EUROMEDITERRANEAN BIOMEDICAL JOURNAL
2023,18 (26) 125-130
(*FORMERLY: CAPSULA EBURNEA*)

Original article

INTENSITY MODULATED RADIATION THERAPY (IMRT) IN THE ADJUVANT TREATMENT OF RESECTED GASTRIC CANCER: A RETROSPECTIVE DOSIMETRIC AND CLINICAL ANALYSIS

Rocco Luca Emanuele Liardo [1], Maria Chiara Lo Greco [2], Giorgia Marano [2], Roberto Milazzotto [1], Vincenzo Salamone [3], Viviana La Monaca [3], Pietro Valerio Foti [4], Stefano Palmucci [4], Antonio Basile [4], Stefano Pergolizzi [2], Corrado Spatola [1]

1. U.O.S.D. Radioterapia Oncologica, Dipartimento di Scienze Mediche, Chirurgiche e Tecnologie Avanzate, Università di Catania, Catania, Italy;
2. U.O.C. Radioterapia Oncologica, Dipartimento di Scienze Biomediche, Odontoiatriche e delle Immagini Morfologiche e Funzionali, Università di Messina, Messina, Italy;
3. U.O.S.D. Fisica Sanitaria, Azienda Ospedaliero Universitaria Policlinico "G. Rodolico - San Marco", Catania, Italy;
4. U.O.C. Radiologia I, Dipartimento di Scienze Mediche, Chirurgiche e Tecnologie Avanzate, Università di Catania, Catania, Italy.

ARTICLE INFO

Article history:
Received 25 Jul 2023
Accepted 12 Sep 2023
Published 05 Oct 2023

Keywords:
Radiotherapy, chemotherapy, chemoradiotherapy, stomach cancer, IMRT.

ABSTRACT

The European Society for Medical Oncology guidelines recommend adjuvant chemoradiation for patients with resected gastric cancer who have not undergone an appropriate D2 lymphadenectomy or have involved margins. In this setting, due to the requirement to cover large irradiation volumes and to deliver concomitant systemic therapy, treatment-related toxicities remain a concern. With the goal of assessing safety and feasibility of adjuvant radiotherapy, we collected data of patients with resected gastric cancer, who underwent Intensity Modulated Radiation Therapy to 50.4 Gy, concurrent with fluoropyrimidine based chemotherapy at our institution, between January 2016 and January 2022. In this study, we examined dose distribution to PTV and organs at risk, demonstrating safety and feasibility of this treatment without significant acute or late toxicities.

1. Introduction

Gastric cancer incidence and mortality have significantly declined during the past five decades, but even so, it remains the fifth most common cancer and the fourth leading cause of deadly cancer in the world. (1) Gastric cancer survival is closely related to the stage of diagnosis. Literature data suggest that the 5-years survival rates of localized, regional, and distant disease is 77.7%, 37.4%, and 10.2%, respectively. (2) Unfortunately, this tumor is often asymptomatic before it progresses, and most patients are diagnosed at an advanced stage.

Nowadays, the cornerstone of advanced gastric cancer treatment is negative gastrectomy with proper lymphadenectomy. However, after surgical resection, different patterns of relapse have been detected, emphasizing the necessity of a multimodality treatment.

Currently, perioperative chemotherapy (ChT) is widely adopted as the standard of care throughout most of the United Kingdom and Europe, while adjuvant chemoradiotherapy (CRT), without the administration of preoperative ChT, is considered the standard therapy in the United States. The European Society for Medical Oncology (ESMO) guidelines recommend adjuvant CRT for patients who have not received preoperative ChT and have not undergone an appropriate D2 lymphadenectomy or for patients with involved margins. (3)

Considering the requirement to cover large irradiation volumes (including the primary tumor bed, resection margins, anastomosis site, duodenal stump, and regional lymph nodes) and the necessity to deliver concomitant systemic therapy, treatment related toxicities remain a concern. (4)

* Corresponding author: Rocco Luca Emanuele Liardo, *lucaliardo@hotmail.com*
DOI: 10.3269/1970-5492.2023.18.26
 ISSN: 2279-7165 - Available on-line at www.embj.org

Over the last decades, aiming to protect normal tissue, radiation therapy techniques have developed from 3-dimensional conformal radiation therapy (3DCRT) to 3-dimensional image guided intensity modulated radiation therapy (IMRT) and volumetric modulated arc radiation therapy (VMAT).

