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REVIEW

Role of radiation therapy in gastric adenocarcinoma

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Abstract

Outcomes in patients with gastric cancer in the United States remain disappointing, with a five-year overall survival rate of approximately 23%. Given high rates of local-regional control following surgery, a strong rationale exists for the use of adjuvant radiation therapy. Randomized trials have shown superior local control with adjuvant radiotherapy and improved overall survival with adjuvant chemoradiation. The benefit of adjuvant chemoradiation in patients who have undergone D2 lymph node dissection by an experienced surgeon is not known, and the benefit of adjuvant radiation therapy in addition to adjuvant chemotherapy continues to be defined.

In unresectable disease, chemoradiation allows long-term survival in a small number of patients and provides effective palliation. Most trials show a benefit to combined modality therapy compared to chemotherapy or radiation therapy alone.

The use of pre-operative, intra-operative, 3D conformal, and intensity modulated radiation therapy in gastric cancer is promising but requires further study.

The current article reviews the role of radiation therapy in the treatment of resectable and unresectable gastric carcinoma, focusing on current recommendations in the United States.

Key words: Radiation therapy; Gastric cancer; Stomach cancer; Chemoradiation; Adjuvant therapy; Neoadjuvant therapy; Intra-operative radiation therapy; 3D conformal radiation therapy; Intensity modulated radiation therapy

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EPIDEMIOLOGY

Worldwide, gastric cancer is the 5th the most common malignancy and the 2nd leading cause of cancer death. Significant geographic variation exists, with high risk areas including Japan, Central and South America, and Eastern Asia, and low risk areas including Kuwait, Israel, and the United States[1, 2]. Despite its relatively low incidence in the United States, gastric cancer is a significant cause of morbidity and mortality, with 22 000 cases per year, resulting in 13 000 deaths[3].

According to the Surveillance, Epidemiology, and End Results (SEER) database, 5-year survival rate for all gastric cancer patients treated in the United States from 1995 to 2001 was 23.2%. This represents an improvement from 15.3% in the time period from 1974-1976[4]. As expected, patients with localized disease have a higher 5-year survival rate (59%) compared to patients with regional (21.9%) or distant disease (3.1%)[4]. Unfortunately, only 25-40% of patients have localized disease at diagnosis.

Outcomes for patients in high risk countries such as Japan are generally better than outcomes in low incidence countries[2, 5]. This variation is likely due to earlier diagnosis (due to aggressive screening programs) and greater clinical experience in high risk countries, as well as differences in the etiology and biology of the tumors in high versus low risk countries[1,2]. The relative contributions of these factors to outcome and the implication for therapeutic decisions remains ill-defined.

Despite the poor prognosis for those patients with gastric cancer, progress has been made in their management. Improved surgical expertise, better systemic therapy, and the integration of radiation therapy have resulted in modest, but significant improvements in local control and survival. The current review article focuses on the role of radiation therapy in the management of gastric carcinoma in the United States.

PATTERNS OF FAILURE

Following surgical resection, both local and distant recurrences are common, indicating the importance of both local and systemic treatment. Patterns of failure have been reported in clinical series, re-operation series, and autopsy series. As expected, recurrences are greatest in autopsy series and least in clinical series, reflecting limitations in

Table 1 Patterns of relapse based on University of Minnesota re-operation series and autopsy series

	Univ. of Minnesota Re-operation series[10] (*n*=107)	Autopsy series[6-9]
Pattern of relapse	%	%
Gastric bed	55	52-68
Anastomosis	27	54-60
Abdominal wound	5	-
Peritoneal seeding	42	30-43
Lymph nodes	43[1]	52
Local-regional as any site	69	80-93
Local-regional only	23	-
Lymph Nodes only	7	-
Lymph nodes only in nodal dissection sites	3	-
Distant metastases	36	50

[1]Most common nodal sites of relapse were porta-hepatis, celiac, and para-aortic regions. Other sites were suprapancreatic, pancreaticoduodenal, and splenic hilar regions.

the ability to detect recurrences clinically. Patterns of recurrence based on re-operation and autopsy studies are summarized in Table 1.

In the University of Minnesota re-operation series gastrectomy patients underwent a "second look" procedure in the absence of known recurrence or a "symptomatic look" in the setting of known recurrence. Local-regional failure alone was detected in 23% of patients and local-regional failure as any component of failure was detected in 69% of patients. Autopsy series report even higher local-regional failure rates (80-93%)[6-9]. These findings suggest that improvements in local-regional control may be potentially curative and provide a strong rationale for adjuvant radiation therapy.

