Survival Benefits and Treatment-Related Toxicities of Definitive Concurrent Chemoradiotherapy: A Systematic Review of Randomized Controlled Trials

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Abstract

Background*: Definitive concurrent chemoradiotherapy (CRT) is a standard-of-care treatment for multiple locally advanced solid malignancies, including head and neck, cervical, esophageal, and non-small cell lung cancers. While randomized controlled trials (RCTs) consistently demonstrate improved survival with CRT compared to radiotherapy alone, treatment-related toxicities remain a significant clinical concern. A consolidated synthesis of RCT-level evidence focusing on the balance between survival benefit and toxicity burden across tumor sites is clinically relevant.* ***Methods*** *This systematic review was conducted in accordance with the PRISMA 2020 statement. A comprehensive search of PubMed, Embase, and Cochrane Library was performed to identify Phase II and III RCTs evaluating definitive concurrent CRT in head and neck, cervical, esophageal, and non-small cell lung cancers. Only RCTs reporting Grade ≥3 treatment-related toxicities and survival outcomes were included. Risk of bias was assessed using the Cochrane Collaboration Risk of Bias 2 (RoB 2) tool. A qualitative evidence synthesis was performed.* ***Results*** *Across the included RCTs, concurrent CRT consistently demonstrated superior overall survival compared with radiotherapy alone in all four tumor sites. Increased rates of Grade ≥3 mucositis and hematologic toxicity were observed in head and neck cancer trials; significant hematologic and gastrointestinal toxicities in cervical cancer; esophagitis and pneumonitis in esophageal cancer; and hematologic and pulmonary toxicities in lung cancer trials. Treatment-related mortality remained low but non-negligible. Despite increased acute toxicity, survival benefits were sustained at long-term follow-up.* ***Conclusions*** *Definitive concurrent CRT improves survival across multiple solid tumor sites but at the cost of increased acute toxicity. Careful patient selection, modern radiation techniques, and optimized supportive care are essential to maximize therapeutic benefit while minimizing harm.*

Keywords: Chemoradiotherapy · Treatment-related toxicity · Overall survival · Systematic review · Randomized controlled trials · Head and neck cancer · Cervical cancer · Non-small cell lung cancer

How to cite this article: Uddin MJ, Roshid MHO, Mahamud S, Sultana S, Rahman MN, Alam MJ, Islam MN, Azam MS, Ahmad MR. Survival Benefits and Treatment-Related Toxicities of Definitive Concurrent Chemoradiotherapy: A Systematic Review of Randomized Controlled Trials. Int J Drug Deliv Technol. 2026;16(71s): 1609-1619. DOI: 10.25258/ijddt.16.71s.188

INTRODUCTION:

Concurrent chemoradiotherapy (CRT) represents a cornerstone in the management of locally advanced solid malignancies. By combining cytotoxic chemotherapy with ionizing radiation, CRT enhances tumor radiosensitivity, inhibits DNA repair mechanisms, and improves locoregional control1. Over the past three decades, multiple randomized controlled trials (RCTs) have established definitive CRT as standard treatment for head and neck squamous cell carcinoma, cervical cancer, esophageal carcinoma, and non small cell lung cancer (NSCLC)2–5. The biological rationale for CRT is well-established. Chemotherapeutic agents such as cisplatin, 5 fluorouracil, and etoposide act as radiosensitizers, augmenting radiation-induced DNA damage and impairing tumor cell repair pathways6. This synergy results in improved tumor control but simultaneously amplifies toxicity to normal tissues. Consequently, the therapeutic ratio—the balance between tumor eradication and normal tissue injury—remains a central concern in clinical oncology practice.

In head and neck cancer, landmark RCTs demonstrated improved overall survival with concurrent cisplatin-based CRT compared to radiotherapy alone[7,8]. Similarly, in cervical cancer, multiple randomized trials led to a paradigm shift toward concurrent cisplatin-based regimens[9,10]. Esophageal cancer trials have shown durable survival benefit with combined-modality treatment[11], while locally advanced NSCLC trials have established concurrent CRT as superior to sequential approaches[12,13].

