La radiologia medica (2019) 124:136–144
https://doi.org/10.1007/s11547-018-0950-z

RADIOTHERAPY

Hypofractionated radiation therapy in the management of locally advanced NSCLC: a narrative review of the literature on behalf of the Italian Association of Radiation Oncology (AIRO)—Lung Working Group

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Received: 28 May 2018 / Accepted: 15 October 2018 / Published online: 27 October 2018

Abstract
A systematic literature was performed to assess the benefit in terms of effectiveness and feasibility of hypofractionated radiotherapy (HypoRT), with or without chemotherapy (CT), in the treatment of locally advanced non-small cell lung cancer (NSCLC). We have identified all studies, published from 2007 onwards, on patients with locally advanced NSCLC treated with HypoRT with radical intent, with a minimal dose per fraction of 2.4 Gy, with or without concurrent chemotherapy. Twenty-nine studies were identified, for a total of 2614 patients. Patients were divided in the concurrent chemo-radiation therapy group (CT-RT) and radiotherapy alone (RT). In RT group, the delivered dose ranged from 45 to 85.5 Gy, with a dose/fraction from 2.4 to 4 Gy. Actuarial 2-year PFS ranged from 13 to 57.8%, and 1, 2- and 3-year overall survival (OS) ranged from 51.3 to 95%, from 22 to 68.7%, and from 7 to 32%, respectively. Acute Grade ≥ 3 esophagitis occurred in 0–15%, while late esophageal toxicity was 0–16%. Acute pneumonitis occured in 0–44%, whereas late pneumonitis occured in 0–47%, most commonly grade $\leq$G3. In CT-RT group, the delivered dose ranged from 52.5 to 75 Gy, with a dose/fraction ranging from 2.4 to 3.5 Gy. Actuarial 2-year PFS ranged from 19 to 57.8%, and OS at 1, 2 and 3 years ranged from 28 to 95%, 38.6 to 68.7%, and 31 to 44%, respectively. Acute Grade 2 and 3 esophagitis occurred in 3–41.7%, while late esophageal toxicity occurred in 0–8.3%. Acute pneumonitis ranged from 0 to 23%, whereas late pneumonitis occured 0–47%. HypoRT seems to be safe in patients with locally advanced NSCLC. The encouraging survival results of several studies analyzed suggest that hypofractionated radiation schemes should be further investigated in the future.

Keywords Hypofractionated radiotherapy · Chemotherapy · NSCLC · Treatment · Toxicity

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide being responsible of one quarter of all deaths [1]. Non-small cell lung cancer (NSCLC) represents the majority of lung cancer diagnosis, and most of these are in locally advanced stage, half of which unresectable [2, 3]. Definitive concurrent chemo-radiation therapy (CRT) represents the cornerstone of curative intent treatment in unresectable patients [4]. The standard radiation scheme is 60–66 Gy delivered in 30–33 fractions [5].

Nevertheless, after standard radiation doses of CRT, the risk of local recurrence remains high and 5-year survival is poor. [6, 7]. Improving outcomes for these unfavorable patients still remains challenging. Radiation Therapy Oncology Group (RTOG) 0617 randomized phase 3 study failed to show a beneficial effect in survival when delivering higher dose of RT at 2 Gy per fraction [8]. In locally advanced NSCLC, a strong correlation between survival and overall treatment time was found [9, 10]. A strategy to increase the biological effective dose (BED) of RT could be obtained using hypofractionated regimens characterized by a reduction in the overall treatment time with dose per fraction higher than 2 Gy [11–13].

Considering the technological worldwide implementation in RT facilities and the issue of maintaining limited waiting list for the patients, hypofractionated was adopted in many centers and in several clinical settings, including lung cancer [14].

Aim of the current narrative review is to assess the benefit of hypofractionated RT, with or without concurrent chemotherapy (CT), in terms of effectiveness and feasibility in the treatment of locally advanced NSCLC.

Materials and methods

All studies included in the present review satisfied the following criteria: (1) patients with locally advanced NSCLC, (2) patients treated with hypofractionated RT with radical intent, (3) with a minimal dose per fraction of 2.4 Gy, (4) patients treated with hypofractionated RT with or without concomitant CT, (5) studies published from 2007 onwards, (6) English manuscripts. Studies were excluded if no detailed information (e.g., clinical outcomes, toxicity) were reported. Meta-analysis, review articles were excluded from the analysis.

