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*Review*

# Chemoradiotherapy in Cancer Treatment: Rationale and Clinical Applications

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**Abstract.** *Chemoradiotherapy (CRT) refers to the combined administration of both chemotherapy and radiotherapy as an anticancer treatment. Over the years, CRT has become an established treatment for a diverse range of locally advanced solid tumours. The rationale for CRT is based on the two concepts of spatial cooperation and in-field cooperation, whereby the end goal is to achieve synergistic antitumour effects from the combination of both treatment modalities. CRT offers notable patient survival benefits and local disease control without significant long-term toxicities. Although the enhancement of cytotoxic effects inevitably increases damage to normal tissues as well as tumour cells, if the damage to normal tissue is lesser than that to tumour cells, CRT is still deemed beneficial. Thus, the search to optimise dose, timings and fractionation of CRT is of particular interest. Considering the recent success achieved with anticancer immunotherapies including immune checkpoint inhibitors, the combination of CRT and immunotherapy has emerged as an exciting field of research with the potential for significant clinical benefit. This report outlines the rationale underlying CRT and discusses its advantages through clinical examples focusing on anal, cervical, non-small-cell lung cancer and bladder cancer.*

Chemoradiotherapy (CRT), the concurrent administration of cytotoxic chemotherapy and radiotherapy, has been established as standard treatment for many locally advanced solid tumours including gastrointestinal malignancies, head and neck cancers, gynaecological cancers, lung cancers, genitourinary cancers as well as glioblastoma and sarcoma. CRT may improve local tumour control and patient survival, while rendering unnecessary the need for surgical organ resection (1-3). Alternatively, CRT may shrink tumours substantially when given neoadjuvantly, thus allowing for curative surgical interventions in patients with tumours initially deemed unresectable (1). The combination of CRT with novel immunotherapies including immune checkpoint inhibitors has emerged as an exciting area of research with many important questions remaining unanswered. Yet the advent of CRT is not recent nor are the theoretical principles underlying its use. This report outlines the rationale underlying CRT and discusses its advantages through clinical examples focusing on anal, cervical, non-small-cell lung cancer (NSCLC), and bladder cancer.



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## Rationale for the Use of CRT – The "Steel Paradigm"

CRT is based on the principles of spatial cooperation and radiation 'sensitization' demonstrated in pre-clinical and clinical studies from the 1950s (4-6). Spatial cooperation, a term coined in 1979 by the English scientists, Steel and Peckham, refers to the eradication of subclinical micro-metastases by systemic chemotherapy and locoregional irradiation of the primary tumour (5). Interaction between chemotherapy and radiotherapy is not required for spatial cooperation (Figure 1), however, differing toxicities are desired to enable effective dosing of both modalities without dose-limiting toxicities (2, 4). Although concurrent dosing of radiotherapy and chemotherapy is often difficult to achieve due to toxicity-driven dose reductions, many studies have successfully demonstrated effective reduction of distant metastases compared to radiotherapy alone.

Radiation sensitization is the second way in which CRT interacts by a 'supra-additive' or 'additive' effect in 'in-field cooperation' (Figure 1). Supra-additive cytotoxicity suggests a greater effect than using both modalities sequentially, while additive cytotoxicity suggests an effect equal to that in sequential use (Figure 2) (2). Conversely, infra-additive effects refer to radioprotective properties of CRT, whereby cytotoxic damage to tumour and normal tissue is reduced due to interaction of the two therapeutic modalities. Infra-additive effects are typically undesirable when radioprotective effects are observed in tumour cells. However, chemotherapeutic drugs with infra-additive effects can also be chosen to selectively target normal tissue to enhance maximal feasible radiation dose. In theory, radiation sensitization is achieved by five CRT interactions: (i) Direct radiation damage enhancement by drug incorporation into DNA, (ii) cellular repair inhibition, (iii) radiosensitive phase cell accumulation or radioresistant phase cell elimination, (iv) hypoxic cell elimination, and (v) inhibition of accelerated cancer cell repopulation (2, 4). Through these mechanisms, chemotherapy sensitizes cancer cells to the effects of ionising radiation, thus increasing tumour-killing effects within the field of radiation (1). Moreover, CRT dose–response curves quantify CRT interaction and although an increase in normal tissue damage is observed, combination therapy is still considered beneficial if a larger increase in cytotoxicity is observed towards the tumour *versus* normal tissue (Figure 3) (2).

Lastly, in addition to improving the rate of tumour shrinkage and treating micro-metastases, CRT theoretically offers the added benefit of independent toxicity (1). Chemotherapy toxicities do not overlap radiotherapy toxicities, hence sparing additive toxic effects of combination treatment. Moreover, the concomitant use of these treatment modalities confers beneficial responses that can overcome cancer resistance to individual treatments (1, 2). Although concurrent CRT inevitably increases acute toxicities by enhancing normal cell damage, late toxicities are not significantly increased. Therefore, CRT offers a therapeutic benefit without significant toxicity risk while improving local disease control and survival. Of note, the temporal distribution of chemotherapy and radiotherapy is important as induction chemotherapy followed by radiotherapy does not always improve local disease control rates (4).