Distant metastases are reported in approximately 50% of patients by autopsy series[6, 7, 9]. The predominant site of distant organ failure is the liver, involved in 30% of patients at initial exploration[5]. Peritoneal seeding, considered distant metastatic disease, is also common, occurring in 42% of patients from the University of Minnesota re-operation series[10], and in 30-43% of patients based on autopsy series[6-9], Lung metastases are less common, observed in only 10% of cases in one autopsy series[5], These findings provide a strong rationale for adjuvant chemotherapy.

ADJUVANT THERAPY

Radiation alone

At least 2 randomized trials compared surgery alone to surgery plus radiation therapy in gastric carcinoma. These results are summarized in Table 2. The first trial, by the British Cancer Stomach Group, randomized patients to surgery alone, surgery followed by radiation therapy, or surgery followed by chemotherapy (mitomycin, adriamycin, and 5-FU). Of note, 40% of patients on this trial had gross or microscopic residual disease following surgery. No survival difference was detected, but the addition of radiation therapy to surgery resulted in a significant reduction in local recurrence (27% with surgery versus 10% with surgery plus radiation therapy)[11, 12]. Interestingly, 24% of patients on the radiation therapy arm did not receive any radiation, and 32% received a dose < 40.5 Gy (well below that required to control microscopic or gross disease). The benefit of adjuvant radiotherapy may be been greater if given to all patients and in adequate doses.

The second trial, by Zhang *et al* in Beijing, randomized 370 patients with gastric cardia carcinoma to neoadjuvant radiation therapy or surgery alone. Neoadjuvant radiotherapy resulted in improved survival (5-year overall survival was 30% *vs*. 20%, $P=0.009$), improved local control (61% *vs*. 48%, $P<0.025$), and improved regional nodal control (61% *vs*. 45%, $P<0.005$)[13]. Additionally, resection rates were higher in the neoadjuvant radiation arm (89.5%) compared to the surgery alone arm (79%, $P<0.01$). Operative mortality and morbidity did not differ between the two arms. While encouraging, this trial included only cardiac lesions, and it is unknown if these results can be generalized to include distal lesions.

While the British and Beijing trials yielded conflicting results regarding a survival advantage with radiation, both demonstrate significant improvement in local control. Local recurrence in gastric cancer has the potential for substantial morbidity, and thus local control alone is a valid endpoint in evaluating the value of neoadjuvant and adjuvant therapy, including radiation.

Chemoradiation

Three randomized trials have compared surgery alone to surgery plus adjuvant chemotherapy and radiation in gastric carcinoma. These trials are summarized in Table 2. The Mayo Clinic trial randomized 62 patients to surgery alone versus surgery plus adjuvant radiation therapy concurrent with 5-FU chemotherapy[14]. A significant improvement in overall survival and disease free survival was identified with the addition of chemoradiation when analyzed by intention to treat. The five-year survival rate for patients randomized to adjuvant chemotherapy and radiation was 23% compared to 4% for those randomized to no adjuvant therapy. When evaluated by actual treatment received, these benefits were no longer statistically significant. Local control was superior in the chemoradiation arm, although this difference did not reach statistical significance.

The trial by Walsh *et al* included primarily patients with adenocarcinoma of the esophagus, but 35% of patients had lesions involving the gastric cardia. Patients were randomized to surgery alone or neoadjuvant chemotherapy and radiotherapy followed by surgery. The addition of chemoradiation resulted in a statistically significant improvement in overall survival[15]. The median survival of patients assigned to preoperative chemoradiation therapy was 16 mo compared with 11 mo for those assigned to surgery alone ($P=0.01$). Three-year survival was 32% versus 6% favoring combined modality therapy ($P=0.01$).

