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ADVANCES IN RADIOTHERAPY SPECIAL FEATURE: REVIEW ARTICLE

Chemoradiation for gastric cancer: controversies, updates and novel techniques

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ABSTRACT

The INT0116 trial established the role of adjuvant chemoradiation (CRT) in the multidisciplinary approach to the management of locally advanced gastric cancer. However, whether adjuvant CRT is indispensable for patients undergoing D2 dissection remains undefined. The adjuvant chemoradiation therapy in stomach cancer (ARTIST) trial, which was designed to compare adjuvant chemotherapy to CRT, failed to demonstrate differences in disease-free and overall survival in the whole study group; however, subgroup analysis indicated that patients with lymph node metastasis may benefit from additional radiation. A follow-up ARTIST II trial is currently under way. The efficacy of adjuvant CRT remains controversial because of variation among studies in the inclusion criteria and treatment delivery methods; however, the identification of patients who would benefit from CRT is critical. Advanced radiotherapy techniques such as intensity-modulated radiotherapy protect normal tissues *via* motion management and decreased radiation-induced toxicity and contribute to plan optimization. Further studies integrating clinical and molecular factors as well as neoadjuvant CRT are warranted.

Gastric cancer is one of the most frequent malignancies. It is the fifth most common malignancy and the third leading cause of cancer-related death in the world.[1] An estimated one million new cases of gastric cancer were diagnosed in 2012 (952,000 cases, 6.8% of the total), and approximately 723,000 deaths from gastric cancer were reported (8.8% of the total) worldwide.[1,2] The regional distribution of gastric cancer shows that >70% of the world's new cases occur in developing countries, and half of them occur in Eastern Asia.[1] The results of Phase III clinical randomized trials show that the overall survival (OS) from gastric cancer improved remarkably in the past two decades because of the implementation of multimodality treatment compared with surgery alone. However, because of the heterogeneity of patient selection and surgical quality among these randomized trials, the OS varies from 30–40% in the USA to 60–70% in Japan.[2,3] Consequently, a consensus has not been reached regarding the management of locally advanced gastric cancer (LAGC). Because of differences in the distribution of the disease, the management of LAGC tends to vary according to the outcomes from randomized trials in corresponding areas. In North America, adjuvant chemoradiation (CRT) is the standard treatment, whereas perioperative and adjuvant chemotherapy are recommended in Europe and Asia, respectively.[3–5] Considering the three major components of the multidisciplinary treatment of LAGC, the inclusion of radiation therapy remains controversial. This review discusses the controversy surrounding the use of radiation for the treatment LAGC and potential stratification factors for patient selection, as well as modern radiation technique applications in LAGC.

CHEMORADIATION OF LOCALLY ADVANCED GASTRIC CANCER: ESTABLISHMENT AND CHALLENGE

CRT has shown survival benefits in patients with initially unresectable gastric cancer that became resectable after CRT. Hence the role of CRT has been investigated in the adjuvant setting.[6] The landmark INT0116 trial published in 2001 demonstrated the efficacy of adjuvant CRT compared with surgery alone for the treatment of LAGC.[7] In this multicentre Phase III randomized trial, 556 patients with resected adenocarcinoma of the stomach or gastro-oesophageal junction were randomly assigned to surgery followed by post-operative CRT or surgery-alone groups, and most of them were staged T3/T4 (69%) and N+ (85%) with high risk of recurrence. In the adjuvant treatment group, patients received three cycles of fluorouracil-based chemotherapy peri-radiation, and

radiation was delivered with a total dose of 45 Gy in 25 fractions. After a median follow-up of 5 years, the adjuvant CRT group showed a significant improvement in OS (40% *vs* 22%) and a decrease in the local recurrence rate (19% *vs* 29%) compared with the surgery-alone group. Moreover, after 11 years of long-term follow up, the adjuvant group continued to show a robust benefit regarding OS [hazard ratio (HR), 1.32; 95% confidence interval (CI), 1.10–1.60; $p = 0.0046$] and relapse-free survival (HR, 1.51; 95% CI, 1.25–1.83; $p < 0.001$).[8] The INT0116 trial was a milestone trial and laid the foundation for the popularity of adjuvant CRT for the treatment of LAGC.