## CRT in Anal Cancer

The first promising results of CRT were observed in the treatment of anal cancer in the 1970s. Three patients treated neoadjuvantly with fluorouracil and mitomycin C plus radiation achieved complete responses. Histologically confirmed complete response was observed in two patients and the third experienced a progression-free survival of 14 months (7). Results from subsequent clinical trials were equally promising. Today, CRT with 5-fluorouracil plus mitomycin C is offered as mainstay curative treatment for anal squamous cell carcinomas with the intent of organ preservation after having repeatedly been shown to be a superior treatment in large-scale clinical trials (8-12). Abdominoperineal resection surgery with formation of end colostomy is reserved for salvage or secondary therapy after disease progression following CRT (13). Furthermore, high-dose irradiation with brachytherapy in patients with residual disease after CRT achieves higher rates of local disease control, and although this has been criticised for increased risk of adverse events, these remain statistically insignificant (13-15). Finally, intensity-modulated radiation therapy, provides a means of delivering curative radiotherapy in CRT without treatment gaps. Intensity-modulated radiation therapy facilitates dose escalation, reduces dosing to surrounding normal critical structures, and maintains excellent targeted tumour coverage (13, 16-18). Nevertheless, these benefits from intensity-modulated radiation therapy do not necessarily correlate to an improved overall survival (OS) (16).

## CRT in Cervical Cancer

In locally advanced cervical cancer, including stage IB2-IVA disease, CRT remains standard treatment. A large 14-year randomised trial concluded that cisplatin-based CRT offers superior disease-free survival compared to neoadjuvant chemotherapy followed by radical surgery (76.7% *versus* 69.3%) (19). Although CRT was found to carry significantly higher risk of rectal, bladder, and vaginal toxicities at 90 days after treatment, these were not significantly different between arms at 24 months for all except vaginal toxicity (19). Furthermore, patients with locally advanced cervical cancer treated with CRT can be stratified into high risk and low risk according to prognostic factors, including lymph node enlargement, tumour diameter, pre-treatment haemoglobin level and clinical stage (20). Novel treatment strategies need to be assessed in high-risk patients to improve outcomes. The most promising novel treatment for high-risk patients has been adjuvant chemotherapy following CRT, while recent studies of metachronous chemotherapy in CRT have yielded promising results in high risk patients who received weekly neoadjuvant carboplatin/paclitaxel chemotherapy followed by radical chemoradiation (21-24).

## CRT in NSCLC

The advantages of chemoradiation are also well established in NSCLC, stage III unresectable non-metastatic disease (25). Lung cancer is the leading cause of cancer-associated death worldwide. NSCLC accounts for 80-85% of lung cancer cases. The majority of patients with NSCLC are diagnosed with non-resectable disease and >30% of cases are

