World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v22.i3.1131

World J Gastroenterol 2016 January 21; 22(3): 1131-1138
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

2016 Gastric Cancer: Global view

Adjuvant radiochemotherapy for gastric cancer: Should we use prognostic factors to select patients?

Linda Agolli, Riccardo Maurizi Enrici, Mattia Falchetto Osti

Linda Agolli, Riccardo Maurizi Enrici, Mattia Falchetto Osti, Radiation Oncology, Sant'Andrea Hospital, 00189 Rome, Italy

Author contributions: Agolli L wrote the paper; Agolli L and Maurizi Enrici R analyzed the literature and selected accurately the cited articles; Osti MF and Maurizi Enrici R critically reviewed/revised the present review; all authors read and approved the final manuscript.

Conflict-of-interest statement: The authors have no conflict of interest to report.

Correspondence to: Linda Agolli, MD, Radiation Oncology, Sant'Andrea Hospital, Via di Grottarossa 1035-1039, 00189 Rome, Italy. linda.agolli@gmail.com
Telephone: +39-63-3776160
Fax: +39-63-3776608

Received: April 29, 2015
Peer-review started: May 12, 2015
First decision: August 25, 2015
Revised: September 24, 2015
Accepted: November 24, 2015
Article in press: November 24, 2015
Published online: January 21, 2016

Abstract

Radiotherapy has a not well-established role in the pre-operative and in the post-operative setting in gastric cancer (GC) patients. Randomized trials report controversial outcomes and impact on survival. In the D2 loco-regional node resection era, after a well-performed radical surgery, local treatment using radiotherapy combined to chemotherapy should be considered for locally advanced GC. Prognostic factors could help the better selection of subgroups that present high risk of loco-regional recurrence. Then, the addition of radiotherapy could improve the disease-free survival and also quality of life. There are no large prospective studies that have assessed specific factors predicting for recurrence or survival, but only retrospective series, some of them including high number of patients with homogeneous characteristics. In locally advanced GC adding radiotherapy to the post-operative chemotherapy seems to improve outcomes and quality of life. Prognostic factors such as T-stage, N-status, nodal ratio, and other histological factors should be considered to submit patients to post-operative combined treatment. Larger prospective series are necessary to investigate the role of combined chemoradiation after radical D2-resection, especially in locally advanced GC. Further prospective investigations are needed to suggest prognostic factors that have significant impact on survival and recurrence, improving the management and outcomes, particularly in locally advanced GC patients.

Key words: Gastric cancer; Adjuvant radiotherapy; Prognostic factors; Locally advanced disease; Selected patients

Core tip: This is a review of the recent literature that analyze the impact of prognostic factors in patients affected by gastric cancer (GC). The results from the principal clinical trials regarding treatment for GC patients are controversial. Adjuvant therapy for locally advanced disease remains undefined in different countries. Prognostic factors can help clinicians to select

those patients who can benefit more from combined post-operative therapy with radiochemotherapy and should be considered in the multidisciplinary meetings.

Agolli L, Maurizi Enrici R, Osti MF. Adjuvant radiochemotherapy for gastric cancer: Should we use prognostic factors to select patients? *World J Gastroenterol* 2016; 22(3): 1131-1138 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i3/1131.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i3.1131

INTRODUCTION

Gastric cancer (GC) is the sixth most common type of cancer in Europe and has a poor prognosis. The 10-year survival for all stages is around 20%[1]. Asian patients have significantly longer median survival (35 mo *vs* 23 mo, $P < 0.0001$) than the Caucasian population[2]. The 5-year survival for GC is 54%-58% in Japan and South Korea and about 40% in other countries[3,4]. Surgery is the primary treatment for patients with resectable GC, but the prognosis of advanced GC remains poor. Therefore, a multidisciplinary approaches required due to the high risk of loco-regional and distant recurrence of GC. Several studies were conducted to find the optimal chemotherapy regimen and radiotherapy (RT) patterns in order to reduce toxicity rates and to increase the efficacy.

Several treatment strategies that include adjuvant chemotherapy, adjuvant chemoradiotherapy (CRT), and pre-operative chemotherapy have been evaluated[5-8]. Also, more intensified regimens have been evaluated in advanced stage GC, but high toxicity rates have been observed. In resectable GC, the benefit of adjuvant chemotherapy has been clearly demonstrated, principally in the locally advanced disease, because of the propensity of this disease to develop distant metastases. Even though, from recent randomized trials has emerged that in D2-resected GC patients the addition of radiotherapy to chemotherapy does not appear to provide any additional advantage[5].

Radical surgery associated to D2 lymph node dissection is widely used for advanced GC[9,10], but there are controversial data in the literature. Studies demonstrated rates of 3-year overall survival (OS), disease-free survival (DFS) and local control of 60.6%, 54.1% and 84.3%, respectively, in patients that received a D2 node resection and adjuvant chemoradiation[11]. Others reported rates of distant relapse from 30% to 50%[12]. A multidisciplinary management, including neoadjuvant combined treatment and targeted therapy has emerged for advanced GC resulting in increased curability and improved survival[13].

Adjuvant radiotherapy associated to concurrent chemotherapy was demonstrated to have favourable effects on survival and disease control. Post-operative combined treatment in high-risk patients with GC reduced loco-regional failure and increased survival rates compared to surgery alone[6], or to adjuvant chemotherapy alone, or to RT alone[14].

Although meta-analyses had shown a small survival benefit after post-operative chemotherapy[15-17] several studies did not demonstrate such survival improvement. In the current clinical practice adjuvant chemotherapy is routinely used for locally advanced GC patients after radical resection. The role of radiation therapy remains controversial. To date, there is no evidence of clear benefit of the use of radiotherapy in the pre-operative or post-operative setting. The association to adjuvant CRT can be useful in the locally advanced GC to prevent loco-regional relapse, but the real benefit on survival remains to be demonstrated compared to the adjuvant chemotherapy alone.