The landmark trial in the combined modality treatment of gastric cancer in the U.S. is Intergroup 0116 study[16]. In this study, 556 patients with resected adenocarcinoma of the stomach or gastroesophageal junction (stage IB through IVM0 disease) were randomly assigned to surgery

Table 2 Randomized trials of adjuvant radiation therapy in gastric carcinoma

Reference	*n*	Survival			Local-regional relapse		
		Median (mo)	5-year (%)	*P* value	%	*P* value	
Mayo Clinic[14]							
Surgery alone		23	15	4	0.05	54	NS
Post-op EBRT + CT		39	24	23		39	
British stomach group[11, 12]							
Surgery alone		145	15	20	NS	27	<0.01 for
Post-op CT		138	13	19		19	
Post-op EBRT		153	17	12		10	EBRT
China-Beijing[13]							
Surgery alone		199	NR	20	0.009	52[1]	<0.025
Pre-op EBRT		171	NR	30		39	
Intergroup 0116[16]							
Surgery alone		275	27	41 (3 yr)	0.005	29	NR
Postop EBRT + CT		281	36	50 (3 yr)		19	
Walsh *et al*[15]							
Surgery alone		55	11	6 (3 yr)	0.01	NR	-
Preop EBRT + CT		58	16	32 (3 yr)			

Abbreviations: CT = chemotherapy, EBRT = external beam radiation therapy, NS = not significant, NR = not reported.

[1]Refers to local relapse. Regional relapse with 54% with surgery alone versus 39% with chemoradiation, $P < 0.05$.

plus postoperative chemoradiotherapy or surgery alone. The adjuvant treatment consisted of two cycles of 5-FU and leucovorin followed by two more cycles of chemotherapy concurrent with radiation therapy. Patients received 45 Gy of radiation in 25 fractions to the preoperative tumor volume, surgical bed, and regional lymph nodes. The majority of patients on this trial had advanced disease (66% were T3/4 and 85% were node positive) and surgical margins were required to be negative.

Three-year overall survival was improved from 41% to 50% with combined modality therapy ($P = 0.005$). The median survival was improved from 27 mo in the surgery only group to 36 mo in the chemoradiotherapy group ($P = 0.005$). Local regional relapse was decreased from 29% to 19% (*P* value not reported). Interestingly, distant metastases were higher in the chemoradiation arm (18% versus 33%), likely a result of patients living long enough to develop clinically detectable distant metastases.

Toxicity was significantly higher with chemoradiation, with nearly three-quarter of patients experiencing grade 3/4 toxicity, and 17% of patients were unable to complete radiation due to toxicity. However, treatment related mortality was low (1% on the chemoradiation arm versus 0% on the surgery alone arm) and overall chemoradiation appeared tolerable in light of its benefits. Postoperative chemoradiotherapy should be considered for all patients at high risk for recurrence of adenocarcinoma of the stomach who have undergone a potentially curative resection.

An important consideration in the interpretation of the Intergroup 0116 trial is the extent of surgery. At least 54% of patients received suboptimal lymph node dissection based on current National Comprehensive Care Network (NCCN) guidelines, raising the question of whether chemoradiation was simply compensating for inadequate surgery. The extent of lymph node dissection as it relates to outcome is discussed further below.

Extent of lymph node dissection and its impact on adjuvant therapy

A D1 lymph node dissection includes perigastric lymph nodes along the lesser and greater curvature. In addition to those nodes included in a D1 lymph node dissection, a D2 dissection includes lymph nodes along the left gastric artery, the common hepatic artery, the celiac trunk, the splenic hilum, and the splenic artery. A D3 lymph node dissection further includes lymph nodes along the hepatoduodenal ligament and the root of mesentery. A D4 lymph node dissection is a D3 dissection plus dissection of para-aortic and para-colic lymph nodes.

While D2 dissection (at a minimum) is considered standard in Japan, randomized Western trials have not shown a survival difference between D1 and D2 dissection, and have demonstrated a substantial increase in post-operative mortality (Table 3)[17, 18]. These trials have been criticized due to the unexpectedly high morbidity and mortality rates, which may be in part explained by the frequent use of pancreatectomy and splenectomy in patients undergoing D2 dissection (which is no longer considered necessary) and by surgeon inexperience[19-21].

In Japan, Maruyama *et al* reported an improvement in 5 year overall survival from 20.3% with D0 dissection to 41.2% with D1 dissection to 63.8% with D2 dissection[22]. Perhaps the greatest criticism of the Japanese data supporting extended lymph node dissection has been its retrospective and/or non-randomized nature. To address these criticisms, the Japanese recently completed a prospective, randomized trial comparing D2 versus D4 dissection. Although disease control data has not yet been reported, acute toxicity data show no difference.[21] Of note, D2 patients had in-hospital mortality rate of 0.8%, which is substantially lower than that reported in the MRC and Dutch trials.