A detailed literature search strategy was developed a priori. Key words and subject terms used in the search included: ("lung neoplasms"[MeSH Terms] OR ("lung"[All Fields] AND "neoplasms"[All Fields]) OR "lung neoplasms"[All Fields] OR ("lung"[All Fields] AND "cancer"[All Fields]) OR "lung cancer"[All Fields]) AND ("drug therapy"[Subheading] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "chemotherapy"[All Fields] OR "drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "chemotherapy"[All Fields]) AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms]) AND locally[All Fields] AND advanced[All Fields]) OR " Hypofractionated Radiotherapy" [All Fields] AND "lung neoplasm"[All Fields].

The search strategy was applied to Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to present. The grey literature was searched by applying a similar strategy to Google Scholar, PubMed and the Proquest Dissertation and Theses databases. Additional references were identified by a manual review of the reference lists of included articles.

Studies that met inclusion criteria were systematically analyzed by all the authors. Disagreement was resolved by consensus; if consensus could not be achieved, the study coordinator provided an assessment of eligibility.

For data extraction, all the papers were scrutinized for the following information: study design (retrospective, prospective); number of patients; number of patients comprise in study with concomitant CT; oncological treatment strategy (RT alone and/or sequential CRT, versus concurrent CRT); total dose; dose per fraction; definition of acute and late toxicity profile clinical outcomes.

Results

Twenty-nine studies [15–43] of hypofractionated RT in locally advanced NSCLC with or without concurrent CT that met the inclusion criteria were identified, for a total of 2614 patients. Among these studies, nine were retrospective, while 20 were prospective. Of these, eight were phase I trials, and ten were phase II trials.

Clinical outcomes in non-concurrent chemotherapy group

Seventeen studies [15–31], for a total of 1730 patients, without concurrent CT that met the inclusion criteria were identified. Three of them predicted a comparison arm with concurrent CT [15, 16, 26]. CT was administered in 15 studies, generally with neo-adjuvant intent (Table 1). In one study, no details regarding CT were reported [29]. The most common CT agents employed were cisplatin (70.5%), predominantly in doublet with, gemcitabine or vinorelbine.

Table 1 Studies of hypofractionated radiation therapy with non-concurrent chemotherapy in locally advanced non-small cell lung cancer

References	Study	*N* Pts	*N* patients comprise in study without concomitant CHT	CHT neo-adjuvant	CHT adjuvant	TD	Fx	D/Fx	EQD2 α/β 10 early toxicity	EQD2 α/β 3 late toxicity	RT
Uitterehoeve [15]	R	131	75	Gem 1250 mg/m^2 + CDDP 75 mg/m^2	NR	66	24	2.75	70.1 Gy	75.9 Gy	3DCRT
Belderbos [16]	Ran Ph II	158	78	Gem 1250 mg/2 + CDDP 75 mg/m^2	NR	66	24	2.75	70.1 Gy	75.9 Gy	3DCRT
Adkison [17]	Ph I D/E	46	46	Allowed data NR	33%	57–80.5	25	2.28–3.22	58.3–88.7 Gy	60.2–100.1 Gy	IMRT–
Kepka [18]	Ph I	173	173	CDDP + V (dose NR)	NR	56.7–60.9	21	2.7–2.9	60–65.5 Gy	64.6–71.9 Gy	3DCRT
Pemberton [19]	R	277	140	26% of Pts CDDP platinum-based doublet	NR	55	20	2.75	58.4 Gy	63.2 Gy	3DCRT
Amini [20]	R	300	119	37% of Pts platinum-based doublet	24%	45 Gy	15	3 Gy	48.8 Gy	54 Gy	IMRT
Cannon [21]	Pro Ph I	79	79	21%	41%	57–85.5	25	2.28–3.42	58.3–95.6 Gy	60.2–109.8 Gy	IMRT
Gomez [22]	Ph I D/E	25	25	No	NR	45–52.5–60	15	3–3.5–4	48.8–59.1–70 Gy	54–68.2–84 Gy	PROTON
Osti [23]	Pro Os	30	30	80% Platinum-based doublet	NR	60	20	3	65 Gy	72 Gy	3DCRT
Din [24]	R	609	609	27% Platinum-based doublet	NR	55 Gy	20	2.75 Gy	58.4 Gy	63.2 Gy	3DCRT
Zhu [25]	Ph II	68	34	Sequential CDDP 25 mg/m^2 + V 25 mg/m^2	Two cycles	65–68	25–26	3	70.4–73.6	78–81.6	3DCRT
Maguire [26]	Ran Ph II	130	60	Sequential CDDP 80 mg/m^2 + V 25 mg/m^2	NR	55 Gy	20	2.75 Gy	58.4 Gy	63.2 Gy	3DCRT IMRT
Westover [27]	Ph I D/E	55	55	No	NR	50–60	15	3.33–4	55.6–70 Gy	63.3–84 Gy	3DCRT
Agolli [28]	Pro	60	60	75% Platinum-based doublet	NR	60 Gy	20	3 Gy	65 Gy	72 Gy	3DCRT
De Dios [29]	Pro	83	83	NR	NR	66	24	2.75	70.1	75.9 Gy	3DCRT
He [30]	R	69	23	70.5% Sequential		60	20	3	65	72 Gy	TOMO
Franceschini [31]	R D/E	41	41	36.6% Platinum-based doublet	NR	50–56	20	2.5–2.8	52.8 59.7	55–64	VMAT