The aim of these review is to analyze the potential prognostic factors that may help to select high-risk categories of patients who may benefit from an adjuvant radiochemotherapy, in the era of radical surgery associated with D2 node dissection and modern techniques of radiation therapy.

ROLE OF ADJUVANT CHEMORADIATION IN THE RANDOMIZED TRIALS

In the United States, post-operative CRT has become the standard of care after radical surgery for locally advanced stage since the randomized trial by Macdonald *et al*[6] that demonstrated a significant survival benefit compared to surgery alone ($P < 0.001$), even after long-term follow up[18]. High rates of severe toxicities were observed, maybe due to the conventional two-dimensional (2D) RT technique, which increased the irradiated volume and the dose to the normal tissue.

In Europe, the most frequent approach for resectable GC is pre-operative and/or post-operative chemotherapy. In 2006, the MAGIC study demonstrated a 5-year OS improvement (36% *vs* 23%, $P = 0.009$) in patients receiving pre-operative chemotherapy and subsequent post-operative chemotherapy compared to those receiving surgery alone[8]. The main limit of this trial was the low adherence to the postoperative chemotherapy, administered to 55% of the patients; only 42% of the patients received the entire treatment because of cancer progression, surgical complications, and toxicity.

The National Cancer Center in South Korea conducted a phase Ⅲ trial that enrolled only locally advanced GC patients (stage Ⅲ/Ⅳ M0) who underwent D2-dissection to compare post-operative chemotherapy alone versus CRT (INT-0116 regimen)[19]. The study was closed due to poor accrual, but the addition of RT significantly prolonged the 5-year loco-regional recurrence-free survival (93.2% *vs* 66.8%, $P = 0.014$) and DFS rates (73.5% *vs* 54.6%, $P = 0.056$) compared to chemotherapy alone.

High rates of severe toxicities have been described

Table 1 Characteristics and outcomes of principal phase Ⅲ randomized trials that compared radiotherapy associated to chemotherapy or chemotherapy in patients affected by gastric cancer

Trial	Year	Surgery (node resection)	Locally advanced	Randomization scheme	RT dose	RT technique	Median FU	OS	DFS, PFS	Limits
SWOG/ INT-0116[6]	2001	D1 90% D2 10%	85%	S-alone *vs* S + CRT	45 Gy	2D	60 mo	3-yr: 50% *vs* 41% (P = 0.005)	3-yr: 48% *vs* 31% (P < 0.001)	Low rates of D2 node dissection
MAGIC[8]	2006	D1 35% D2 77%	71%	S-alone *vs* CT + S + CT	-	-	49 mo	5-yr: 23% *vs* 36% (P = 0.009)	3-yr: 26% *vs* 38% (P < 0.001)	Low adherence to post-operative CT
NCC, South Korea[19]	2012	D2 100%	98%	S + CT *vs* S + CRT	45 Gy	2D/3D	87 mo	5-yr: 65% *vs* 55% (P > 0.05)	5-yr: 61% *vs* 50% (P > 0.05)	Poor accrual
ARTIST[7]	2012	D2 100%	86%	S + CT + CRT + CT *vs* S + CT	45 Gy	2D/3D	53 mo	NR	3-yr: 78% *vs* 74% (P = 0.086)	Planned events not reached

RT: Radiotherapy; FU: Follow up; OS: Overall survival; DFS: Disease-free survival; PFS: Progression-free survival; S: Surgery; CT: Chemotherapy; CRT: Chemoradiotherapy; 2D: 2-dimensional; 3D: 3-dimensional; NR: Not reported.

in patients treated with combined adjuvant therapy due to 2D RT technique that increased the irradiated volume. Modern RT techniques such as 3D conformal RT and intensity modulated radiotherapy (IMRT) allow high doses to be delivered to the target and lower doses to the surrounding sparing normal tissues leading to lower toxicity rates[20].

The ARTIST trial investigated the role of post-operative CRT (capecitabine + cisplatin followed by capecitabineand concurrent RT 45Gy) *vs* chemotherapy alone (capecitabine + cisplatin) in 458 patients with curatively resected GC who underwent D2 lymph node dissection[7]. Overall, the addition of RT to the chemotherapy did not significantly prolong DFS. However, in the subgroup of patients with positive pathologic lymph nodes at the time of surgery (n = 396), randomly assigned to the adjuvant chemoradiation arm experienced superior DFS when compared with those who received chemotherapy alone (P = 0.0365). The statistical significance was retained at multivariate analysis (P = 0.047). Only the 41% of the patients had a locally advanced stage in the ARTIST trial, including also a high percentage of patients with early stage who may present low risk of loco-regional recurrence after a well-conducted D2-resection. The principal randomized studies, their outcomes and limits are summarized in Table 1.

The ongoing ARTIST Ⅱ trial aims to evaluate this issue; the benefit of adjuvant combined therapy only in pN+ patients. The ongoing CRITICS trial aims to evaluate the clinical outcome in patients treated with pre-operative chemotherapy (epirubicin, cisplatin and capecitabine) followed by surgery with adequate node dissection and concurrent chemoradiation (45 Gy, cisplatin and capecitabine)[21].

The role of adjuvant RT remains unclear after an adequate lymphadenectomy, but is seems that a selected category of patients may benefit from local treatments having also impact on survival.

POST-OPERATIVE CHEMORADIATION AFTER D2 LYMPH NODE RESECTION

However, it is difficult to estimate the N stage, to predict survival rate in each stage and to decide treatment pre-operatively based on the clinical TNM stage[22]. In the INT-0116 a longer survival was demonstrated for patients in the chemoradiation arm, but the study was criticized because only 10% of included patients underwent a D2 lymphadenectomy (Figure 1). Therefore, the benefit of extended lymph-adenectomy (D2/D3) remains a controversial issue[6].