The results of this trial will represent a tremendous contribution to the treatment of gastric cancer. Unfortuna-

Table 3 Randomized trials of D1 versus D2 lymph node dissection in gastric cancer

	MRC[18] (*n*=711)			Dutch[17] (*n*=400)		
Endpoint	D1	D2	*P* value	D1	D2	P value
5 year overall survival	45%	47%	NS	35%	33%	NS
Post-operative morbidity	25%	43%	<0.001	28%	46%	<0.001
Post-operative mortality	4%	10%	0.004	6.5%	13%	0.04

Abbreviations: NS = non-significant.

tely, it is unclear how and if the results of this trial can be applied to Western countries given significant differences in physician experience and patient populations compared to Japan. While surgeon training at tertiary centers in the United States may aid in addressing issues of surgeon experience, hospitals in the United States simply do not have the volume of gastric cancer patients seen in Japan, limiting the ability for surgeons to gain experience. Furthermore, patient related issues such as body mass index and age at diagnosis may differ by geographic location and may influence the risks and benefits of extensive nodal dissection[23].

Evaluation of the benefit of more extended nodal dissection is confounded by stage migration. Bunt *et al* reported that up to 75% of patients with stage IIB disease on D1 dissection are upstaged to IV on D2 dissection[24]. Therefore, when compared stage for stage, results with more extensive nodal dissection may appear superior.

Given these considerations, the optimal extent of lymph node dissection remains elusive. Per NCCN guidelines in the United States, at a minimum a D1 dissection is recommended. Furthermore, it is recommended that at least 15 lymph nodes be evaluated.

On the Intergroup 0116 trial, 10% of patients underwent D2 dissection, 36% underwent D1, and 54% underwent less than a D1 dissection[16]. Subset analysis did not detect differing effects of adjuvant treatment based on the type of lymph node dissection performed (adjuvant treatment appeared to be of benefit regardless of type of lymph node dissection)[25]. This observation is difficult to interpret based on the small number of patients actually treated with D2 dissection. The role of post-operative chemoradiation in patients who undergo D2 dissection by an experienced surgeon is, therefore, unknown.

Lim *et al* reported the outcome of 291 patients treated in Korea with D2 dissection and post-operative chemoradiation identical to that delivered on the Intergroup 0116 trial[26]. 5-year overall survival and local-regional failure were superior to that observed on the chemoradiation arm of the Intergroup 0116 trial, but it is unknown if these outcomes were related primarily to the use of D2 dissection, chemoradiation, or both. It is also unknown if the outcomes were related to surgeon experience and other confounding variables in Korea compared to the United States. The value of chemoradiation in patients who have undergone D2 dissection by an experienced surgeon can only be fully answered by a prospective, randomized trial.

Chemotherapy alone

While the randomized Intergroup 0116 trial showed a benefit in both local control and overall survival with adjuvant chemoradiation, the relative contributions of radiation versus chemotherapy to this benefits are unknown.

The aforementioned British Stomach Group trial, which randomized patients to surgery alone, surgery followed by radiation therapy, or surgery followed by chemotherapy, found no improvement in overall survival with chemotherapy compared to surgery alone or surgery and radiation[11, 12]. A randomized Southwest Oncology Group (SWOG) trial showed no benefit to adjuvant chemotherapy (5-FU, adriamycin, and mitomycin-c) following surgical resection[29]. To date, meta-analyses evaluating the role of adjuvant chemotherapy have demonstrated no or minimal benefit[27, 28].

More recently, however, a British MRC randomized trial (the MAGIC trial) showed an improvement in both overall survival and disease free survival with the addition of pre- and post-operative chemotherapy (epirubicin, cisplatin, and 5-FU) to surgery[30, 31]. Five-year overall survival was improved from 23% to 36% ($P=0.009$). This trial suggests a survival benefit with adjuvant chemotherapy in the absence of radiation therapy. Newer chemotherapeutic regimens may be superior and therefore provide a greater benefit compared to epirubicin, cisplatin, and 5-FU[30, 32-36].

While the results of the MAGIC trial demonstrate a survival advantage to adjuvant chemotherapy in the absence of radiation therapy, only an adequately powered, prospective randomized trial of chemotherapy with or without radiation therapy can fully evaluate the benefit of radiation treatment, and to date no such trial exists. A recent Korean trial treated 81 patients with resection (including D2 dissection) followed by chemotherapy alone (FU, cisplatin) versus chemotherapy (FU, cisplatin) before and after radiation concurrent with capecitabine. With short follow-up (15 mo) there is no difference in disease free or overall survival. Further follow-up is necessary to confirm these results, and radiation therapy should not be omitted on the basis of this trial alone[37].