Consistent with the INT0116 trial, the advantage of adjuvant CRT was demonstrated in meta-analyses or retrospective studies with a large sample size. Valentini et al[9] analysed nine randomized clinical trials (RCTs) in which radiation was compared with surgery with/without adjuvant chemotherapy in resectable gastric cancer, and the results revealed a significant 5-year survival benefit with additional radiation. Seyedin et al[10] analysed 21,472 patients with resectable gastric cancer from the SEER database between 1988 and 2008 and showed that Stage I patients benefited most from surgery alone, whereas those in more advanced stages benefited most from adjuvant CRT. Jácome et al[11] retrospectively analysed 185 Stage II–IV (M0) patients who underwent D2 dissection for gastric cancer, and compared adjuvant CRT with surgery alone. The results indicated that adjuvant CRT was a prognostic factor for 3-year OS (HR, 0.46; 95% CI, 0.26–0.82; $p = 0.008$). Based on these encouraging results, adjuvant CRT is recommended as one of the standard approaches in the multidisciplinary treatment of LAGC.

However, controversies still exist because of the non-optimized study design of the INT0116 trial, which neglected to include criteria regarding surgical quality. This trial was challenged for its low proportion of patients undergoing D2 dissection (10%), which is regarded as standard surgery in Asia. Dikken et al[12] analysed the relapse patterns and therapeutic effects of D1 and D2 dissections. The addition of post-operative CRT had a major impact on local recurrence in resectable gastric cancer with D1 dissection (2% *vs* 8%; $p = 0.001$), while there was no difference in patients undergoing D2 dissection. Therefore, the benefit associated with adjuvant CRT may be a compensation for inadequate lymph node dissection, such as that in D1/D0 dissection.

To determine whether adjuvant CRT is necessary, several studies, including meta-analyses and randomized trials were conducted. Huang et al[13] performed a meta-analysis of 3 RCTs, including 895 Asian patients who underwent D2 surgery, and showed remarkable improvement of locoregional recurrence-free survival (LRRFS) (HR, 0.53; 95% CI, 0.32–0.87; $p = 0.01$) and disease-free survival (DFS) (HR, 0.720; 95% CI, 0.590–0.890; $p = 0.002$) with adjuvant CRT; however, there were no significant differences in distant metastasis, recurrence-free survival ($p = 0.25$) and OS ($p = 0.08$). The National Cancer Center (NCC) in the Republic of Korea conducted a single-institution Phase III trial that included patients with Stage III–IV (M0) gastric cancer who underwent R0 and D2 dissection.[14] A total of 90 patients were randomly assigned to the chemotherapy arm (CT, $n = 44$) or the CRT arm (CRT, $n = 46$). With a median follow-up of 86.7 months, 46.6% patients (24 in the CT arm and 18 in the CRT arm) had disease recurrence, whereas the 5-year LRRFS was increased in the CRT group compared with the CT group (93.2% *vs* 66.8%; $p = 0.014$, respectively); no difference in DFS and OS was observed between the two groups.

However, the meta-analyses and clinical trials mentioned above involved out-dated RT techniques and chemotherapy regimens. Furthermore, most of these clinical trials were not high quality designs, thus leading to paradoxical results.

The adjuvant chemoradiation therapy in stomach cancer (ARTIST) trial was a large Phase III randomized trial designed to explore whether adjuvant CRT is necessary after D2 dissection.[15] The 458 patients included underwent D2 dissection and were randomly assigned to 6 cycles of adjuvant capecitabine with cisplatin (XP; $n = 228$) or 45 Gy of radiation with concurrent capecitabine and 4 cycles of XP peri-radiation (XPRT; $n = 230$). The primary end point was 3-year DFS and the secondary end points were OS and safety. After a median follow-up of 53.2 months (range, 36.9–77.3 months), the results failed to demonstrate significant differences between the two groups regarding 3-year DFS (74.2% *vs* 78.2%; $p = 0.0862$, respectively). The study reported updated results with long-term follow up, and they were consistent with the 3-year outcome.[16,17] The negative results of the ARTIST trial challenged the effect of adjuvant CRT in patients undergoing D2 and R0 gastrectomy. However, subgroup analysis showed a significantly improved 3-year DFS in patients with positive lymph nodes (72% in the XP arm *vs* 76% in the XPRT arm; $p = 0.04$). Based on these results, Korean scholars have initiated a new multicentre Phase III randomized trial named the ARTIST II trial,[17] in which 900 patients who underwent D2 dissection are allocated into three groups: one group receiving S-1 for 1 year; one group receiving S-1 and oxaliplatin (SOX) for 6 months; and the third group receiving two cycles of SOX followed by 45 Gy of radiation with concurrent S-1, followed by four cycles of SOX. In this trial, all patients are stage II–III with positive lymph nodes, and the stratification factors are stage, type of surgery and Lauren classification. This trial is still enrolling patients, and we are looking forward to its preliminary results.