In Eastern countries, the D2 node dissection is widely performed as standard surgical procedure. A Korean study demonstrated an advantage of adjuvant CRT for patients with GC who underwent D2 node resection[23]. On the other hand, a Dutch randomized trial[24] did not support a survival improvement even after a long-term follow-up of 15 years, but showed lower loco-regional recurrence and GC-related death in the D2-group compared to the D1 group (Figure 2). Moreover, a higher rates of complications and post-operative deaths after D2 dissection[25-27].

The current opinion in the identification of high-risk subgroups for loco-regional recurrence among D2-dissected patients is of higher priority than assessing adjuvant CRT in all D2-dissected GC patients, principally after the recent ARTIST trial results[7].

The subgroup analysis in the ACTS-GC trial demonstrated a survival advantage after post-operative S-1 chemotherapy compared to observation in very advanced stage GC with pN3 nodal involvement over N0-N2 patients[28]. These findings may indicate that the employment of RT could improve outcomes in patients at high risk for loco-regional recurrence with high number of positive lymph nodes.

Only a few small prospective or retrospective studies have investigated the role of adjuvant CRT in D2-dissected GC patients[23,29-31], reporting lower

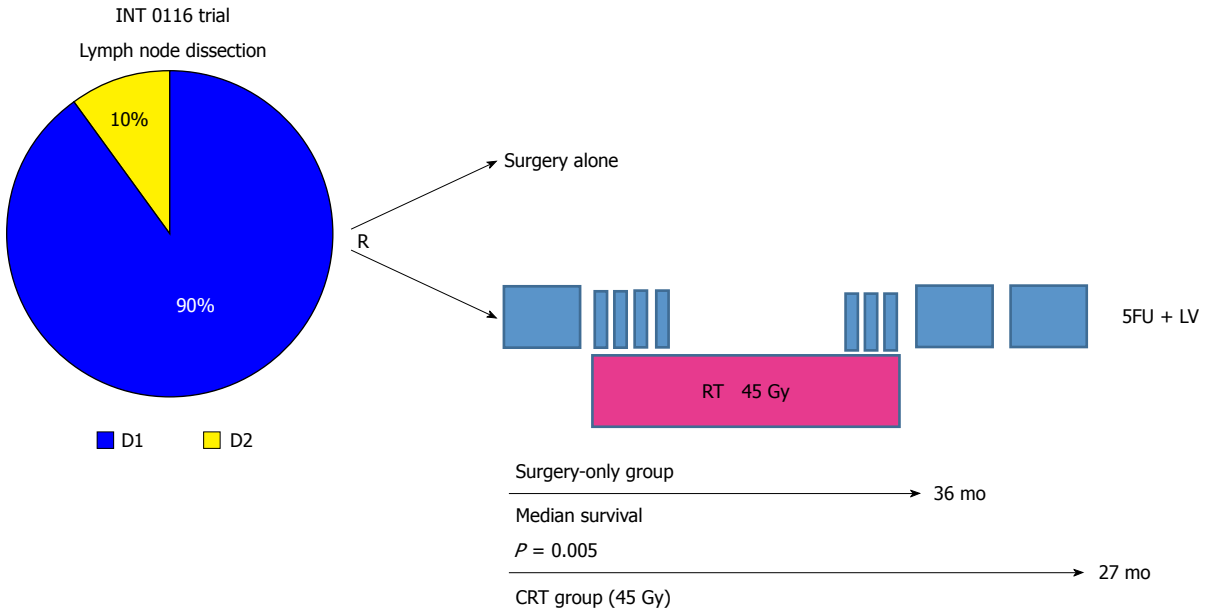

Figure 1 Randomization, treatment schemes and outcomes of the INT-0116 trial by Macdonald *et al*. LV: Leucovorin; 5-FU: 5-fluorouracil; RT: Radiotherapy; CRT: Chemoradiotherapy.

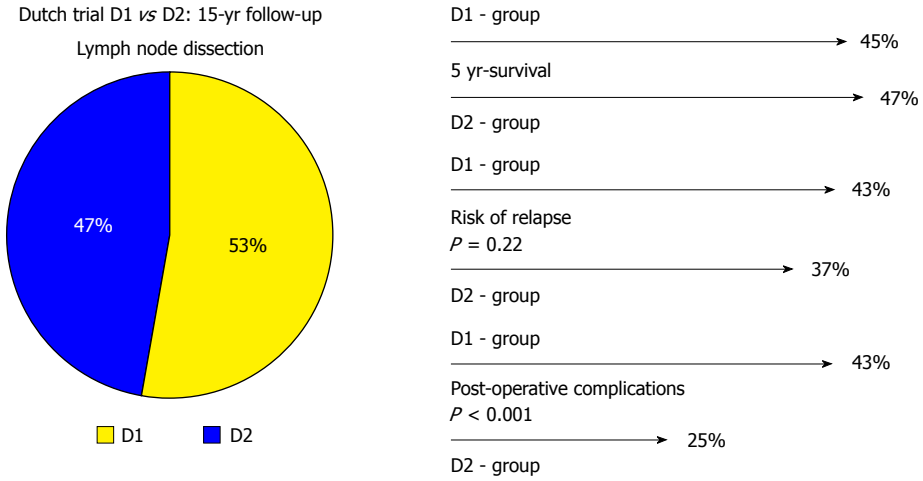

Figure 2 Long-term outcomes after 15 years follow up of the Dutch randomized trial by Bonenkamp *et al* D1 *vs* D2 node dissection.

recurrence rates obtained with adjuvant CRT after D1-dissection, but not after D2 dissection. However, the updated analysis of the INT-0116 study after a median follow-up of 10-years[18] demonstrated a persistent benefit of post-operative CRT regarding the loco-regional control of the disease, but not the distant recurrence.

A randomized multicenter Chinese study[32] compared 45 Gy IMRT plus concurrent chemotherapy (C-IMRT) with chemotherapy alone in GC patients after D2 resection. Survival was not significantly different between the two groups. The C-IMRT was associated with increased median duration of RFS (36 mo *vs* 50 mo, $P = 0.029$) (Figure 3). On the multivariate analysis lymph nodes metastases and TNM stage were both independent prognostic factors, but not correlated to treatment modality. Rates of all grade adverse events were similar in the two treatment groups.