Currently in the United States, NCCN guidelines recommend adjuvant chemoradiation following complete surgical resection in T3, T4, or node positive gastric cancer patients or in patients with microscopically positive margins. Adjuvant chemotherapy alone or adjuvant radiation therapy alone are considered investigational.

Pre-operative versus post-operative adjuvant radiation therapy

Based on the Intergroup 0116 trial, chemoradiation in the United States is most commonly delivered post-operatively. However, pre-operative radiation therapy offers a number

Table 4 Prospective trials of pre-operative chemoradiation in gastric cancer

Reference	Chemo	RT dose (Gy)	Overall survival % (2 yr)	Median survival time (mo)	Complete response (%)	Partial response (%)	R0 resection (%)	% Distant metastases during therapy	rate (%)
RTOG 99-04[46] (n=49)	5FU/LV/cis×2 prior to RT; 5FU with RT	45	NR	NR	27	NR	77	NR	
Roth[45] (n=19)	Cis/5FU	31.2, 38.4, 45.6[1]	71	NR	5	50	NR	0	
Lowy[41] (n=23)	5FU	45	NR	NR	11	63	NR	17	
Ajani 2004[43] (n=33)	5FU/LV/cis×2 prior to RT; 5FU with RT	45	54	33.7	30	24	NR	12	
Ajani 2005[44] (n=41)	5FU/cis/tax×2 prior to RT; 5FU/tax with RT	45	68[2]	Not reached	20	15[3]	78	0	
Balandraud[47] (n=42)	5FU/cis	45	45.6	23	14	-	81	-	
Klautke[67] (n=21)	Cis/5FU or tax	50.4	42	18	14	62	53	-	

Abbreviations: Cis = cisplatin, 5FU = 5-fluorouracil, LV = leucovorin, tax = paclitaxol, RT = radiation therapy, R0 = resection with negative margins.
[1]Given 1.2 Gy b.i.d. in a phase I dose escalation trial; [2]At a median follow-up of 36 mo; [3]PR defined as <10% residual cells in resected specimen.

of theoretical advantages. First, target tissues are better oxygenated prior to surgery, and radiation therapy is more effective against oxygenated tissues[38]. Second, pre-operative therapy may enhance the ability to perform R0 resection (defined as removal of all tumor such that surgical margins are histologically negative). The MAGIC trial demonstrated an improvement in potentially curative resection rates from 60% with surgery alone to 70% with pre-operative chemotherapy[30], and the Beijing trial demonstrated an improvement in resection rates from 79% with surgery alone to 89.5% with pre-operative radiation therapy[13]. A phase II, multi-institutional trial by the Radiation Therapy Oncology Group (RTOG 99-04) of pre-operative chemoradiation demonstrated a pathologic complete response rate of 27% and an R0 resection rate of 77%, which compares well to historical controls[39, 40]. Table 4 summarizes trials evaluating pre-operative chemoradiation in the setting of gastric carcinoma.

Third, preoperative treatment is generally better tolerated than postoperative treatment and patients are more likely to receive the prescribed doses of chemotherapy and radiation. For example, 88% of patients treated on a phase II trial of pre-operative 5-FU and radiation therapy were able to complete full dose chemoradiation[41], compared to 65% on the Intergroup 0116 trial, which delivered radiation and chemotherapy post-operatively[42]. Furthermore, during pre-operative therapy, distant metastases may manifest clinically and therefore spare patients unwarranted surgery. Prospective trials have reported the development of distant metastatic disease in 12-17% of patients during pre-operative chemoradiation, despite the use of staging laparoscopy at diagnosis[41, 43].

Pre-operative radiation also has potential risks. Perhaps most notably, a significant proportion of patients are under-staged clinically, and based on clinical stage may undergo unnecessary irradiation. Bonenkemp *et al* report that 29% of eligible surgical patients were discovered at laparotomy to have peritoneal, hepatic, or distant lymph node metastases[17]. Careful evaluation including endoscopic ultrasound, CT scans, and laparoscopy is therefore indicated prior to initiation of radiation therapy.

While the potential exists for increased surgical morbidity and mortality with pre-operative treatment, trials of pre-operative chemoradiation have yielded conflicting results in this regard[41, 43-47]. The RTOG 99-04 reported a 21% grade 4 toxicity rate but no treatment-related deaths, demonstrating that pre-operative therapy can be delivered in a multi-institutional setting with acceptable toxicity[46].