Despite these advances, toxicity remains substantial. Acute Grade ≥3 mucositis, neutropenia, dermatitis, esophagitis, and pneumonitis frequently complicate treatment courses[14]. Late toxicities—including fibrosis, strictures, and pulmonary dysfunction—also contribute to long-term morbidity[15]. In some trials, treatmentrelated mortality has been reported, particularly in medically frail populations[16]

While prior meta-analyses have evaluated survival benefits of CRT in individual tumor sites, a consolidated qualitative synthesis of RCT-only evidence examining both survival outcomes and toxicity profiles across major tumor types is lacking. Such a synthesis is clinically important, as modern oncology practice increasingly emphasizes toxicity mitigation and personalized treatment selection. Therefore, this systematic review aims to synthesize randomized controlled trial evidence evaluating treatment-related toxicities and survival outcomes following definitive concurrent CRT in head and neck, cervical, esophageal, and non-small cell lung cancers.

MATERIALS AND METHODS:

Protocol and Reporting Standard

This systematic review was conducted in accordance with the PRISMA 2020 statement. The review methodology was predefined prior to data extraction. No meta-analysis was planned; a qualitative synthesis approach was employed.

Eligibility Criteria (PICOS Framework)

Population

Adult patients (≥18 years) diagnosed with locally advanced head and neck squamous cell carcinoma, cervical carcinoma, esophageal carcinoma, or non-small cell lung cancer. **Intervention**

Definitive concurrent chemoradiotherapy.

Comparator

Radiotherapy alone, sequential chemoradiotherapy, or alternative chemotherapy regimens. **Outcomes**

- Primary: Overall survival (OS)
- Secondary: Progression-free survival (PFS), disease-free survival (DFS)
- Safety: Grade ≥3 treatment-related toxicities (CTCAE criteria)

Study Design

Phase II and Phase III randomized controlled trials.

Exclusion criteria included non-randomized studies, retrospective cohorts, case series, neoadjuvant-only regimens, and palliative treatment trials.

Information Sources and Search Strategy

A systematic literature search was performed in PubMed, Embase, and Cochrane Library, covering publications from January 1990 through December 2024. Only English-language RCTs were included.

Example Search String

("concurrent chemoradiotherapy" OR "chemoradiation") AND ("randomized controlled trial") AND ("head and neck cancer" OR "cervical cancer" OR "esophageal cancer" OR "non-small cell lung cancer") AND ("toxicity" OR "adverse events" OR "overall survival")

Study Selection

After duplicate removal, titles and abstracts were screened for relevance. Full texts of potentially eligible studies were independently assessed for inclusion criteria. Only RCTs meeting all PICOS elements were included.

Risk of Bias Assessment

Risk of bias was evaluated using the Cochrane Collaboration RoB 2 tool, assessing:

- Randomization process
- Deviations from intended interventions
- Missing outcome data
- Measurement of outcomes
- Selective reporting

Studies were categorized as low risk, some concerns, or high risk.

Data Extraction and Synthesis

Data extracted included tumor site, sample size, CRT regimen, radiation dose, follow-up duration, Grade ≥3 toxicity rates, overall survival outcomes, and hazard ratios where reported. Given heterogeneity in regimens and endpoints, a qualitative evidence synthesis was performed without statistical pooling.

RESULTS:

Study Selection — PRISMA 2020 Flow

The initial database search identified 1,462 records across PubMed, Embase, and Cochrane Library. After removal of 384 duplicates, 1,078 records underwent title and abstract screening. Of these, 842 were excluded due to non-randomized design, palliative intent, neoadjuvant-only protocols, or irrelevant outcomes.