The D2 dissection has been recently recommended as the standard surgical method worldwide, data on the influence of clinical results is now available from both Eastern and Western studies[27]. Larger prospective series are necessary to investigate the role of combined chemoradiation after radical D2 resection, especially in locally advanced GC.

T-STAGE, N-STATUS AND NODAL RATIO

The TNM classification has an appropriate prognostic value for predicting the OS of GC patients after curative surgery[33]. Therefore, for stage IB GC patients (T1N1M0 and T2N0M0) the relapse rates are low and the OS are around 87.3%-95.5% at 3-years and 81.8%-95.5% at 5-years, respectively, presenting

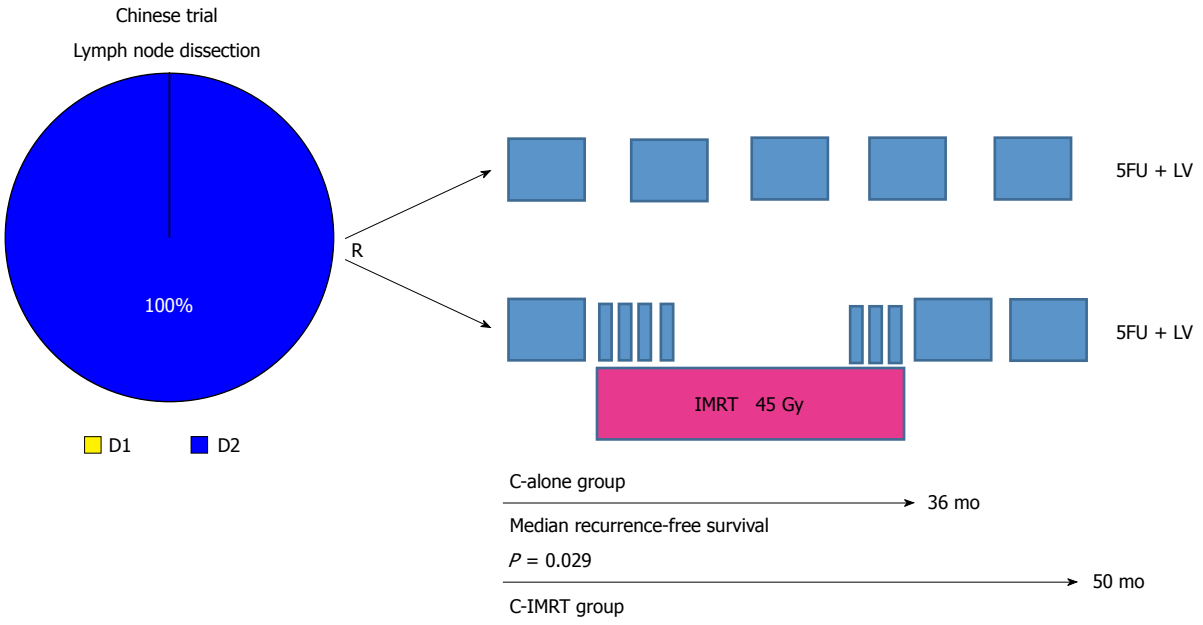

Figure 3 Randomization, treatment schemes and outcomes of the Chinese trial by Zhu *et al*. LV: Leucovorin; 5-FU: 5-fluorouracil; IMRT: Intensity modulated radiotherapy; C: Chemotherapy.

lower rates for upper third located tumors, when no post-operative therapy is administered after radical resection[34]. This means that locally advanced stage could benefit more from an intensified additional treatment with chemotherapy associated or not to radiotherapy.

Prognostic factors could help the better selection of subgroups that present high risk of loco-regional recurrence. Then, the addition of radiotherapy could improve the DFS and also quality of life. There are no large prospective studies that have assessed specific factors predicting for recurrence or survival, but only retrospective series, some of them including high number of patients with homogeneous characteristics.

Gross inspection and the macroscopic diagnosis of tumor invasion through the serosa seem to have a strong impact on tumor recurrence in GC patients. A total of 370 patients with locally advanced pT2-T4a GC who underwent curative surgery were evaluated for potential correlation between pT-stage and recurrence[35]. Significant differences were observed in the 5-year DFS according to the pathological T-stage between pT2 (83.2%), pT3 (64.5%), and T4a (28.0%) patients. On the multivariate analysis macroscopic diagnosis (P = 0.019) and lymph node metastasis (P < 0.001) were independent risk factors for recurrence. Consequently, the gross appearance of serosal invasion should be considered as a factor to predict prognosis and to select high-risk patients.

A retrospective study from a large series of 244 patients with long term follow up time (median 99 mo) treated with postoperative CRT (46 Gy) *vs* RT alone, analyzed long-term survival probability and the impact of variables on survival[36]. The 1-, 3-, 5- and 10-year actuarial OS were 79%, 37%, 24% and 16%, respectively. Actuarial progression free survival was 69%, 34%, 23% and 16% in the same consecutive order. On the multivariate analysis, stage Ⅰ-Ⅱ disease, subtotal gastrectomy and adjuvant CRT were significantly associated with improved OS and PFS. Surgical margin status and/or lymph node dissection type (D0 *vs* D1 *vs* D2-3) were not prognostic factors for survival.

A multicenter retrospective analysis of 232 patients with pT3 GC who underwent curative gastrectomy and D2 node dissection demonstrated that the median survival of patients with small tumor size (≤ 8 cm) was significantly better than for patients with large tumor size (> 8 cm) (107 mo *vs* 18.2 mo, P < 0.001). In the univariate analysis, tumor size (P < 0.001), pN stage (P = 0.000), metastatic lymph node ratio (LNR) (P = 0.005), lymphatic vessel invasion (P = 0.000), blood vessel invasion (P = 0.000), and perineural invasion (P = 0.006), were found to be significant prognostic factors for OS[37].