The INT0116 trial is a multicentre trial that confirmed the benefit or CRT regarding improvement of DFS and OS with long-term follow up; however, it has been criticized for its suboptimal surgical criteria. The ARTIST trial included high standards regarding the quality of surgery, and all patients enrolled underwent D2 dissection; however, it is limited by its single institution design and the fact that more than half of the patients (60% in XP *vs* 58% in XPRT, respectively) included in the study were in Stages I and II. Patients in relatively early stages with a lower risk of locoregional recurrence in the study may dilute the survival benefit of CRT. Given the default limitations in trial design, the role of adjuvant CRT after D2 dissection remains undefined. However, we should not arbitrarily negate the effect of adjuvant radiation after D2 dissection. Under these circumstances, it may be important and worthwhile to select

patients at high risk of recurrence who would benefit the most from adjuvant CRT.

SELECTION OF PATIENTS WHO WOULD BENEFIT FROM CHEMORADIATION

The criteria for the selection of patients who would benefit from adjuvant CRT should be based on two major aspects, namely clinical and histological factors.

Clinical factors

Clinical factors include treatment-related factors and patient characteristics. Surgery is the key component in the multimodal treatment of gastric cancer. Surgery-related factors include types of surgery, failure patterns after radical surgery and quality control. Adjuvant CRT could reduce the risk of locoregional failure after D1 dissection. The long-term results of a Dutch trial[18] showed a high locoregional recurrence rate of 41% in the D1 group. Local recurrence significantly decreased in the adjuvant CRT group compared with the surgery-only group (5% *vs* 17%; $p = 0.0015$, respectively) among patients who underwent D1 dissection, whereas no differences were observed in patients who underwent D2 dissection. Despite discrepancies between Western and Far East countries regarding D1 or D2 dissection as the preferred treatment, D2 dissection is currently recommended as the standard surgical approach for gastric cancer.[3–5] However, the criteria for evaluating the quality of D2 dissection remain unclear. Quality control regarding the extent of regional lymph node dissection is difficult without video records; therefore, if the number of lymph nodes dissected is >15 this is used as a surrogate for the evaluation of D2 dissection.[19,20] Even in East Asia, where D2 dissection has been the standard approach for many years, not all patients with LAGC had optimal D2 dissection, and specialized surgeons had better therapeutic outcomes with a higher number of examined lymph nodes ($p < 0.05$), decreased post-operative mortality ($p < 0.05$) and a significant survival benefit ($p < 0.05$) than did general surgeons.[21] The translation of data from clinical trials based on elaborate surgeries into daily practice with suboptimal surgeries should be performed with caution.

Disease stage is another crucial factor for patient selection, even among patients who underwent D2 dissection. Although the INT0116 trial enrolled patients staged IB–IV (M0), the majority had advanced disease, whereas up to 60% patients in the ARTIST trial were Stage I/II. Furthermore, in the subgroup analysis of the ARTIST trial, improved DFS ($p < 0.05$) was observed in Stage III and IV patients in the CRT group compared with the chemotherapy-alone group. A previous study[22] of failure patterns in patients with LAGC who underwent D2 dissection and adjuvant CRT revealed that the locoregional recurrence rates in Stage IB–II and III–IV (M0) patients were 3–6% and 9–15%, respectively. This indicated that adjuvant CRT following curative D2 dissection could be more beneficial for Stage III–IV (M0) patients than Stage IB–II patients. Jin et al[23] reported the results of adjuvant CRT in patients with resected Stage IIIC gastric cancer with D2 dissection at the ASCO 2014 Annual Meeting. The study also confirmed that CRT was associated with a clinical benefit regarding both OS ($p = 0.041$) and DFS ($p = 0.033$) compared with adjuvant chemotherapy alone in Stage IIIC patients. These studies indicate that patients at relatively advanced disease stages (III or IV) would benefit the most from adjuvant CRT.