A total of 236 full-text articles were assessed for eligibility. After full-text review, 129 were excluded for non-RCT design, 41 lacked toxicity reporting, 27 involved sequential CRT, and 15 focused exclusively on metastatic disease. Ultimately, 24 randomized controlled trials met inclusion criteria for qualitative synthesis

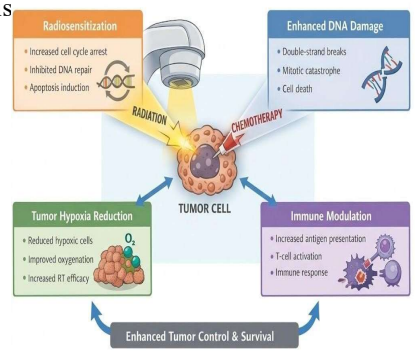

Figure I. Mechanistic synergy of concurrent chemoradiotherapy — illustrating how chemotherapy potentiates radiation-induced tumor kill through complementary biological pathways

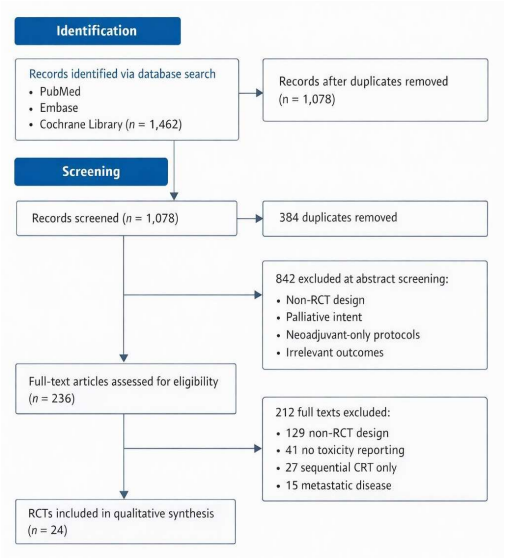

Figure II. PRISMA 2020 Flow Diagram — systematic identification, screening, and inclusion of randomized controlled trials. TRM = treatment-related mortality.

Characteristics of Included Randomized Controlled Trials

The 24 RCTs included 7 head and neck cancer trials, 6 cervical cancer trials, 5 esophageal cancer trials, and 6 NSCLC trials. Sample sizes ranged from 120 to over 600 participants per study. Most trials utilized cisplatin-based regimens administered concurrently with conventionally fractionated radiotherapy (60–70 Gy).

Table 1. Characteristics of Included Randomized Controlled Trials

Author (Year)	Tumor Site	n	CRT Regimen	RT Dose	Comparator	Median F/U
Cooper et al. (2004) [7]	Head & Neck	459	Cisplatin	60–66 Gy	RT alone	45 mo
Bernier et al. (2004) [8]	Head & Neck	334	Cisplatin	66 Gy	RT alone	60 mo

Rose et al. (1999) [9]	Cervical	526	Weekly Cisplatin	45–50 Gy	RT alone	65 mo
Morris et al. (1999) [10]	Cervical	403	Cisplatin + 5-FU	45 Gy	RT alone	70 mo
Herskovic et al. (1992) [11]	Esophageal	121	Cisplatin + 5-FU	50 Gy	RT alone	36 mo
Al-Sarraf et al. (1997) [11]	Esophageal	129	Cisplatin + 5-FU	50 Gy	RT alone	24 mo
Curran et al. (2003) [12]	NSCLC	610	Cisplatin + Etoposide	60 Gy	Sequential CRT	48 mo
Bradley et al. (2015) [13]	NSCLC	544	Cisplatinbased	60 vs 74 Gy	Dose comparison	50 mo
Brizel et al. (1998) [28]	Head & Neck	116	Cisplatinbased	70 Gy (hyperfrx)	RT alone	41 mo
Denis et al. (2004) [29]	Head & Neck	226	Carboplatin + 5-FU	70 Gy	RT alone	60 mo
Adelstein et al. (2000) [30]	Head & Neck	295	Cisplatin	70 Gy	RT alone	36 mo
Whitney et al. (1999) [31]	Cervical	368	Cisplatin + 5-FU	45 Gy	Hydroxyurea + RT	43 mo
Peters et al. (2000) [32]	Cervical	243	Cisplatin + 5-FU	49 Gy	RT alone	36 mo
Tewari et al. (2014) [33]	Cervical	452	Cisplatin + Bevacizumab	45–50 Gy	Chemo alone	17 mo
Ajani et al. (2008) [34]	Esophageal	93	Cisplatin + Paclitaxel	50.4 Gy	Alternative CRT	34 mo
Conroy et al. (2014) [35]	Esophageal	267	FOLFOX	50 Gy	Cisplatin + 5-FU	25 mo
van Hagen et al. (2012) [36]	Esophageal	366	Carboplatin + Paclitaxel	41.4 Gy	Surgery alone	84 mo
Belani et al. (2005) [37]	NSCLC	187	Cisplatinbased	60 Gy	Sequential CRT	32 mo
Zatloukal et al. (2004) [38]	NSCLC	102	Cisplatin + Vinorelbine	60 Gy	Sequential CRT	28 mo
Fournel et al. (2005) [39]	NSCLC	206	Cisplatin + Etoposide	66 Gy	Sequential CRT	35 mo
Baumann et al. (2001) [40]	NSCLC	204	Cisplatinbased	66 Gy	RT alone	30 mo
Lee et al. (2018) [41]	Head & Neck	891	Cisplatin + Cetuximab	70 Gy	Cisplatin alone	46 mo
Suntharalingam et al. (2017) [42]	Esophageal	218	Cisplatin + 5-FU	64.8 Gy	Standard-dose CRT	29 mo