Kim *et al*[38] showed after a retrospective analysis of 679 resected GC patients that pre-operative CA125 level was an independent risk factor for distant/loco-regional recurrence (P = 0.02).

The lymph node status and a cut-off of ratio between the involved and the removed lymph nodes have consented to select patients with better prognosis. The involvement of 1-2 lymph nodes (N1) was associated with a better prognosis compared to N2 (3-6 positive nodes) involvement with a significant difference in (P = 0.04) 5-year OS rates (67.5% for N1 *vs* 43% for N2)[39].

Usually, the LNR is higher in patients with stage Ⅲ GC than in those with stage Ⅰ or Ⅱ disease. Advanced stage patients with GC are more at risk to develop

loco-regional/distant relapse. The prognostic value of metastatic LNR was investigated in patients who received radical resection and D2 lymphadenectomy in 365 patients with stage Ⅲ gastric GC[40]. The LNR is an independent prognostic factor for survival in stage Ⅲ GC and is superior to the pN category in TNM staging. It may be considered as a prognostic variable in future staging system.

Prognostic factors were evaluated in 120 resected GC patients treated in a single Institution using the Intergroup 0116 study regimen[41]. On multivariate analysis, surgical positive margin and advanced sage were significant prognostic factors for loco-regional recurrence ($P = 0.03$, $P = 0.04$).

A SEER database that investigated the impact postoperative radiotherapy on survivals in the INT0116 results, reported among lymph node-positive patients a significant survival benefit from RT compared with no-RT ($P < 0.0001$)[42]. The median survival and the 5-year OS among lymph node-positive patients were 29 mo and 34%, respectively, for post-operative RT group, and 19 mo and 20%, respectively, for no-RT. The multivariate analysis demonstrated that removing ⩾ 15 lymph nodes was an independent predictor for improved survival, whereas tumor classification, lymph node status, tumor size, and tumor location were independent predictors of death.

A retrospective study including patients with GC who underwent D2 lymphadenectomy followed by adjuvant CRT or was not analyzed to find individuals category that could benefit from combined post-operative treatment. Patients who had lymph node metastasis presented a significant improvement in OS ($P = 0.023$) with the addition of adjuvant CRT[43]. Patients with N1 and N2 tumors and higher N-ratio had similarly superior survival numbers with the addition of CRT, even the results were not statistically significant.

Another retrospective study[44], including only patients affected by locally advanced GC (T3-4 and/orN+) who underwent gastrectomy + D2 lymph node dissection followed by adjuvant CRT, or CRT + intra-operative radiotherapy (IORT) 12-15Gy, revealed that adjuvant IORT was an independent prognostic factor for both loco-regional control and OS ($P = 0.02$ and $P = 0.04$, respectively). Other significant prognostic factors for loco-regional control included the positive surgical margin ($P = 0.005$) and positive pN status ($P = 0.03$). In contrast, pT and pN stage were significant prognostic factors for OS. Intensified local therapy could also improve survival in locally advanced stage GC patients, in particular in those with high number of positive lymph nodes at the histological examination allowing acceptable toxicity rates. Other recent retrospective studies reported that LNR and N-stage were the most important prognostic factors for OS, DFS and loco-regional control[12,41,45].

Considering the above reported outcomes, the addition of radiation therapy could improve the RFS in patients with large gastric tumors, advanced stage and high number of involved lymph nodes even after D2-resection.

POSITIVE SURGICAL MARGIN (R1), HISTOLOGICAL SUBTYPE AND PERINEURAL INVASION

A microscopically positive (R1) resection is an adverse prognostic factor GC patients after radical surgery[46]. However, the prognostic significance of an R1 resection in GC patients treated with post-operative CRT has been hardly studied. The surgical margin status was rarely evaluated as a prognostic factor to recurrence. A retrospective analysis included 110 patients to evaluate the effect of an R1 resection on RFS in GC patients who received CRT (45 Gy/25 fractions) after surgery. Three-year RFS (45% *vs* 35%, $P = 0.34$) and OS (47% *vs* 48%, $P = 0.58$) did not significantly differ between patients who had undergone an R0 or R1 resection[47]. Maybe the adjuvant CRT is useful in this subgroup of patients, but larger series are necessary to confirm this issue. In a recent update of the INT-0116 study, the benefit of adjuvant CRT after a radical (R0) resection for GC was confirmed[18].

There are no studies assessing histological subtype for predicting response to therapy, relapse or survival. There is reported that intestinal subtype is more common and less aggressive compared to the diffuse subtype. Lauren classification has emerged as a significant independent predictors of survival in retrospective analysis[48], but less is known about patterns of recurrences in this subgroup of patients affected by locally advanced GC. No direct correlation with local recurrences still described in the literature.

Perineural invasion (PI) has been investigated as a possible prognostic factor in 30590 GC patients who had undergone curative gastrectomy from 24 studies. The median rate of positive PI was 41% and it resulted an independent prognostic factor for OS and recurrence ($P = 0.000$, respectively), but this effect was independent of lymph node status, tumor size and the depth of invasion on multivariate analysis[49].

Patients affected by advanced GC that present some particular characteristics at the definitive histological examination such as positive surgical margin (R1), PI, or diffuse histological subtype may be considered as high-risk categories. These finding are supported only by some retrospective analyses and seem to significantly correlate with survival[36,43]. This category of patients may benefit from more intensified treatment adding local irradiation to prevent recurrence.

