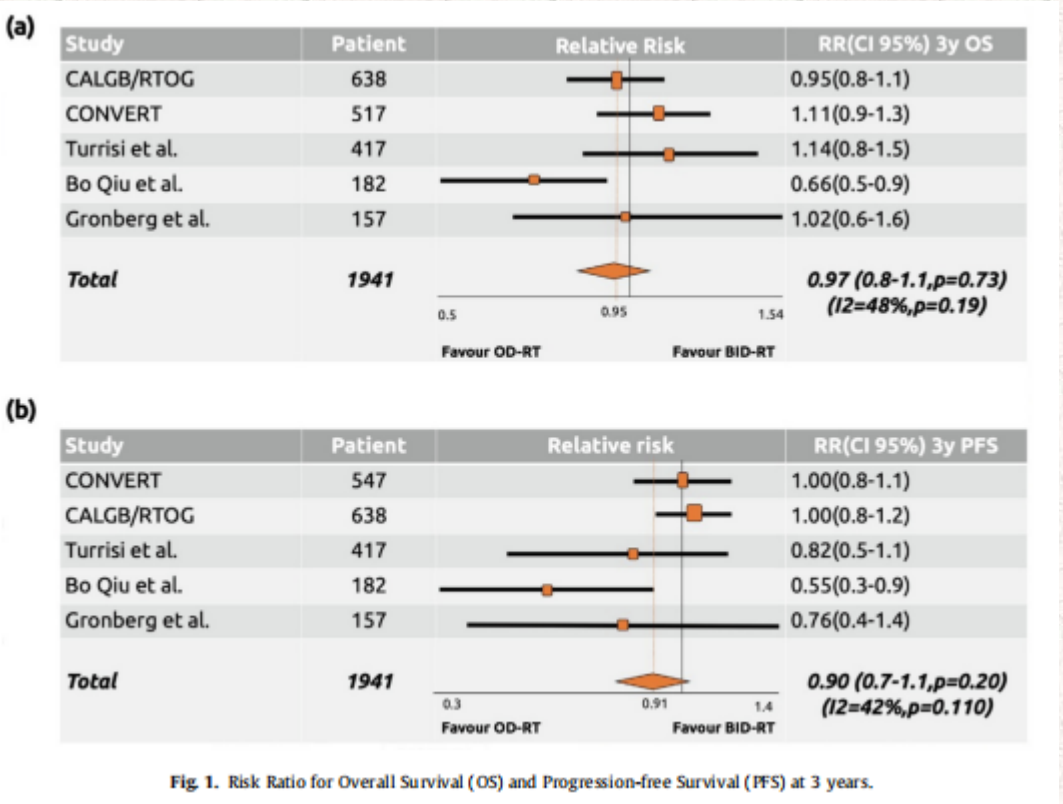

Fig. 1. Risk Ratio for Overall Survival (OS) and Progression-free Survival (PFS) at 3 years.

The start of radiotherapy (W1 or W4), BED, PCI & ENI had no significant effect on OS & PFS.

Conclusion:

- For LS-SCLC, OD conventional chemoradiation results in similar outcomes to BID chemoradiation.
- In contrast, hypofractionated radiotherapy was associated with a better OS and PFS than BID.
- Additional randomized phase III trials exploring hypofractionation with systemic therapy are warranted to validate our findings.

Thank You

- Currently, the ASTRO guidelines recommend 45 Gy/30 BID as a standard treatment and OD with CONV as an acceptable alternative.
- However, HYPO was omitted and not routinely recommended owing to insufficient evidence.

- The use of 3DRT and IMRT in more recent trials has reduced the rate of severe esophagitis by about 10% with BID (Turrisi et al. 27% grade 3 esophagitis and CALGB 19%)
- Even in the dose-escalation studies using HYPO or CONV, the grade 3 esophagitis was maintained at an acceptable level (<20%) [9].
- Although ENI was employed in two trials, it was not associated with increase in OS and PFS