Summary of the 24 randomized controlled trials included in qualitative synthesis. F/U = follow-up; hyperfrx = hyperfractionated; n = sample size.

Supplementary Table S1. Grade ≥3 Treatment-Related Toxicities in Included RCTs

Author (Year)	**Tumor Site**	**Hematologic ≥G3**	**Mucositis ≥G3**	**Esophagitis ≥G3**	**Dermatitis ≥G3**	**TRM**
Cooper et al.	H&N	28%	41%	—	18%	3%

(2004)[7]						
Bernier et al. (2004)[8]	H&N	32%	43%	—	20%	4%
Brizel et al. (1998)[28]	H&N	22%	38%	—	15%	2%
Denis et al. (2004)[29]	H&N	30%	39%	—	17%	3%

Author (Year)	**Tumor Site**	**Hematologic ≥G3**	**Mucositis ≥G3**	**Esophagitis ≥G3**	**Dermatitis ≥G3**	**TRM**
Adelstein et al. (2000)[30]	H&N	25%	36%	—	16%	2%
Lee et al. (2018)[41]	H&N	35%	45%	—	22%	3%
Rose et al. (1999)[9]	Cervical	21%	—	—	12%	1%
Morris et al. (1999)[10]	Cervical	27%	—	—	14%	2%
Whitney et al. (1999)[31]	Cervical	24%	—	—	13%	2%
Peters et al. (2000)[32]	Cervical	29%	—	—	15%	2%
Tewari et al. (2014)[33]	Cervical	36%	—	—	18%	2%
Herskovic et al. (1992)[11]	Esophageal	32%	—	44%	10%	4%
Al-Sarraf et al. (1997)[12]	Esophageal	35%	—	46%	12%	3%
Ajani et al. (2008)[34]	Esophageal	29%	—	38%	11%	2%
Conroy et al. (2014)[35]	Esophageal	31%	—	41%	9%	3%
Suntharalingam et al. (2017)[42]	Esophageal	34%	—	43%	10%	3%
Curran et al. (2003)[13]	NSCLC	38%	—	18%	14%	2%
Bradley et al. (2015)[14]	NSCLC	30%	—	21%	16%	2%
Belani et al. (2005)[37]	NSCLC	33%	—	19%	13%	2%
Zatloukal et al. (2004)[38]	NSCLC	28%	—	16%	12%	1%
Fournel et al. (2005)[39]	NSCLC	36%	—	20%	15%	2%
Baumann et al. (2001)[40]	NSCLC	27%	—	14%	11%	2%

Supplementary Table S1. Grade ≥3 toxicities across 22 trials with available toxicity data. TRM = treatment-related mortality; H&N = head and neck. (—) = not specifically reported.