CONCLUSION

Nowadays, radiotherapy has a not well-established role in the pre-operative and in the post-operative setting in GC patients. Randomized trials report

controversial outcomes and impact on survival. In the D2 resection era, after a well-performed radical surgery, local treatment using radiotherapy combined to chemotherapy should be considered for locally advanced GC. Even there are no strict indications to combined adjuvant therapy, a multidisciplinary discussion should guide definitive decision. Prognostic factors may help clinicians to select high-risk categories of patients who may benefit from a more intensified regimen including radiotherapy. Unfortunately, only retrospective series indicate selection criteria providing low level of evidence, but large and homogeneous population of patients have been evaluated. Further prospective investigations are needed to suggest prognostic factors that have significant impact on survival and recurrence, improving the management and outcomes, particularly in locally advanced GC patients.

REFERENCES

1 **Yao JC**, Mansfield PF, Pisters PW, Feig BW, Janjan NA, Crane C, Ajani JA. Combined-modality therapy for gastric cancer. *Semin Surg Oncol* 2003; **21**: 223-227 [PMID: 14648779]

2 **Wang J**, Sun Y, Bertagnolli MM. Comparison of gastric cancer survival between Caucasian and Asian patients treated in the United States: results from the Surveillance Epidemiology and End Results (SEER) database. *Ann Surg Oncol* 2015; **22**: 2965-2971 [PMID: 25631065 DOI: 10.1245/s10434-015-4388-4]

3 **Allemani C**, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, Bannon F, Ahn JV, Johnson CJ, Bonaventure A, Marcos-Gragera R, Stiller C, Azevedo e Silva G, Chen WQ, Ogunbiyi OJ, Rachet B, Soeberg MJ, You H, Matsuda T, Bielska-Lasota M, Storm H, Tucker TC, Coleman MP. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet* 2015; **385**: 977-1010 [PMID: 25467588 DOI: 10.1016/S0140-6736(14)62038-9]

4 **Gomez SL**, Noone AM, Lichtensztajn DY, Scoppa S, Gibson JT, Liu L, Morris C, Kwong S, Fish K, Wilkens LR, Goodman MT, Deapen D, Miller BA. Cancer incidence trends among Asian American populations in the United States, 1990-2008. *J Natl Cancer Inst* 2013; **105**: 1096-1110 [PMID: 23878350 DOI: 10.1093/jnci/djt157]

5 **Oh DY**, Bang YJ. Adjuvant and neoadjuvant therapy for gastric cancer. *Curr Treat Options Oncol* 2013; **14**: 311-320 [PMID: 23686725 DOI: 10.1007/s11864-013-0238-4]

6 **Macdonald JS**, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; **345**: 725-730 [PMID: 11547741]

7 **Lee J**, Lim do H, Kim S, Park SH, Park JO, Park YS, Lim HY, Choi MG, Sohn TS, Noh JH, Bae JM, Ahn YC, Sohn I, Jung SH, Park CK, Kim KM, Kang WK. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. *J Clin Oncol* 2012; **30**: 268-273 [PMID: 22184384 DOI: 10.1200/JCO.2011.39.1953]

8 **Cunningham D**, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**: 11-20 [PMID: 16822992]

9 **An JY**, Cheong JH, Hyung WJ, Noh SH. Recent evolution of surgical treatment for gastric cancer in Korea. *J Gastric Cancer* 2011; **11**: 1-6 [PMID: 22076195 DOI: 10.5230/jgc.2011.11.1.1]

10 **Lee JH**, Kim KM, Cheong JH, Noh SH. Current management and future strategies of gastric cancer. *Yonsei Med J* 2012; **53**: 248-257 [PMID: 22318810 DOI: 10.3349/ymj.2012.53.2.248]

11 **Leong CN**, Chung HT, Lee KM, Shakespeare TP, Mukherjee RK, Wong LC, Lu JJ, Tey J, Lim R, So JB, Back MF. Outcomes of adjuvant chemoradiotherapy after a radical gastrectomy and a D2 node dissection for gastric adenocarcinoma. *Cancer J* 2008; **14**: 269-275 [PMID: 18677137 DOI: 10.1097/PPO.0b013e318178d23a]

12 **Spych M**, Serbiak B, Rychter A, Jesien-Lewandowicz E, Gottwald L, Fijuth J. Post-operative radiochemotherapy in patients with gastric cancer: one department's experience of 56 patients. *Br J Radiol* 2011; **84**: 457-463 [PMID: 21304007 DOI: 10.1259/bjr/25406515]

13 **An JY**, Kim HI, Cheong JH, Hyung WJ, Kim CB, Noh SH. Pathologic and oncologic outcomes in locally advanced gastric cancer with neoadjuvant chemotherapy or chemoradiotherapy. *Yonsei Med J* 2013; **54**: 888-894 [PMID: 23709422 DOI: 10.3349/ymj.2013.54.4.888]

14 **Hallissey MT**, Dunn JA, Ward LC, Allum WH. The second British Stomach Cancer Group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer: five-year follow-up. *Lancet* 1994; **343**: 1309-1312 [PMID: 7910321]

15 **Earle CC**, Maroun JA. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials. *Eur J Cancer* 1999; **35**: 1059-1064 [PMID: 10533448]

16 **Janunger KG**, Hafström L, Glimelius B. Chemotherapy in gastric cancer: a review and updated meta-analysis. *Eur J Surg* 2002; **168**: 597-608 [PMID: 12699095]

17 **Valentini V**, Cellini F, Minsky BD, Mattiucci GC, Balducci M, D' Agostino G, D'Angelo E, Dinapoli N, Nicolotti N, Valentini C, La Torre G. Survival after radiotherapy in gastric cancer: systematic review and meta-analysis. *Radiother Oncol* 2009; **92**: 176-183 [PMID: 19586672 DOI: 10.1016/j.radonc.2009.06.014]

18 **Smalley SR**, Benedetti JK, Haller DG, Hundahl SA, Estes NC, Ajani JA, Gunderson LL, Goldman B, Martenson JA, Jessup JM, Stemmermann GN, Blanke CD, Macdonald JS. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol* 2012; **30**: 2327-2333 [PMID: 22585691 DOI: 10.1200/JCO.2011.36.7136]