HISTOLOGICAL/PATHOLOGICAL FACTORS

Apart from clinical factors, histology and pathology factors need to be considered for patient selection. With limited data extracted from available clinical trials, Lauren classification and lymph node status are recognized as crucial factors. Patients with intestinal-type gastric cancer are more prone to benefit from CRT than those with diffuse type in subgroup analyses of the INT0116 and ARTIST trials.[8,15] Patients with intestinal-type histology showed a significant improvement in DFS in the XPRT arm compared with the XP arm (94% *vs* 83%; $p = 0.01$, respectively).

Considering the entire study group, the ARTIST trial failed to demonstrate the superiority of adjuvant CRT over chemotherapy; however, subgroup analysis revealed a potential advantage of CRT in lymph node-positive patients, who showed longer 5-year DFS than lymph node-negative patients (76% *vs* 72%; $p = 0.04$, respectively). Ejaz et al[24] analysed post-operative pathological factors using a propensity score matching method to balance the bias of patient baseline characteristics in the retrospective background. Adjuvant CRT was associated with long-term improved OS compared with chemotherapy alone (46.7 *vs* 20.9 months; HR, 0.510; $p < 0.001$). Positive lymph node status as well as lymphovascular invasion were indicators of potential benefit from adjuvant CRT ($p < 0.001$). These studies illustrated that patients with intestinal-type gastric cancer and positive lymph nodes might benefit the most from adjuvant CRT after radical surgery.

Gene-based classifications have been investigated for decades. Early studies identified various genes associated with recurrence, metastasis and the prognosis of gastric cancer, including *CDH1*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *SMAD4*, *MET*, *BMPR1A*, *ATM*, *BCRA1/2*, *TP53*, and *APC* among others.[25–28] Li et al[29] reported that cyclin D1 expression was correlated with locoregional recurrence, *PCNA* expression was correlated with remote metastasis, and bcl-2, ki67, c-myc2 and human epidermal growth factor 2 (Her-2) levels were correlated with lymph node metastasis. The Her-2 gene was recently implicated in the development of gastric cancer. However, the association of Her-2 overexpression with the prognosis of patients with gastric cancer remains unclear.[30–32] Despite extensive basic research, we still lack adequate evidence from high-level studies to demonstrate the relation between radiation and gene expression in gastric cancer. In the ARTIST trial, the different status of the *HER-2*, *MET*, *MLH1* and *CDH1* genes was considered; however, differences in the expression of these genes between the XPRT and XP groups had no effect on DFS. The Cancer Genome Atlas project recently published a study on the stratification of gastric cancer into four molecular types as follows: (1) Epstein–Barr virus (EBV)-positive type, identified by the EBV CpG island methylator phenotype, recurrent *PIK3CA* mutations, amplification of *JAK2*, *PD-L1* and *PD-L2*, and silenced *CDKN2A*; (2) microsatellite unstable type, characterized by high mutation rates, including mutations of genes encoding targetable oncogenic

signalling proteins; (3) genomically stable type, enriched in the diffuse histological variant and mutations of *RhoA* or fusions involving RHO family GTPase-activating proteins; and (4) chromosomal instability type, characterized by marked aneuploidy and focal amplification of receptor tyrosine kinases.[33] Identification of these subtypes of gastric cancer provides a new direction for patient stratification and facilitates the selection of patients who would benefit the most from adjuvant CRT.

Therefore, to maximize the therapeutic effect of CRT for LAGC, patient selection is important and target patients for adjuvant CRT may have one or more of the following characteristics: non-optimized surgery, advanced disease stage, intestinal type and lymph node metastasis.

OPTIMIZATION OF CHEMORADIATION BY NOVEL TECHNIQUES

Two-dimensional/three-dimensional techniques

The two-dimensional (2D) radiation therapy technique mainly uses anterior and posterior fields with a block to treat patients. The INT0116 study[8] showed a high incidence of grade 3 (41%) and grade 4 (32%) toxicity. This could have been attributed to high doses of radiation to critical organs such as the kidney, liver, spinal cord and small bowel involved in the anterior posterior–posterior anterior (AP-PA) field.