References	Primary end point	2-year PFS %	1-year OS %	2-year OS %	3-year OS %	ENI	AE%	AP%	LE%	LP%
Uitterehoeve [15]	Efficacy and Toxicity	30	53	28	19	Yes	NR	NR	5	18
Belderbos [16]	Survival	44.5 (1 y)	69	33.6	21.6	Yes	5	8	4	13
Adkison [17]	Maximum tolerated dose	20	64	46.8	NR	Not	15	NR	NR	13
Kepka [18]	Maximum tolerated dose	40	69	32	19	Yes	7	5	2	4
Pemberton [19]	Survival	20	65	45	7	Not	11	14	NR	NR
Amini [20]	Efficacy and toxicity	13	53	22	12	Not	10.1	11.8	NR	NR
Cannon [21]	Late toxicity	NR	NR	NR	29	Not	0	0	16	0
Gomez [22]	Safety	NR	NR	NR	NR	NR	0.2	NR	NR	20
Osti [23]	Response rate	38		36		Not	3	17	3	27
Din [24]	Survival	NR	NR	50	NR	Not	0	0	NR	20
Zhu [25]	Survival and toxicity	29.8	68	38.2	32	Not	6	3	0	29.4

Table 1 (continued)

References	Primary end point	2-year PFS %	1-year OS %	2-year OS %	3-year OS %	ENI	AE%	AP%	LE%	LP%
Maguire [26]	Safety	45	83	46	27	Not	8.5	5.2	NR	NR
Westover [27]	Maximum tolerated dose	NR	NR	25	NR	Not	1.1	NR	NR	NR
Agolli [28]	Survival	33.5	57	40	NR	Not	5	19	2	9
De Dios [29]	Survival	NR	NR	41.5	NR	Not	9.6	0	NR	1.2
He [30]	Toxicity response rate; survival	57.8	95	68.7	NR	Not	0	44.1	2.9	47
Franceschini [31]	Maximum tolerated dose	50.1	51.3	NR	NR	Not	0	2.5	NR	13.2

All value are expressed in Gy

N number, *Pts* patients, *CHT* chemotherapy, *CBDCA* carboplatin; *CDDP* cisplatin, *Ox* oxaliplatin, *P* paclitaxel, *V* vinorelbine, *LD* liposomal doxorubicin, *C* cetuximab, *D* docetaxel, *Gem* gemcitabine, *R* retrospective, *Ran* randomised, *Ph* phase, *D/E* dose escalation, *Pro* prospective, *Os* observational, *ENI* elective nodal irradiation, *TOMO* tomotherapy, *VMAT* volumetric modulated arc therapy, *NR* not reported, *D/Fx* dose/fractions, *Fx* fractions, *TD* total dose, *SIB* simultaneous integrated boost, *AE* acute esophagitis, *AP* acute pneumonitis, *LE* late esophagitis, *LP* late pneumonitis, *PFS* progression free survival, *OS* overall survival

*Cumulative (both concurrent and non-concurrent)

The most common RT technique was 3D-conformal radiation therapy (3D-CRT) (64.7%), whereas intensity-modulated RT (IMRT) was employed in only three studies (23.5%); in one study patients were treated with protons. The delivered dose ranged from 45 to 85.5 Gy, with a dose per fraction ranging from 2.4 to 4 Gy. The equivalent doses at 2-Gy fractions (EQD2) calculated considering an alpha/beta ratio of 10 Gy and 3 Gy, according to Fowler et al. [44], ranged from 48.8 to 95.6 Gy, and from 54 to 109.8 Gy, respectively. Actuarial 2-year progression free survival (PFS), which was reported in 12 studies, ranged from 13 to 57.8%, and 1-, 2- and 3-year overall survival (OS) ranged from 51.3 to 95%, from 22 to 68.7%, and from 7 to 32%, respectively.