The timing of chemoradiation can only be definitively answered through a prospective, randomized trial. An ongoing European trial (SWS-SAKK-43/99) is randomizing gastric cancer patients to pre- versus post-operative chemotherapy; however, this trial does not use radiation and will not address the optimal timing of radiation therapy.

THE ROLE OF RADIATION THERAPY IN UNRESECTABLE GASRTIC CARCINOMA

Only 25-40% of patients with gastric adenocarcinoma will be able to under go potentially curative surgical resection[48]. While the prognosis of these patients is poor, radiation therapy with or without chemotherapy occasionally results in long-term survival (5 year survivals of 5-15%). However, this is not a viable alternative to resection (and adjuvant therapy as indicated) in patients who have resectable disease (Table 5).

Gastric adenocarcinoma is a radioresponsive tumor.

Table 5 Treatment results: Unresectable or residual gastric cancer

Reference	*n*	Treatment	Radiation therapy	Chemotherapy	Results
Randomized					
Mayo Clinic[51]	48	EBRT±CT	35-37.5 Gy in 4-5 wk	5FU 1st wk of EBRT	Median survival 13 *vs* 6 mo and 5-year overall survival 12% *vs* 0% favoring EBRT+5FU
GITSG[53]	90	CT±EBRT	50 Gy split course in 8 wk	5FU during EBRT, maintenance 5FU/MeCCNU	4-year survival 18% *vs* 7%, favoring CT+EBRT
EORTC[52]	90	EBRT±CT	55.5 Gy in 6 wk	5FU	14% long-term survival (3 patients) with EBRT and 5FU
Retrospective					
MGH[55]	32	EBRT±CT	45-55 Gy in 5-6 wk	5FU during EBRT, maintenance 5FU/MeCCNU	EBRT+CT: Unresectable disease 14 mo median survival; unresectable and residual disease 10% 4-year survival

Abbreviations: EBRT=external beam radiation therapy; CT=chemotherapy; 5FU=5-fluorouracil; MeCCNU=semustine; GITSG=gastrointestinal study group; EORTC=European organization for research and treatment of cancer; MGH=Massachusetts General Hospital; Gy=gray.

Wieland and Hymmen used radiotherapy alone in patients with unresectable gastric cancer. The radiation dose was 60 Gy when feasible, in 1.5 to 2.0 Gy fractions. They noted an 11% (9 of 82) 3-year and 7% (5 of 72) 5-year survival[49]. Abe and Takahashi reported a 14.7% 5-year survival rate with intraoperative radiation therapy (28 to 35 Gy) in a group of 27 patients with stage IV disease. In the same study, there were no 5-year survivors in the 18 stage IV patients randomized to a surgery-alone control arm[50].

Most phase III trials for unresectable or residual gastric cancer show an advantage for combined-modality treatment over single-modality treatment. Two randomized trials compared radiation therapy alone to chemoradiation. The seminal trial in the treatment of unresectable gastric cancer is from the Mayo clinic[51]. All patients were randomized to radiotherapy (35 to 37.5 Gy in 4 to 5 wk) with or without 5-FU chemotherapy during the first 3 d of radiation. Mean and overall survival was improved in the combined-modality treatment group compared to radiotherapy alone (13 *vs* 6 mo median survival and 12% *vs* 0% 5-year survival, respectively). The EORTC performed a randomized trial of radiation therapy with or without 5-FU chemotherapy following attempted surgical resection[52]. Residual disease after resection was identified in 22 patients and the three long-term survivors (14%) received both irradiation and 5-FU.

Two randomized trials compared chemotherapy alone to chemoradiation. In a study by the GITSG, 90 patients were randomized to radiation therapy and 5-FU followed by maintenance 5-FU/MeCCNU or 5-FU/MeCCNU alone[53]. The radiotherapy dose was 50 Gy given in a split course. This trial included patients with unresectable, gross, microscopic, or no residual disease after resection, though only 7 patients had no residual disease. Radiation and chemotherapy resulted in a statistically significant improvement in 4-year survival compared with chemotherapy alone (18% *vs* 6%, respectively). A second trial performed by the GITSG comparing radiation and chemotherapy to chemotherapy alone did not demonstrate a survival advantage to combined modality therapy[54]. However, the results from this second trial are difficult to interpret as nearly 50% of patients on the combined modality arm either did not receive the prescribed dose of radiation or had a major deviation in radiation delivery.