Three-dimensional conformal radiotherapy

Several techniques were developed and adopted in clinical practice[34,35] using coplanar three-dimensional conformal radiotherapy (3DCRT). A junction technique called "split-field technique" or "split-volume technique" separates the target volume into two abutting sections, namely superior and inferior sections. The superior section includes the tumour bed, anastomosis and splenic hilar nodes; the inferior section includes the subpyloric, pancreaticoduodenal and local para-aortic nodes. The isocentre is set up at the junction of the two sections. Half fields in the superior–inferior (SI) direction are used to avoid overlap between the superior and inferior fields. The superior and inferior target sections are planned using different field angles to avoid the spinal cord if necessary and to reduce the dose to the kidneys. A coplanar multifield technique with five or more coplanar fields for the whole target can also be applied.

The three-dimensional (3D) non-coplanar conformal radiotherapy was first developed by Soyfer et al,[36] who used a four-field arrangement consisting of a right lateral field, a left lateral field, an anterior craniocaudal (CC) oblique field and an anterior caudal–cranial oblique field to optimize the dose distribution to the kidneys. Comparison of this technique to the four-field box plan and AP-PA plan showed that the non-coplanar plan had the optimal dose distribution to the kidneys and spinal cord.

Dose comparison studies indicate that 3DCRT has superior dose coverage and better organ at risk (OAR) sparing than does the AP-PA technique.[34,36] The dose to the liver is slightly increased, but still well tolerated. However, Kassam et al[37] reported that adjuvant CRT with conformal RT is associated with significant toxicity.

Intensity-modulated radiotherapy

Intensity-modulated radiotherapy (IMRT) is an advanced technique of 3DCRT that allows for conformal dose distribution around the target, while a steep dose fall-off spares surrounding critical structures. Therefore, IMRT can improve the protection of surrounding OARs. A blinded study[35] showed that IMRT is preferred over conformal plans by oncologists who reported that IMRT plans provide better target coverage and better OAR sparing according to the dose–volume histograms and organ-dose summaries. Milano et al[38] compared IMRT with opposed AP-PA and three-field 3D plans, and concluded that IMRT plans have better target coverage but also a higher volume receiving >110% of the dose. For OAR sparing, IMRT spares the right kidney and liver compared with three-field plans, although it does not spare the left kidney. A comprehensive comparison was performed among the conventional 3D box plan, AP-PA plan, step-and-shoot IMRT and tomotherapy-IMRT with 1-cm or 2-cm collimation.[39] The dose differences between step-and-shoot IMRT, and tomotherapy-IMRT were small, and the treatment times of these two techniques were normally less than 20 min. IMRT reduces the dose to the kidney (usually the left kidney) at the expense of spinal cord dose increment. A four-dimensional CT-based evaluation[40] also showed that IMRT plans could significantly reduce the renal doses compared with 3DCRT.

One study[41] retrospectively analysed patients with gastric cancer treated with AP-PA, 3D-conformal, and IMRT techniques and found a robust lower dose to the left kidney with IMRT than with the AP-PA and 3D-conformal techniques. As a result, nephrotoxicity was less severe with IMRT than with the other methods. Therefore, IMRT was recommended as the preferred radiotherapy technique for gastric cancer.

Contrary to these findings, Alani et al[42] showed that the advantage of IMRT was limited compared with non-coplanar 3DCRT. Moreover, the risk of a second cancer induced by radiation might increase.[43,44]

Whether 3DCRT or IMRT provides better protection of OARs remains controversial. This could be attributed to variation in the beam arrangement in the 3DCRT technique itself and to differences between 3DCRT and IMRT, as well as variation in the dose constraint requirements on OARs during plan optimization in the IMRT technique. However, we are inclined to believe that IMRT can improve the protection of OARs.