Although IMRT theoretically provides more precise tumor coverage with greater sparing of organs at risk (OARs), it is less commonly used in gastric cancer due to difficulties with beam arrangements. (5)

For this retrospective/single center study, we collected data of patients with resected gastric cancer, who underwent CRT with IMRT to 50.4 Gy, concurrent with fluoropyrimidine based chemotherapy, at the Department of Oncological Radiotherapy, "G. Rodolico-San Marco" Medical Center, between January 2016 and January 2022.

With the goal of assessing safety and efficacy, a dosimetric analysis of IMRT plan was performed to examine dose distribution to Planning Target Volume (PTV) and OARs, namely the heart, lungs, bilateral kidneys, liver, small bowel, and spinal cord.

Furthermore, the study evaluated whether these dosimetric advantages translated into meaningful clinical improvement.

2. Methods

Patient Population

After a careful review of history, physical and hematological evaluation, all patients underwent an endoscopic examination with esophagogastroduodenoscopy and forceps biopsy, to pathologically confirm gastric cancer diagnosis and to identify molecular profiles.

All patients underwent contrast enhanced Computed Tomography (CT) of brain, thorax, abdomen, and pelvis to determine local tumor extension, nodal status and to identify distant metastasis.

All patients were staged according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM (tumor-node-metastasis) 8th edition staging manual. Each recruited patient was IB-III stage, therefore surgical resection with radical or subtotal gastrectomy, including a D2 lymphadenectomy, was recommended. According to ESMO guidelines, after an accurate explanation of risks and benefits, adjuvant CRT was proposed to all patients who had not previously received preoperative ChT and had not undergone an appropriate D2 lymphadenectomy or had involved margins (R1). (3)

After multidisciplinary discussions, CRT was also proposed to patients who had not previously received preoperative ChT and resulted with negative histological prognostic factors after surgery, such as N3 or lymph nodes ratio >25%.

Twenty patients surgically treated for gastric cancer who underwent fluoropyrimidine based CRT 6-8 weeks after surgery, were selected for this study inclusion. Treated patients who did not complete their treatment course, were excluded.

Individual characteristic and stage distribution are shown in table 1. Acute toxicities were checked weekly. Late toxicity was recorded during follow-up. Both types of toxicities were scored using the Common Terminology Criteria for Adverse Events (CTCAE version 5.0). (6)

Radiation treatment planning

To design a unique treatment plan for each individual case, every patient underwent a radiotherapy simulation process through an abdomen-pelvis CT scan (3 mm thickness) without contrast enhancement, performed encompassing the area from the 7^{th} thoracic vertebrae to the 4^{th} lumbar vertebrae. To ensure an optimum set-up, all patients were placed in the supine position with arms overhead and with a dedicated support for legs and feet stability (knee-fix).

Furthermore, to guarantee treatment reproducibility, all patients were instructed to avoid deep breathing and not to eat any meals or drink for at least 3-6 hours before both the planning CT and all the treatment fractions.

During the contour delineation phase, the Clinical Target Volume (CTV) was defined including the stomach bed or remnant stomach, the resection margins, anastomosis site, duodenal stump, and regional lymph nodes. The inclusion of the left abutment of the diaphragm was considered in case of locally advanced proximal tumors. The delineation of lymph node target volumes was performed according to the tumor localization. (7)

For proximal third tumors, nodal CTV included perigastric lymph nodes, left gastric artery, common hepatic artery, celiac tripod, and splenic artery stations. In N+ patients, infradiaphragmatic, hepatic peduncle, para-aortic and pillars (in case of posterior location) stations were included.

For middle third tumors, nodal CTV include the perigastric lymph nodes, left gastric artery, common hepatic artery, celiac axis, splenic artery, hepatic peduncle, posterior pancreatic and superior mesenteric artery stations. In N+ patients, anterior pancreatic and para-aortic lymph node stations were included.