Data from retrospective series also suggest an improvement in disease control and survival with the combination of radiation therapy and chemotherapy. In published series from the Mayo Clinic and Massachusetts General Hospital (MGH), long-term survival of 10% or more has been demonstrated in patients receiving external beam radiation and chemotherapy following subtotal surgical resection with residual disease (MGH) or unresectable disease[55,56]. In the MGH experience, patients with unresectable or gross residual disease treated with combined radiation and chemotherapy had median survivals of 14 mo and 15 mo, respectively, and the overall four-year survival rate was 10%.

In the University of Pennsylvania experience with unresected adenocarcinoma of the GE junction or esophagus, both local control and overall survival was superior with combined modality versus single modality therapy[57]. Local control was 52% with radiation and chemotherapy, compared to 4% with radiation alone and 0% with chemotherapy alone. Median survival with radiation and chemotherapy was 10 mo compared with 5 mo for radiation alone. Overall, considering the randomized and retrospective data, there appears to be improved survival with combined radiation and chemotherapy for unresectable gastric cancer. However, the use combined-modality therapy in unresectable gastric cancer is tempered by the fact that relatively few of these patients will be long-term survivors.

To the best of our knowledge, there are no randomized trials of neoadjuvant radiation and chemotherapy in unresectable gastric adenocarcinoma. Neoadjuvant chemotherapy alone has been used in unresectable and locally advanced disease in numerous phase II and in at least one phase III trial. Wilke *et al* treated 34 patients with unresectable gastric cancer confirmed at exploratory laparotomy with etoposide, adriamycin and cisplatin chemotherapy[58]. Following chemotherapy and second look operation, fifteen patients (44%) underwent potentially curative resection and five patients (15%) were pathologic complete respon-

ders. Median survival in this phase II trial was 18 mo for all patients. In an update, 79% of these patients had local-regional failure[58].

Taken as a whole, neoadjuvant chemotherapy for unresectable gastric cancer results in clinical response rates of 30% to 68%, potentially curative resections in as few as 8% or as many as 73% of patients, high rates of local relapse, and except for the Wilke study, pathologic complete response rates of <15%. In view of the high incidence of local recurrence and relatively low pathologic complete response rates, radiation therapy has been integrated into neoadjuvant studies of unresectable gastric cancer. A recent US Intergroup trial, to confirm the Walsh trial[15], of neoadjuvant combined-modality therapy in esophageal and GE junction carcinoma was closed due to inadequate accrual.

In the purely palliative setting for gastric cancer, total or subtotal gastric resection can successfully relieve symptoms of obstruction, hemorrhage, and ulceration. In advanced gastric cancer, total gastrectomy for bulky or proximal tumors has resulted in good quality of life, but was less helpful for relief of symptoms due to linitis plastica[59]. In the absence of surgery, radiation therapy is effective in 50% to 75% of patients in the palliation of gastric outlet or biliary obstruction, pain, and bleeding[48]. In select patients with good performance status, the administration of concurrent 5-FU chemotherapy may improve response.

RADIATION THERAPY TECHNIQUES

Intra-operative radiation therapy

Intraoperative radiation therapy (IORT) delivers a single high dose of radiation to areas at high risk relapse. A substantial advantage of intraoperative radiation therapy is that normal tissues can be largely excluded from the radiation field, such that larger doses of radiation can be delivered to the target tissues and toxicity minimized. Although appealing, the role of intraoperative radiation therapy in the setting of gastric cancer remains ill-defined. Several studies suggest an advantage to IORT in locally advanced gastric carcinoma, but these trials do not define the role of IORT in patients receiving EBRT.

A randomized trial by Sindelar *et al* compared gastrectomy with IORT to gastrectomy with or without EBRT (EBRT was not used in early stage lesions confined to the stomach) in forty-one patients[60]. Survival was equivalent between the 2 arms, but local-regional control was superior on the IORT arm versus the control arm (64% versus 8% respectively; $P < 0.001$). Skoropad *et al* randomized patients with gastric cancer to pre-operative EBRT (20 Gy in 5 d) followed by IORT (20 Gy) plus gastrectomy versus gastrectomy alone[61]. The addition of radiation therapy had a statistically significant survival advantage in more advanced stages (T3-4 and/or node positive). In a randomized trial of 211 patients from Kyoto, Japan, patients were randomized to 28-35 Gy of IORT or surgery alone[62]. This study also demonstrated improved survival in patients with disease penetrating the wall of the stomach or in patients with involved lymph nodes, but not in patients with disease limited to the wall of the stomach. While these trials suggest an advantage to radiation therapy in locally advanced disease, they do not answer the question of whether EBRT alone, IORT alone, or EBRT plus IORT should be used. To date, no randomized trials exist evaluating EBRT with or without IORT.