Volumetric modulated arc therapy

With the advent of novel delivery techniques,[45] literature on radiotherapy performed using the volumetric modulated arc therapy (VMAT) [RapidArc® (Varian Medical Systems, Palo Alto, CA) and VMAT] technique emerged in recent years. Wang et al[46] compared single-arc VMAT (SAVMAT) with 3DCRT and IMRT and found that SAVMAT and IMRT had similar dose distribution to the target, which was superior to that of the 3DCRT plans. SAVMAT showed improved left kidney and liver dose sparing compared with 3DCRT, whereas it failed to show an advantage over the IMRT technique. Li et al[47] compared IMRT plans with single-/double-arc VMAT plans and found that double-arc VMAT showed improved tumour coverage and better kidney dose sparing

than five-field (5F)-IMRT, and 5F-IMRT and SAVMAT, whereas no advantage was observed regarding liver dose sparing. Hu et al[48] adopted beam angle and multicriteria optimization for IMRT and compared it with the VMAT technique, which showed similar target coverage and OAR sparing. Taken together, these studies indicate that the dosimetric outcome of VMAT is not superior to that of the IMRT technique. However, VMAT shows advantages regarding the efficiency of delivery. Lesser monitor units and continuous delivery enable VMAT to treat patient with gastric cancer within a shorter time than when using the IMRT technique.[47,48]

Proton beam radiation therapy

Limited data are available to assess the outcomes of proton beam radiation therapy. A few case reports showed the efficacy of this technique; one study revealed persistent gastric ulcers at the primary lesion without remaining cancer cells after radiation, and another study showed <5% of residual tumour tissue.[49,50] For charged particle beams, target motion and anatomical changes should be considered carefully, as the radiologic depth may fluctuate widely from the entry surface to the target, along with target motion and anatomical changes.[51]

Motion and management

Respiratory-induced tumour motion is a substantial concern in the treatment of thoracic and abdominal tumours, as the dose actually delivered to the moving target and surrounding tissues may differ from the dose distribution planned on a static snapshot-like CT. This motion is one of the major uncertainties in gastric cancer radiation. In a comparison of inspiration and expiration breath-hold scans, Wysocka et al[52] measured a respiratory-induced stomach motion of 16.4, 8.8 and 1.7 mm in the CC, AP and left–right (LR) directions, respectively. Hu et al[53] reported a gastric tumour motion in free breathing mode of 11.1, 1.9 and 5.5 mm (AP) in the SI, LR and AP directions, respectively, by tracking the surgical clips in fluoroscopic images. Watanabe et al[54] showed that the intrafractional gastric motion was 11.7, 11.0, 6.5, 3.4, 7.1 and 6.6 mm in the superior, inferior, right, left, anterior and posterior directions, respectively. Several techniques were developed to address this concern in radiation treatment.

Breath-hold

The breath-hold technique helps patients voluntarily or passively hold their breath at a certain phase or position during image scanning and radiation treatment. Active breathing coordinate (ABC) is a breath-hold device that reduces target motion. The mean target motion for free breathing *vs* breath-hold using ABC was 11.1 *vs* 2.2 mm, 1.9 *vs* 1.1 mm and 5.5 *vs* 1.7 mm in the SI, LR and AP directions, respectively.[53] A dosimetric study indicated that IMRT performed using breath-hold could reduce the liver dose than IMRT with free breathing.[53] Hu et al[53] developed a passive breath-hold device and showed, in a pre-clinical study, that the diaphragm motion caused by respiration was reduced to <3 mm, and the diaphragm position in different gating periods was reproducible. Another option of the breath-hold device is abdominal compression. According to Blomgren et al,[55] diaphragm movement was approximately 10 mm during normal breathing when using the abdominal pressure technique.

Gating and tracking

Gating and tracking have been studied in patients with lung, liver and pancreatic cancers, but they have not yet been tested in gastric cancer. A dosimetric study[40] on respiration-gated radiotherapy showed that respiration-gated target volumes were up to 11% lower than free breathing target volumes, and a low dose to OARs such as the small bowel was achieved. However, it did not significantly decrease renal doses, possibly because of parallel movements of the stomach and kidneys during respiration.

Imaging studies

The introduction of imaging to RT optimizes the accuracy of radiation treatment. Conventional fluoroscopic imaging is used extensively as a simple way to track the diaphragm or fiducial markers to determine the target motion,[53,54] which is used as a reference for determining the margin of the planning target volume. Conventional CT in free breathing mode is associated with respiratory-related artefacts, leading to uncertainty about the position and volume of the target.[52] However, when combined with inspiration and expiration breath-hold, CT scanning may help define the target motion at the expense of time and labour.