In only three studies (17.6%), elective lymph nodes were irradiated. Acute esophagitis occured in 0–15% of patients, while late esophageal toxicity occurred in 0–16%. Regarding pulmonary toxicity, acute pneumonitis occured in 0–44%, whereas late pneumonitis occured in 0–47%, most commonly ≤ Grade 3.

Clinical outcomes in concurrent chemotherapy group

Sixteen studies of hypofractionated RT [15, 16, 26, 30, 31] delivered concomitantly with CT were identified, for a total of 884 treated patients (Table 2). The most common CT agents employed were cisplatin 50%, carboplatin 25% and vinorelbine 37.5%; other agents employed less frequently were, liposomal doxorubicin, docetaxel, gemcitabine, cetuximab and ALK-inhibitors. The most common RT technique was 3D-CRT (68.75%), whereas IMRT was employed in 31.25% of the studies. The delivered dose ranged from 52.5 to 75 Gy, with a dose per fraction ranging from 2.4 to 3.5 Gy. The equivalent doses at 2-Gy fractions (EQD2) calculated considering an alpha/beta ratio of 10 Gy and 3 Gy, ranged from 58.4 to 81.2 Gy, and from 63.2 to 90 Gy, respectively. Two studies included the elective nodal irradiation. Actuarial 2-year PFS, which was reported in seven articles, ranged from 19 to 57.8%. OS at 1, 2 and 3 years ranged from 28 to 95%, from 38.6 to 68.7%, and from 31 to 44%, respectively. Two studies did not report any survival results [37, 39]. Acute esophagitis occurred in 0–41.7%, while late esophageal toxicity occurred in 0–8.3%.

The overall incidence of acute pneumonitis ranged from 0 to 23%, whereas late pneumonitis occured in 0–47%, similarly to the non-concomitant CT group.

Discussion

Most of NSCLC patients with locally advanced disease have poor prognosis [45]. A key element for lung cancer treatment is the achievement of local control. In fact, the treatment

failure of the primary NSCLC has a detrimental impact in terms of PFS, metastasis-free survival and OS [46].

To date, the standard of care is represented by RT using conventional fractionation, with concurrent or sequential platinum-based CT [47]. Several studies hypothesized the potential usefulness of a dose-escalated approach to improve the oncological outcomes. In the RTOG-0617 trial, the standard dose RT was compared to high-dose conformal RT with concurrent and consolidation platinum-based CT. At a median follow-up of 22.9 months, 74 Gy given in 2 Gy per fractions with concurrent CT showed to be not better than 60 Gy for patients affected by stage III NSCLC. The authors concluded that high-dose conformal RT might be potentially harmful [8].

On the other hand, it has been demonstrated that a long duration of RT in NSCLC seems to be detrimental in terms of tumor control and survival, due to accelerated repopulation of tumor cells, with a loss of local control of 1.66% per day of lengthening over 6 weeks [9, 10]. Thus, alternative strategies to increase the effective dose by reducing the overall treatment time could be achieved with hypofractionated regimens. In the present review, we analyzed the available literature data concerning the role of hypofractionated RT in the management of locally advanced NSCLC distinguishing two main groups: (1) non-concurrent CT patients and (2) concomitant CT patients.

Looking at the first patients' category, 1-, 2- and 3-year OS ranged between 51 and 95%, 22 and 68%, and 7 and 32%, respectively; 2-year PFS varied from 13 to 58%. These results seem promising if compared to the outcomes of conventional fractionation by historical cohorts. Specifically, in the meta-analysis by Auperin et al. [5], exploring the impact of concomitant versus sequential CT in combination with conventional RT in locally advanced NSCLC, a 3-year OS rate of 18.1% was registered in the non-concurrent arm. In the same meta-analysis [5], there was a significant benefit of CRT as compared with sequential CRT with an absolute survival benefit of 5.7% at 3 years, and an increased survival to 23.8% in the concomitant arm. The PFS analysis showed an absolute benefit of 2.9% at 3 years, increasing the PFS from 13.1 to 16.0% with concomitant CRT. Acute esophageal toxicity (Grade 3–4) was higher in concomitant CRT comparing to the sequential strategy (18% versus 4%). There was no significant difference regarding pulmonary toxicity.