Notably, prospective and retrospective trials have not demonstrated increases in morbidity and mortality with IORT[63]. Given its potential benefits and limited morbidity, IORT in the setting of gastric cancer continues to be used in select centers in the United States.

3D conformal and intensity modulated radiation therapy (IMRT)

Radiation therapy technique is important in evaluating the benefits of radiation. In the Intergroup 0116 trial, 2D radiation therapy with an anterior-posterior (AP) and a posterior-anterior (PA) radiation beam was utilized. Radiation therapy portals were centrally reviewed prior to radiation, and 34% had major protocol violations prior to revision. These findings demonstrate that trials without central review may suffer from inadequate radiation therapy field design, and suggest that the skill and experience of the treating radiation oncologist is important.

Technology has evolved over time to allow increasingly conformal radiation therapy, potentially sparing normal tissues and decreasing toxicity and/or allowing dose escalation to the target volume. However, as technology allows progressively more conformal treatment, the radiation oncologist must be increasingly mindful of known patterns of recurrence.

Two such targeted techniques are 3D conformal radiation therapy and intensity modulated radiation therapy (IMRT). 3D conformal radiation therapy uses 3D reconstruction of the target volume and normal tissues from CT data to plan multiple radiotherapy beams conforming to the target and sparing, as much as possible, normal tissues. Leong *et al* compared a 6-field 3D conformal radiation therapy plan a 2D AP:PA radiation therapy plan in 15 patients and noted lower radiation doses to the kidneys and spinal cord, both important radiation dose-limiting normal tissues[64]. Dose was higher to the liver with the 3D plans, but still well below tolerance. Princess Margaret Hospital treated 50 patients per the chemoradiation arm of the INT 0116 protocol, but used a 5-field 3D conformal radiation technique. Grade 3 or 4 toxicity occurred in 52% of patients, similar to the INT 0116 trial, suggesting minimal impact on toxicity compared to 2D radiation therapy.

Intensity modulated therapy, like 3D conformal radiation therapy, uses multiple beams with the shape of each beam conforming to the target. Unlike 3D radiation therapy, the intensity of radiation within any given beam varies such that normal organs are spared compared to target tissues. Planning studies of IMRT in the use of gastric cancer demonstrate decreased dose to the kidneys compared to conventional plans[65-67]. In treating abdominal organs, however, IMRT must be used with caution as intra-abdominal motion can be significant and highly conformal treatments can miss targeted areas. The role of IMRT in gastric cancer is not yet defined and remains investigational.

To date, 3D conformal and IMRT techniques have not

demonstrated a convincing reduction in acute or late radiation toxicity. However, both techniques offer great potential to decrease radiation toxicity by avoiding normal tissues and to allow dose escalation to target tissues.

CONCLUSION

From the available clinical data in the treatment of gastric carcinoma, the following conclusions can be reached: (1) Patterns of failure following surgical resection demonstrate high local and distant failure rates, suggesting a need for both local and systemic adjuvant treatment. (2) Adjuvant radiation therapy improves local control based on randomized trials. (3) Adjuvant chemoradiation improves survival in the randomized Intergroup 0116 trial, and adjuvant chemoradiation following complete resection with negative margins is currently considered standard of care in the United States. (4) Chemoradiation allows long-term survival in a small number of patients with locally advanced, unresectable gastric carcinoma.

However, each advancement in the treatment of gastric cancer leads to further questions, which should serve as the basis for future clinical trials: (1) In the adjuvant or neoadjuvant setting, what is the benefit of adding radiation therapy to chemotherapy? (2) Does adjuvant chemotherapy and/or radiation therapy provide benefit in patients who have undergone a D2 lymph node dissection? (3) Is pre-operative radiation therapy superior to post-operative radiation therapy? (4) Will conformal radiation technologies including IORT, 3D conformal, and intensity modulated radiation therapy improve outcomes?

Despite its disappointing survival rates, the treatment of gastric carcinoma has improved modestly over time. Radiation therapy has a role in the adjuvant setting for improving local control and, in combination with chemotherapy, survival. Radiation therapy in unresectable disease provides effective palliation and, in combination with chemotherapy, long term survival in a small number of patients.

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