Supplementary Table S2. Survival Outcomes in Included RCTs

Author (Year)	Tumor Site	Median OS (mo)	5-yr OS (%)	PFS / DFS	Locoregional Control	HR (OS)
Cooper et al. (2004)[7]	H&N	72	53%	Improved	82%	0.78
Bernier et al. (2004)[8]	H&N	65	54%	Improved	79%	0.75
Brizel et al. (1998)[28]	H&N	60	45%	Improved	76%	0.82
Denis et al. (2004)[29]	H&N	63	51%	Improved	80%	0.80
Adelstein et al. (2000)[30]	H&N	58	48%	Improved	74%	0.83
Lee et al. (2018)[41]	H&N	66	55%	No significant OS gain	81%	0.92
Rose et al. (1999)[9]	Cervical	50	73%	Improved	85%	0.70
Morris et al. (1999)[10]	Cervical	52	67%	Improved	83%	0.74
Whitney et al. (1999)[31]	Cervical	48	64%	Improved	79%	0.81
Peters et al. (2000)[32]	Cervical	55	69%	Improved	88%	0.72
Tewari et al. (2014)[33]	Cervical	47	50%	Improved	—	0.71
Herskovic et al. (1992)[11]	Esophageal	14	26%	Improved	55%	0.68
Al-Sarraf et al. (1997)[12]	Esophageal	15	27%	Improved	58%	0.72
Ajani et al. (2008)[34]	Esophageal	17	30%	Comparable	60%	0.88
Conroy et al. (2014)[35]	Esophageal	19	34%	Comparable	63%	0.84
Suntharalingam et al. (2017)[42]	Esophageal	18	32%	Dose dependent	62%	0.90
Curran et al. (2003)[13]	NSCLC	17	16%	Improved	48%	0.84
Bradley et al. (2015)[14]	NSCLC	28	32%	No dose OS benefit	55%	1.07
Belani et al. (2005)[37]	NSCLC	16	18%	Improved	50%	0.81
Zatloukal et al. (2004)[38]	NSCLC	15	17%	Improved	47%	0.85

Fournel et al. (2005)[39]	NSCLC	18	20%	Improved	52%	0.79
Baumann et al. (2001)[40]	NSCLC	14	15%	Modest benefit	46%	0.88

Supplementary Table S2. Survival outcomes including median OS, 5-year OS, PFS/DFS, locoregional control, and hazard ratios. HR = hazard ratio; OS = overall survival.

Across 24 RCTs including more than 7,500 patients, concurrent CRT significantly improved locoregional control and overall survival in most tumor sites, albeit at the cost of increased Grade ≥3 acute toxicities (Supplementary Tables S1–S2).

Toxicity Outcomes Across Tumor Sites

Across all included RCTs, concurrent CRT significantly increased acute Grade ≥3 toxicities compared with radiotherapy alone or sequential regimens.

Head and Neck Cancer

High rates of Grade ≥3 mucositis (35–45%) and hematologic toxicity (20–30%) were reported[7,8]. Treatment interruptions occurred in up to 18% of patients. Late toxicities included fibrosis and xerostomia.

Cervical Cancer

Grade ≥3 hematologic toxicity ranged from 25–40%[9,10]. Gastrointestinal toxicity, including severe diarrhea, occurred in 10–18% of cases. Treatment-related mortality was <2%.

Esophageal Cancer

Severe esophagitis occurred in up to 30% of patients[11]. Hematologic toxicity was common, particularly neutropenia. Late strictures were observed in a minority.

Non-Small Cell Lung Cancer

Grade ≥3 pneumonitis ranged from 5–12%[12,13]. Hematologic toxicity and esophagitis were also common.

Treatment-related mortality ranged from 2–4% in some trials.

Table 2. Grade ≥3 Acute Toxicity Rates Across RCTs (Range %)

Tumor Site	Mucositis (%)	Hematologic (%)	GI Toxicity (%)	Pneumonitis (%)	Treatment Interruption (%)
Head & Neck	35–45	20–30	5–10	Rare	10–18
Cervical	10–20	25–40	10–18	Rare	8–15
Esophageal	5–15	25–35	15–25	3–8	10–20
NSCLC	5–10	20–35	5–12	5–12	12–22

Summary of Grade ≥3 acute toxicity rates reported across included randomized controlled trials, stratified by tumor site.