19 **Kim TH**, Park SR, Ryu KW, Kim YW, Bae JM, Lee JH, Choi IJ, Kim YJ, Kim DY. Phase 3 trial of postoperative chemotherapy alone versus chemoradiation therapy in stage III-IV gastric cancer treated with R0 gastrectomy and D2 lymph node dissection. *Int J Radiat Oncol Biol Phys* 2012; **84**: e585-e592 [PMID: 22975616 DOI: 10.1016/j.ijrobp.2012.07.2378]

20 **Kassam Z**, Lockwood G, O'brien C, Brierley J, Swallow C, Oza A, Siu L, Knox JJ, Wong R, Cummings B, Kim J, Moore M, Ringash J. Conformal radiotherapy in the adjuvant treatment of gastric cancer: Review of 82 cases. *Int J Radiat Oncol Biol Phys* 2006; **65**: 713-719 [PMID: 16626887]

21 **Dikken JL**, van Sandick JW, Maurits Swellengrebel HA, Lind PA, Putter H, Jansen EP, Boot H, van Grieken NC, van de Velde CJ, Verheij M, Cats A. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). *BMC Cancer* 2011; **11**: 329 [PMID: 21810227 DOI: 10.1186/1471-2407-11-329]

22 **Wu XJ**, Miao RL, Li ZY, Bu ZD, Zhang LH, Wu AW, Zong XL, Li SX, Shan F, Ji X, Ren H, Ji JF. Prognostic value of metastatic lymph node ratio as an additional tool to the TNM stage system in gastric cancer. *Eur J Surg Oncol* 2015; **41**: 927-933 [PMID: 25913059 DOI: 10.1016/j.ejso.2015.03.225]

23 **Kim S**, Lim DH, Lee J, Kang WK, MacDonald JS, Park CH, Park SH, Lee SH, Kim K, Park JO, Kim WS, Jung CW, Park YS, Im YH, Sohn TS, Noh JH, Heo JS, Kim YI, Park CK, Park K. An observational study suggesting clinical benefit for adjuvant postoperative chemoradiation in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. *Int J Radiat Oncol Biol Phys* 2005; **63**: 1279-1285