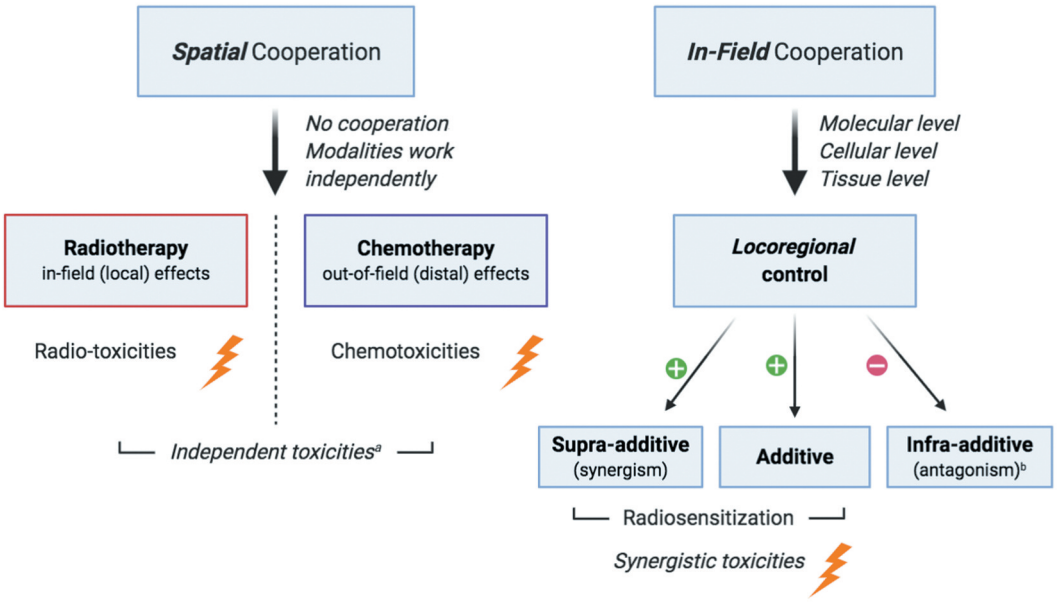


Figure 1. *Idealised theoretical framework for concurrent chemoradiotherapy. The two distinct mechanisms describing the interaction of chemotherapy and radiotherapy are spatial and in-field cooperation. [a]Theoretical advantage of chemoradiotherapy as increased toxicity is often observed in clinical application. [b]Typically undesirable as it may confer tumour protection. Adapted from (2).*

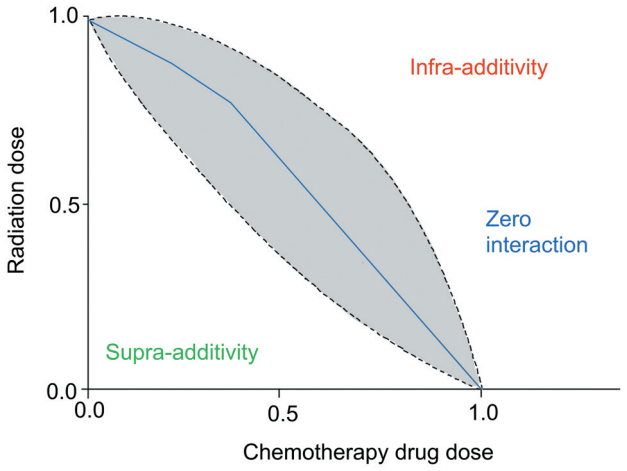


Figure 2. *Schematic isobologram demonstrating the possible effects resulting from the combination of radiotherapy and chemotherapy. The x and y axes represent the isoeffective levels for chemotherapy and radiation dose, respectively. The blue line demonstrates additive cytotoxicity whereby the combination of both therapies confers effects equal to sequential use. The additivity envelope, shaded in grey, is based on combined standard errors. Anything above the additivity envelope curve represents an infra-additive antagonistic effect, while anything below the additivity curve represents a supra-additive synergistic effect. Adapted from (2).*

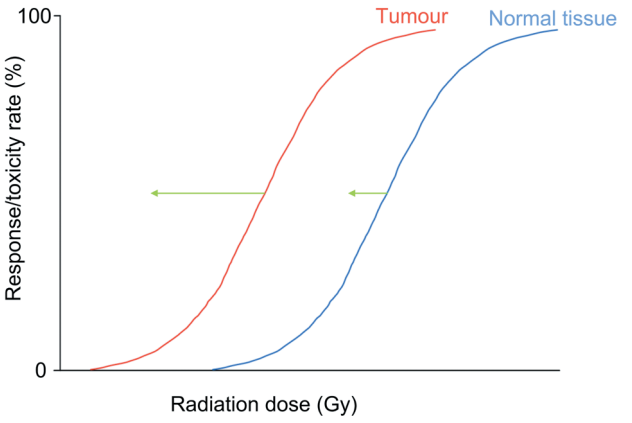


Figure 3. *Dose–response curves for tumour cells (in red) and normal tissue (in blue) versus radiation dose. The addition of concurrent chemotherapy increases radiotherapy efficacy as indicated by the green arrows shifting both curves to the left. A stronger shift is desired for the tumour curve, as indicated by the longer arrow, in order for chemoradiotherapy to be deemed beneficial. Adapted from (2, 4).*

locally advanced (26). Radiotherapy alone has been the standard approach for stage IIIA/B NSCLC offering reasonable response rates, however, outcomes with this were poor featuring low survival, poor local disease control, and early metastases; with median survival of 9-11 months, 2-year survival of 10-20%, and 3-year survival of only 5-10% (27, 28). Furthermore, disease heterogeneity requires a multidisciplinary treatment approach which caused disagreement on the best standard of treatment (25, 29).

With sequential CRT, an increase in OS from 5% to 10% was noted at 5 years (30-32). This rate was increased to 15% with concurrent CRT, with a 4.5% absolute survival benefit

(33). Although OS improved with concurrent CRT therapy, sequential therapy carries less toxicity risk for oesophagitis and pneumonitis (34, 35). Hence, concurrent CRT is preferred for fit patients while sequential therapy is preferred for the elderly or unfit patients (25, 35). Currently, the custom treatment for localised inoperable NSCLC is concurrent CRT with a platinum-based doublet and 60 Gy radiotherapy delivery daily over 6 weeks followed by two cycles of consolidation chemotherapy, particularly for paclitaxel and carboplatin regimens (36). Yet although the current regimen has curative intent, survival rates are low with median survival of 20-28 months and 5-year OS of 15-20%, which has plateaued (37).