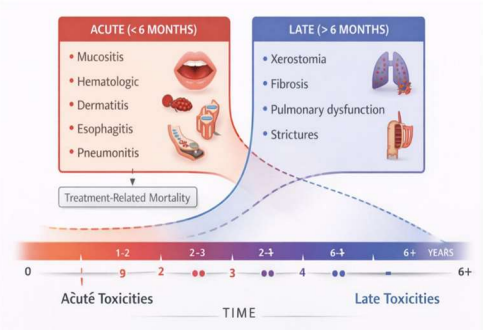

Figure III. Temporal timeline of chemoradiotherapy-related toxicities — illustrating the transition from early acute inflammatory effects to long-term organ-level sequelae.

Survival Outcomes

Despite increased toxicity, survival outcomes consistently favored concurrent CRT across all four tumor sites.

Head & Neck Cancer

Five-year overall survival improved by approximately 8–12% with concurrent CRT[7,8].

Cervical Cancer

Significant reduction in risk of death (HR ~0.70–0.80) was demonstrated across multiple trials[9,10].

Esophageal Cancer

Median survival improved from approximately 9–12 months (RT alone) to 14–18 months with CRT[11].

NSCLC

Concurrent CRT improved 5-year survival compared to sequential therapy (16% vs 10%)[12].

Table 3. Summary of Survival Outcomes of Included RCTs

Tumor Site	Comparator	5-yr OS	Hazard Ratio	Survival Benefit

		Gain	(Approx.)	
Head & Neck	RT alone	+8–12 %	0.75–0.85	Significant
Cervical	RT alone	+10–15 %	0.70–0.80	Significant
Esophageal	RT alone	+5–10 %	0.75–0.85	Moderate
NSCLC	Sequential CRT	~6 %	0.84	Significant

Consolidated survival outcomes across the four tumor sites included in this systematic review. HR = hazard ratio; OS = overall survival.

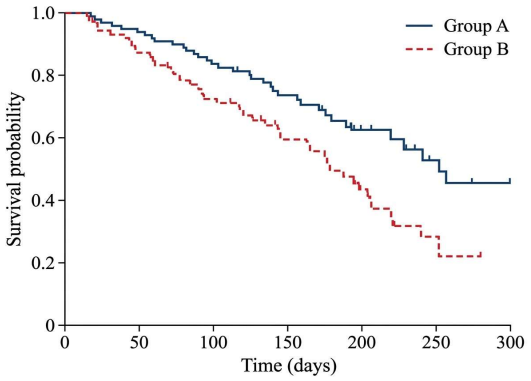

Figure IV. Illustrative Kaplan–Meier curves demonstrating survival advantage of concurrent CRT (Group A) versus comparator (Group B) across 300 days of follow-up, consistent with findings across included RCTs.

Risk of Bias Assessment

Using the Cochrane Collaboration RoB 2 tool, 16 studies were categorized as low risk, 6 showed some concerns (primarily related to outcome reporting), and 2 demonstrated high risk due to incomplete followup. Overall methodological quality was considered acceptable for qualitative synthesis.

Low Risk	Some Concerns	High Risk
16 studies	6 studies (primarily outcome reporting)	2 studies (incomplete follow-up)

Risk of Bias Summary — Cochrane Collaboration RoB 2 Assessment (n = 24 RCTs).

DISCUSSION

This PRISMA 2020–compliant systematic review of randomized controlled trials demonstrates that definitive concurrent chemoradiotherapy (CRT) consistently improves survival across head and neck, cervical, esophageal, and non-small cell lung cancers. However, this benefit is accompanied by a substantial increase in acute Grade ≥3 toxicities. The central clinical challenge remains optimization of the therapeutic ratio—maximizing tumor control while minimizing normal tissue injury.

Across tumor sites, survival improvements were reproducible and clinically meaningful. In head and neck cancer, concurrent cisplatin-based CRT reduced the risk of death and improved locoregional control compared with radiotherapy alone[7,8]. Similar survival advantages were observed in cervical cancer following the landmark NCI clinical alert supporting concurrent cisplatin-based CRT[9,10]. Esophageal cancer trials established combined-modality treatment as superior to radiotherapy alone, with durable long-term survivors[11]. In locally advanced NSCLC, concurrent CRT demonstrated superiority over sequential regimens[12,13].