[PMID: 16099596]
24 **Bonenkamp JJ**, Hermans J, Sasako M, van de Velde CJ, Welvaart K, Songun I, Meyer S, Plukker JT, Van Elk P, Obertop H, Gouma DJ, van Lanschot JJ, Taat CW, de Graaf PW, von Meyenfeldt MF, Tilanus H. Extended lymph-node dissection for gastric cancer. *N Engl J Med* 1999; **340**: 908-914 [PMID: 10089184]
25 **Moehler M**, Lyros O, Gockel I, Galle PR, Lang H. Multidisciplinary management of gastric and gastroesophageal cancers. *World J Gastroenterol* 2008; **14**: 3773-3780 [PMID: 18609699 DOI: 10.3748/wjg.14.3773]
26 **Hartgrink HH**, van de Velde CJ, Putter H, Bonenkamp JJ, Klein Kranenbarg E, Songun I, Welvaart K, van Krieken JH, Meijer S, Plukker JT, van Elk PJ, Obertop H, Gouma DJ, van Lanschot JJ, Taat CW, de Graaf PW, von Meyenfeldt MF, Tilanus H, Sasako M. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. *J Clin Oncol* 2004; **22**: 2069-2077 [PMID: 15082726]
27 **Songun I**, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 2010; **11**: 439-449 [PMID: 20409751 DOI: 10.1016/S1470-2045(10)70070-X]
28 **Sasako M**, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T, Ohashi Y. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *J Clin Oncol* 2011; **29**: 4387-4393 [PMID: 22010012 DOI: 10.1200/JCO.2011.36.5908]
29 **Chang JS**, Koom WS, Lee Y, Yoon HI, Lee HS. Postoperative adjuvant chemoradiotherapy in D2-dissected gastric cancer: is radiotherapy necessary after D2-dissection? *World J Gastroenterol* 2014; **20**: 12900-12907 [PMID: 25278687 DOI: 10.3748/wjg.v20.i36.12900]
30 **Lee HS**, Choi Y, Hur WJ, Kim HJ, Kwon HC, Kim SH, Kim JS, Lee JH, Jung GJ, Kim MC. Pilot study of postoperative adjuvant chemoradiation for advanced gastric cancer: adjuvant 5-FU/cisplatin and chemoradiation with capecitabine. *World J Gastroenterol* 2006; **12**: 603-607 [PMID: 16489675 DOI: 10.3748/wjg.v12.i4.603]
31 **Kim S**, Kim JS, Jeong HY, Noh SM, Kim KW, Cho MJ. Retrospective analysis of treatment outcomes after postoperative chemoradiotherapy in advanced gastric cancer. *Radiat Oncol J* 2011; **29**: 252-259 [PMID: 22984678 DOI: 10.3857/roj.2011.29.4.252]
32 **Zhu WG**, Xua DF, Pu J, Zong CD, Li T, Tao GZ, Ji FZ, Zhou XL, Han JH, Wang CS, Yu CH, Yi JG, Su XL, Ding JX. A randomized, controlled, multicenter study comparing intensity-modulated radiotherapy plus concurrent chemotherapy with chemotherapy alone in gastric cancer patients with D2 resection. *Radiother Oncol* 2012; **104**: 361-366 [PMID: 22985776 DOI: 10.1016/j.radonc.2012.08.024]
33 **Jiang N**, Deng JY, Ding XW, Liu Y, Liang H. Tumor volume as a prognostic factor was superior to the seventh edition of the pT classification in resectable gastric cancer. *Eur J Surg Oncol* 2015; **41**: 315-322 [PMID: 25601610 DOI: 10.1016/j.ejso.2014.11.045]
34 **Aoyama T**, Yoshikawa T, Fujikawa H, Hayashi T, Ogata T, Cho H, Yamada T, Hasegawa S, Tsuchida K, Yukawa N, Oshima T, Oba MS, Morita S, Rino Y, Masuda M. Prognostic factors in stage IB gastric cancer. *World J Gastroenterol* 2014; **20**: 6580-6585 [PMID: 24914380 DOI: 10.3748/wjg.v20.i21.6580]
35 **Kim DJ**, Lee JH, Kim W. Impact of Intraoperative Macroscopic Diagnosis of Serosal Invasion in Pathological Subserosal (pT3) Gastric Cancer. *J Gastric Cancer* 2014; **14**: 252-258 [PMID: 25580357 DOI: 10.5230/jgc.2014.14.4.252]
36 **Misirlioglu HC**, Coskun-Breuneval M, Kucukpilakci B, Ugur VI, Elgin Y, Demirkasimoglu T, Kara SP, Ozgen A, Sanri E, Guney Y. Adjuvant radiotherapy for gastric carcinoma: 10 years follow-up of 244 cases from a single institution. *Asian Pac J Cancer Prev* 2014; **15**: 8871-8876 [PMID: 25374221]
37 **Bilici A**, Uygun K, Seker M, Ustaalioglu BB, Aliustaoglu M, Temiz S, Aksu G, Gezen C, Yavuzer D, Kaya S, Salepci T, Mayadagli A, Gumus M. The effect of tumor size on overall survival in patients with pT3 gastric cancer: experiences from 3 centers. *Onkologie* 2010; **33**: 676-682 [PMID: 21124038 DOI: 10.1159/000322215]
38 **Kim DH**, Yun HY, Ryu DH, Han HS, Han JH, Yoon SM, Youn SJ. Preoperative CA 125 is significant indicator of curative resection in gastric cancer patients. *World J Gastroenterol* 2015; **21**: 1216-1221 [PMID: 25632195 DOI: 10.3748/wjg.v21.i4.1216]
39 **Zurleni T**, Gjoni E, Ballabio A, Casieri R, Ceriani P, Marzoli L, Zurleni F. Sixth and seventh tumor-node-metastasis staging system compared in gastric cancer patients. *World J Gastrointest Surg* 2013; **5**: 287-293 [PMID: 24520426 DOI: 10.4240/wjgs.v5.i11.287]
40 **Ke B**, Song XN, Liu N, Zhang RP, Wang CL, Liang H. Prognostic value of the lymph node ratio in stage III gastric cancer patients undergoing radical resection. *PLoS One* 2014; **9**: e96455 [PMID: 24811256 DOI: 10.1371/journal.pone.0096455]
41 **Chang AT**, Ng WT, Law AL, Ku KM, Lee MC, Lee AW. Adjuvant chemoradiation for resected gastric cancer: a 10-year experience. *Gastric Cancer* 2011; **14**: 63-71 [PMID: 21327926 DOI: 10.1007/s10120-011-0011-y]
42 **Shridhar R**, Dombi GW, Finkelstein SE, Meredith KL, Hoffe SE. Improved survival in patients with lymph node-positive gastric cancer who received preoperative radiation: an analysis of the Surveillance, Epidemiology, and End Results database. *Cancer* 2011; **117**: 3908-3916 [PMID: 21365627 DOI: 10.1002/cncr.25995]
43 **Costa WL**, Coimbra FJ, Fogaroli RC, Ribeiro HS, Diniz AL, Begnami MD, Mello CA, Fanelli MF, Silva MJ, Fregnani JH, Montagnini AL. Adjuvant chemoradiotherapy after d2-lymphadenectomy for gastric cancer: the role of n-ratio in patient selection. results of a single cancer center. *Radiat Oncol* 2012; **7**: 169 [PMID: 23068190 DOI: 10.1186/1748-717X-7-169]
44 **Fu S**, Lu JJ, Zhang Q, Yang Z, Peng L, Xiong F. Intraoperative radiotherapy combined with adjuvant chemoradiotherapy for locally advanced gastric adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2008; **72**: 1488-1494 [PMID: 18538489 DOI: 10.1016/j.ijrobp.2008.03.012]
45 **Osti MF**, Agolli L, Bracci S, Monaco F, Tubin S, Minniti G, De Sanctis V, Enrici RM. Adjuvant chemoradiation with 5-fluorouracil or capecitabine in patients with gastric cancer after D2 nodal dissection. *Anticancer Res* 2012; **32**: 1397-1402 [PMID: 22493376]
46 **Raziee HR**, Cardoso R, Seevaratnam R, Mahar A, Helyer L, Law C, Coburn N. Systematic review of the predictors of positive margins in gastric cancer surgery and the effect on survival. *Gastric Cancer* 2012; **15** Suppl 1: S116-S124 [PMID: 22138928]
47 **Stiekema J**, Trip AK, Jansen EP, Boot H, Cats A, Ponz OB, Verheij M, van Sandick JW. The prognostic significance of an R1 resection in gastric cancer patients treated with adjuvant chemoradiotherapy. *Ann Surg Oncol* 2014; **21**: 1107-1114 [PMID: 24306660 DOI: 10.1245/s10434-013-3397-4]
48 **Ott K**, Blank S, Becker K, Langer R, Weichert W, Roth W, Sisic L, Stange A, Jäger D, Büchler M, Siewert JR, Lordick F. Factors predicting prognosis and recurrence in patients with esophagogastric adenocarcinoma and histopathological response with less than 10 % residual tumor. *Langenbecks Arch Surg* 2013; **398**: 239-249 [PMID: 23269519 DOI: 10.1007/s00423-012-1039-0]
49 **Deng J**, You Q, Gao Y, Yu Q, Zhao P, Zheng Y, Fang W, Xu N, Teng L. Prognostic value of perineural invasion in gastric cancer: a systematic review and meta-analysis. *PLoS One* 2014; **9**: e88907 [PMID: 24586437 DOI: 10.1371/journal.pone.0088907]

P- Reviewer: Kuramitsu Y, Mastoraki A **S- Editor**: Ma YJ
L- Editor: A **E- Editor**: Ma S

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327