*Combination of CRT with immunotherapy in NSCLC*. With the advent of immunotherapy, and with exceptional results shown thus far in the treatment of advanced NSCLC with programmed cell death protein 1 (PD1) and programmed cell death ligand-1 (PD-L1) immune checkpoint inhibitors, several studies are underway (38-42) to evaluate CRT-immunotherapy combination in the setting of NSCLC (37). Radiotherapy can modulate the immune system and mount an immune response causing immunogenic cell death by enhancing tumour antigen retrieval (43). Additionally, radiotherapy has pro-immunogenic effects on the tumour microenvironment, initiating innate and adaptive immunity (44, 45). The abscopal effect, whereby patients exhibit diffuse systemic response to radiotherapy at distant sites after local radiotherapy administration, has generated substantial interest following promising results in metastatic melanoma treated with ipilimumab, an antibody-based cytotoxic T-lymphocyte-associated protein-4 immune checkpoint inhibitor, and response is thought to be driven by T-cells (43, 46). A recent phase I trial concluded that administration of pembrolizumab, an anti-PD-L1 immune checkpoint inhibitor, together with CRT was safe and tolerable as a first-line therapy for patients with stage III NSCLC (37). However, further research is required to optimise dose, timings, and fractionation of immunotherapy with CRT, while the increased risk of immune-related adverse events, especially pneumonitis and myocarditis, warrants caution in prospective clinical trials (47, 48).

## CRT in Bladder Cancer

Finally, bladder cancer has emerged as a promising field of CRT research. Multiple large studies have demonstrated that concurrent CRT offers superior survival compared to radiotherapy alone for muscle invasive bladder cancer (MIBC) [reviewed in (49)]. However, compared to radical cystectomy, CRT offers a lower median OS (32.8 *versus* 36.1 months) (50, 51). Tri-modality therapy consisting of neoadjuvant CRT followed by radical cystectomy has become an acceptable option for the treatment of MIBC, although bladder conservation is not achieved (52). Additionally, there have been critical developments regarding systemic treatment modalities. Cisplatin-based multi-agent chemotherapy has traditionally been the cornerstone systemic treatment for locally advanced and metastatic MIBC in combination with gemcitabine, while carboplatin and taxane-based regimes have been regarded as second-line treatments (53-55).

*Combination of CRT with immunotherapy in bladder cancer*. Recently, immunotherapy has achieved ground-breaking results in treating bladder cancer. Immune checkpoint inhibitors have gradually replaced cisplatin-based chemotherapy becoming first-line treatment, thus changing the treatment landscape for locally advanced urothelial cancer (56). Moreover, preliminary results from studies suggest that radiation plus immunotherapy not only offers synergistic antitumour effects, notable partial or complete responses, but also an abscopal effect, without excess toxicity (57-59). Thus, combination immunotherapy plus radiotherapy is set to replace CRT alone. Ongoing phase II trials indicate that pembrolizumab plus CRT may be a promising therapeutic option in MIBC (60, 61). Thus, a phase III, global, multicentre, double-blind, placebo-controlled, randomized trial has been initiated to evaluate the efficacy and safety of pembrolizumab plus CRT *versus* placebo plus CRT in MIBC (62). Additionally, the Southwest Oncology Group trial, a randomized phase III study, plans to enrol 475 patients to evaluate CRT-based bladder preservation therapy with and without atezolizumab, a monoclonal antibody to PD-L1 (63). The treatment regimen will include radiotherapy, the physician's choice of chemotherapy, and atezolizumab or placebo. This study is expected to provide more definitive evidence of whether the addition of immunotherapy to CRT increases the chance of successful bladder preservation in patients with MIBC. Results from these trials are awaited.

## Conclusion

CRT is based on the synergistic effects of radiation and chemotherapy in targeting cancer cell death *via* different mechanisms. Since its original discovery for anal cancer by Nigro, *et al*. in the 1970s, the use of CRT has expanded vastly, becoming standard therapy for numerous different tumours including cervical, NSCLC, and bladder cancer discussed herein. CRT offers notable patient survival benefits and local disease control without significant increase in long-term toxicities. Yet further research is required to optimise treatments. The advent of immunotherapy is set to change the field remarkably in upcoming years. Several trials are underway to investigate combination regimens of immunotherapy with chemotherapy, radiation, and surgery.

## Conflicts of Interest

The Authors declare that they have no competing interests.

## Authors' Contributions

K.S.R. contributed to the conceptualization of the work, reviewing the literature, drafting and revising the article, figure illustrations, and final approval of the version to be published. T.H.L.Y. contributed to drafting and revising the article, figure illustrations, and final approval of the version to be published. M.S. contributed to revising the article, supervising the work, and final approval of the version to be published.

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