Analyzing the clinical outcomes of hypofractionated RT administered concomitantly with CT, 3-year OS ranged from 31 to 44%, whereas 2-year PFS varied between 19 and 58%. Speculatively, potential higher rates of oncological outcomes compared to conventional CRT could be expected using a hypofractionation regimen in non-concurrent than in concomitant hypofractionated RT for NSCLC. This phenomenon could be related to a potential higher sensitivity of NSCLC cells to higher radiation dose per fraction. Obviously, these last assumptions need to be confirmed and a direct comparison between different fractionation schedules requires well-designed randomized studies before to draw any kind of definitive conclusion.

Radiobiological modelings suggest that shortened treatment schedules might increase the risk of late toxicity. These last concerns are heightened with hypofractionated regimens when larger doses per fraction are used, particularly in the context of concurrent CRT [48]. In the available data here reported, acute esophagitis occurred in 0–15% in the non-concurrent group comparing to 0–41.7% in the concomitant arm. Regarding pulmonary toxicity, acute pneumonitis occurred in 0–44%, whereas late pneumonitis was recorded until to 47% of cases, most commonly ≤ Grade 3. A similar pulmonary toxicity profile was noted in the non-concomitant hypofractionated group.

Conclusions

In summary, in the current review of the literature an extreme heterogeneity was noted in terms of the RT-treatment schedules, in terms of the adopted techniques as well as the administered drugs in combination with irradiation. However, several data appear to be more robust: an overall low toxicity profile was documented both in the concomitant and non-concomitant chemotherapy groups, when using RT schedule of 2.7–4.0 Gy/fraction.

Our review suggests a potential positive relationship between the overall treatment time with the PFS and the OS in NSCLC. However, the efficacy of hypofractionated RT schemas has to be proved yet in prospective trials.. These conditions associated with the rapid evolution of technologies and the hypothesis of association with new target agents and immunotherapy could constitute, in the future, a potential new frontier in the treatment of locally advanced NSCLC.

Author contribution statements In our review are listed 13 authors. The authors' contribution is listed: GP and MT wrote the article independently reviewed the citations and were responsible for analyzing and interpreting the data. RM wrote the manuscript in consultation with GP and MT. PC, GT, AF, DF, FN, AB, MP NJL, FA, VS contributed to design, bibliographic search and implementation of the review. FN drafted the article. All authors contributed to the analysis of the results, discussed the results and commented the manuscript. GP and MT revised its content to its final version. All authors approved the final manuscript.

Compliance with ethical Standards

Conflict of interest All authors declare no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Table 2 Studies of hypofractionated radiation therapy concomitant chemotherapy in locally advanced non-small cell lung cancer

References	Study	*N* Pts	*N* patients comprise in study with concomitant CHT	CHT	TD	Fx	D/Fx	EQD2 α/β 10 early toxicity	EQD2 α/β 3 late toxicity	RT
Uitterehoeve [15]	R	131	56	CDDP 6 mg/m^2	66	24	2.75	70.1 Gy	75.9 Gy	3DCRT
Koukourakis [32]	R	31	31	LD 25 mg/m^2 + Ox 50 mg/m^2	52.5	15	3.5	59.1 Gy	68.2 Gy	3DCRT
Belderbos [16]	Ran Ph II	158	80	CDDP 6 mg/m^2	66	24	2.75	70.1 Gy	75.9 Gy	3DCRT
Tsoutsou [33]	R	14	14	V 20 to 30 mg/m^2 + LD 20 mg/m^2	52.5	15	3.5	59.1 Gy	68.2 Gy	3DCRT
Matsuura [34]	R	10	10	CBDCA AUC 1.5–2 + P 30–35 mg/m^2	65	26	2.5	67.7	71 Gy	3DCRT
Casas [35]	Pro Ph II	32	32	P 45 mg/m^2	61.64	23	2.68	65.1	70.02	3DCRT
Chen [36]	R	171	171	CDDP 6 mg/m^2	66	24	2.75	70.1 Gy	75.9 Gy	IMRT
Lin [37]	Ph I	13	13	CBDCA AUC 5 + V 25 mg/m^2	66–69–72	22–24	3	71.5–78	79.2–86.4	3DCRT
Bearz [38]	Ph I D/E	37	33	D 10 mg/m^2	60	25	2.4	62 Gy	64.8 Gy	TOMO
Liu [39]	Prospective Ph I	26	26	CBDCA AUC 5 + V 25 mg/m^2	60–75	20–25	3	65–81.2 Gy	72–90 Gy	3DCRT
Van de Heuel [40]	Ran Ph II	102	102	CDDP 6 mg/m^2 +/− C 400 mg/m^2	66	24	2.75	70.1 Gy	75.9 Gy	3DCRT IMRT
Maguire [26]	Ran Ph II	130	70	CDDP 20 mg/m^2–V 15 mg/m^2	55	20	2.75	58.4 Gy	63.2 Gy	3DCRT IMRT
Ren [41]	Pro Ph II	12	12	CBDCA AUC 5 + V 25 mg/m^2	69	23	3	74.7	82.8	IMRT
Waltraven [42]	Ran Ph II	102	102	CDDP 6 mg/m^2 +/− C 400 mg/m^2	66	24	2.75	70.1 Gy	75.9 Gy	IMRT
Landau [43]	Ran D/E Ph I/II	84	81	CDDP 75 mg/m^2–V 15 mg/m^2	63–73	30	2.1 2.43	63.5–75.6	64.2–79.2	3DCRT IMRT
He [30]	R	69	11	Platinum based	60	20	3	65	72	TOMO