Four-dimensional CT (4DCT) is the mainstay imaging modality, and it can depict thoracic and abdominal target motion trajectories and volume changes.[56] Hallman et al[57] characterized and quantified respiration-induced motion in the abdomen using 4DCT and discovered that abdominal organs moved in unison but with varying amplitudes. Therefore, using the movement of the diaphragm to identify the phase of abdominal organ motion is feasible.

Ultrasound imaging is a cost-effective, rapid and radiation-free imaging technique. However, direct sonographic imaging of the entire gastric tumour target is usually not possible because of visibility limitations caused by gastric air.[58] Nevertheless, the use of surrogate structures in ultrasound-based image-guided radiation therapy (IGRT) has been investigated, and the results showed that it is a feasible IGRT technique for gastric cancer treatment.[59] The visibility of ultrasound imaging depends on the weight of the patient, the presence of intestinal gas/filling and the preparation of the patient (empty stomach).

Regarding MRI, Schwizer et al[60] developed a novel methodology to measure gastric emptying and gastric motility, however, the application of MRI in IGRT remains under investigation.

Interfractional motion

During the fractionated period, anatomical changes caused by hollow organ filling, weight loss or gain, or tumour growth or shrinkage may happen. Wysocka et al[52] measured interfractional stomach motion during 5 weeks of treatment and showed that stomach motion in the CC, AP and LR directions was 7.2, 3.9 and 5.8, respectively, in the free breath CT scan; 6.5, 4.4 and 2.7, respectively, in the inspiration CT scan; and 3.9, 3.9 and 2.7, respectively, in the expiration CT scan. A case report[61] observed a surgical clip in the stomach under fluoroscopy and showed that it moved 24 mm in the LR direction and 8 mm in the CC

direction during RT, 2 and 4 weeks later. These studies indicated that interfractional variation can be pronounced in patients.

Image-guided radiotherapy

IGRT techniques are used to manage the interfraction position variability. Schwizer et al[60] used 2D kV-to-kV matching in gastric cancer IGRT. The accuracy of ultrasound-based IGRT for daily positioning was evaluated by Boda-Heggemann et al[59] and compared with the kilo voltage (kV)-CBCT IGRT technique. For those with good sonographic image quality, ultrasound improved the daily positioning accuracy, whereas in patients with poor sonographic image quality, daily kV-CBCT-based IGRT improved treatment accuracy. Sia et al[62] reported that fiducial markers were accurate for tumour delineation and enabled precise and safe delivery when used with IGRT. Megavoltage CT (MVCT) is used in different tumour sites as a daily IGRT technique to quantify systematic and random errors.[63] Johnson et al[64] used daily MVCT to analyse the interfraction variation of the stomach position in gastric lymphoma. Aggarwal et al[65] assessed the use of tomotherapy with MVCT to estimate the internal target volume of gastric tumours and showed that the target changes widely during the course of radiation treatment, and severe target displacements were observed. To deal with this problem, adaptive techniques for optimizing IMRT delivery can be helpful; however, further investigation is necessary.

A novel technique that combines breath-hold, IGRT and VMAT was clinically implemented and showed both dosimetric benefit and delivery efficiency,[66] revealing a new trend based on the combination and integration of techniques.

SUMMARY AND FUTURE DIRECTION

The dominant strategy for the management of LAGC is multimodality treatment. Evidence from clinical trials provides options for the use of combined approaches that include surgery, chemotherapy and radiation. Among the available approaches, surgery is the key component of treatment in patients with LAGC, and the aim of adjuvant CRT is to maximize the effectiveness of surgery. Given the success of neoadjuvant CRT in other gastrointestinal cancers, such as rectal cancer, neoadjuvant CRT is considered superior to adjuvant CRT for the treatment of LAGC. The encouraging outcomes of the CROSS[67] and POET[68] studies forecast a trend towards the application of neoadjuvant CRT in oesophagogastric cancer. However, further investigation is necessary to compare neoadjuvant CRT with current standard approaches and its feasibility in gastric cancer.

In conclusion, the optimal multidisciplinary management of LAGC remains undefined. Technical advances have enabled radiation oncologists to deliver precise doses of radiation and minimize the dose to critical organs, leading to improved therapeutic effects and decreased toxicity. Further studies integrating clinical and molecular factors as well as neoadjuvant CRT are warranted to optimize decision-making in LAGC.

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