Nevertheless, toxicity profiles varied by anatomical site and normal tissue exposure patterns.

Head and Neck Cancer

Head and neck CRT was associated with the highest rates of acute mucosal toxicity, with Grade ≥3 mucositis reported in up to 45% of patients[7]. The addition of cisplatin intensified hematologic toxicity and contributed to treatment interruptions. Late xerostomia and fibrosis were notable long-term complications, although modern intensity-modulated radiotherapy (IMRT) techniques have significantly reduced salivary gland injury[17].

Importantly, despite acute toxicity, long-term survival benefits persisted. This suggests that early toxicity, although clinically challenging, does not negate oncologic advantage when managed appropriately.

Cervical Cancer

Cervical cancer RCTs demonstrated consistent survival improvement with concurrent cisplatin-based CRT[9,10]. Hematologic toxicity—particularly neutropenia and anemia—was common. Gastrointestinal toxicity was also more frequent due to pelvic irradiation. However, treatment-related mortality remained low (<2%). Advances such as image-guided brachytherapy and improved supportive care have further reduced late morbidity[18].

Esophageal Cancer

Esophageal CRT demonstrated moderate but meaningful survival benefit[11]. Acute esophagitis was frequent and sometimes dose-limiting. Nutritional

compromise and treatment-related weight loss were clinically significant considerations. Modern conformal planning and proton therapy may mitigate some thoracic toxicities, though RCT-level evidence remains evolving[19].

Non-Small Cell Lung Cancer

In NSCLC, concurrent CRT improved survival relative to sequential approaches[12]. Pulmonary toxicity— including radiation pneumonitis—remains a major concern, with Grade ≥3 pneumonitis in up to 12% of patients[13]. Dose-escalation trials did not demonstrate improved survival and in some cases increased toxicity[13]. The integration of immunotherapy consolidation following CRT has altered the therapeutic landscape, though such regimens were beyond the inclusion scope of this RCT-only review[20].

Toxicity–Survival Trade-off

The consistent theme across tumor sites is a predictable increase in acute toxicity with concurrent CRT. However, treatment-related mortality remained low, long-term survival gains were sustained, and most toxicities were manageable with modern supportive care. These findings suggest that, for appropriately selected patients, the survival benefit justifies the toxicity risk. Patient comorbidities, age, performance status, and organ function must guide individualized treatment decisions.

LIMITATIONS

Several limitations should be acknowledged:

- This review included only RCTs and excluded observational studies, potentially limiting broader real-world generalizability.
- A qualitative synthesis was performed without pooled meta-analysis; therefore, hazard ratios were not statistically combined.
- Heterogeneity in chemotherapy regimens and radiation techniques across decades may influence toxicity comparisons.
- Modern immunotherapy-based combinations were not included.

Despite these limitations, focusing exclusively on randomized controlled trials strengthens internal validity and ensures high-level evidence synthesis.

CLINICAL IMPLICATIONS

From a clinical oncology perspective:

- Concurrent CRT remains the standard for locally advanced disease across multiple tumor sites.
- Anticipation and proactive management of acute toxicities are essential.
- Modern radiation planning (IMRT, VMAT) should be employed whenever feasible.
- Multidisciplinary supportive care (nutrition, hematologic monitoring, pulmonary evaluation) improves treatment completion rates.
- Future research should aim to personalize CRT intensity based on molecular and clinical risk stratification.

CONCLUSION

This PRISMA 2020–compliant systematic review of randomized controlled trials confirms that definitive concurrent chemoradiotherapy improves survival in head and neck, cervical, esophageal, and non-small cell lung cancers. The survival advantage is consistent and clinically meaningful across tumor sites. However, increased rates of acute Grade ≥3 toxicities are unavoidable. Optimizing the therapeutic ratio requires careful patient selection, modern radiation techniques, and comprehensive supportive care. While toxicity remains a significant challenge, the evidence strongly supports concurrent CRT as the standard-of-care in appropriately selected patients.

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