References	Primary end point	2-year PFS %	1-year OS %	2-year OS %	3-year OS %	ENI	AE%	AP%	LE%	LP%
Uitterehoeve [15]	Efficacy and toxicity	NR	57	NR	31	Yes	NR	NR	5*	18*
Koukourakis [32]	Efficacy and toxicity	58	63	45	NR	Not	22.5	0	NR	0.9
Belderbos [16]	Survival	NR	55.9	38.6	29	Yes	17	9	5	18
Tsoutsou [33]	Response and survival	19 ± 10	28 ± 12	NR	NR	Not	0	0	NR	NR
Matsuura [34]	Efficacy and toxicity	NR	90	58.3	44	Not	0	0	0	0
Casas [35]	Efficacy and safety	NR	59	NR	34	Not	6	3	0	0
Chen [36]	Toxicity	NR	69	NR	NR	Not	18.7	NR	7	NR
Lin [37]	Survival and toxicity	NR	NR	NR	NR	Not	15	8	NR	NR
Bearz [38]	Lung toxicity	45	NR	45	NR	Not	3	0	0	0

Table 2 (continued)

References	Primary end point	2-year PFS %	1-year OS %	2-year OS %	3-year OS %	ENI	AE%	AP%	LE%	LP%
Liu [39]	Feasibility	NR	NR	NR	NR	Not	15.4	23.1	8	15.4
Van de Heuel [40]	Local control rate	54	80	NR	NR	Not	23	6	8	4
Maguire [26]	Safety	47	73	50	38	Not	8.8	3.1	NR	NR
Ren [41]	Toxicity	NR	78.6	NR	NR	Not	41.7	28.6	8.3	25
Waltraven [42]	Survival	NR	74.5	59.4	NR	Not	NR	NR	NR	NR
Landau [43]	Toxicity and survival	48.5	87.8	68.0	NR	Not	6.1	3.7	NR	NR
He [30]	Toxicity overall response rate; survival	57.8	95	68.7	NR	Not	0	45	2.9	47

All value are expressed in Gy

N number, *Pts* patients; *CHT* chemotherapy; *CBDCA* carboplatin, *CDDP* cisplatin *Ox* oxaliplatin, *P* paclitaxel, *V* vinorelbine, *LD* liposomal doxorubicin, *C* cetuximab, *D* docetaxel, *Gem* gemcitabine, *R* retrospective, *Ran* randomised, *Ph* phase, *D/E* dose escalation, *Pro* prospective, *Os*= observational, *ENI*= elective nodal irradiation, *TOMO*= tomotherapy, *VMAT*= volumetric modulated arc therapy, *NR*= not reported, *D/Fx*= dose /fracti, *Fx* fractions, *TD* total dose, *SIB* simultaneous integrated boost, *AE* acute esophagitis, *AP* acute pneumonitis, *LE* late esophagitis, *LP* late pneumonitis, *PFS* progression free survival, *OS* overall survival

*Cumulative (both concurrent and non-concurrent)

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