For distal third tumors, nodal CTV include the perigastric lymph nodes, left gastric artery, hepatic artery, celiac tripod, proximal splenic artery, hepatic peduncle, posterior pancreatic, superior mesenteric artery, and para-aortic stations. In N+ patients, anterior pancreatic lymph node stations were included. The Planning Target Volume (PTV) was obtained as a 10 mm expansion to the CTV, to account for daily set-up error and organ motion.

The prescription dose to the PTV was 50.4 Gy, delivered in 28 fractions, 5 fractions per week. The target volumes and organs at risk (OARs) were established according to the International Commission on Radiation Units and Measurements (reports 62).

IMRT radiation plans were performed using ElektaXio® and Elekta Monaco® software (Elekta AB, Stockholm, Sweden). Beam energy levels included 6 megavolts (MV), 15 MV, or a mix of 6 and 15 MV. Radiation intensity modulation was obtained through a static step-and-shoot technique using 7-9 fields, with a variable number of segments (range 36-59, median 46). The Dosimetry Check software (Math Resolutions) provided patient-specific pre-treatment dose quality assurance of IMRT plans.

Dosimetric Analysis

All plans were assessed using a dose-volume histogram (DVH). The PTV was evaluated in terms of minimum, maximum, and mean dose. The conformity index (CI) and homogeneity index (HI) were calculated to analyze the PTV dose coverage and uniformity, respectively. The CI represents the relationship between isodose distributions and target volume, and it was used to quantitatively assess the quality of radiotherapy treatment plans. The HI represents the relationship between maximum isodose delivered to the target and the reference isodose, and it was used for analyzing and quantifying dose homogeneity in the target volume. In an ideal scenario, the CI should be equal to 1 and HI should be < 2. CI less than 1 indicates that the target volume is not adequately irradiated and a value greater than 1 means that the irradiated volume is greater than the target volume. (8,9)

Furthermore, for each patient's plan, we analyzed the dose distribution to OARs, namely the heart, lungs, bilateral kidneys, small bowel, spinal cord, and liver. ICRU constraints [Vx=volume (%) receiving dose (Gy) or higher] were based on a Quantitative Analysis of Normal Tissue Effects in the Clinic Summary: heart (Dmean <26 Gy, V30 <46%), lung (V20 <30%) spinal cord (Dmax <50 Gy), small bowel (V45 <195 c.c.), whole liver (Dmean <30 Gy) and bilateral kidneys (Dmean <18 Gy, V20 <32%, V23 <30%, V28 <20%). (10-12)

3. Results

PTV and OARs doses

IMRT plans were generated using inverse planning, which produces optimal intensity-modulated profiles using a simulated annealing algorithm. Seven to nine-field coplanar plans were used.

The PTV and normal structure dose–volume constraints were iteratively adjusted to ensure optimal target coverage while minimizing dose to the bowel, right and left kidneys, liver, and spinal cord, thus optimizing the PTV and normal tissue DVHs.

The IMRT plans were optimized to minimize the volume of PTV, receiving 95% of the prescribed dose and the volume receiving 110% of the prescribed dose.

Therefore, the initial plans were considered acceptable with 2–4% of the PTV receiving 100% of the prescribed dose, 5% of the PTV receiving 110% and 1% receiving 115%. The median PTV volume was 494 cm3 and the median Dmean was 51,13 with standard deviation (SD) ±2,6 Gy. Both HI and CI were calculated: HI=1,078±0,008 (range= 1,07-1,09); CI=0,92±0,13 (range 0,8-1,1).

Dosimetric verifications performed for OARs, demonstrated the ability of IMRT to cover large PTV while maintaining lower dosimetric parameters to normal tissue. (13,14)

Heart median Dmean was 5,57±3,52 Gy, median V30 was 10,55%. Right and left lung median Dmean were respectively 2,68±1,45 Gy and 3,21±1,16 Gy, median V20 was 5,3%. Spinal Cord median Dmean was 24,1±7,43 Gy, median Dmax was 39,37±4,24 Gy. Small bowel median Dmean was 26,97±8,95 Gy, median V45 was 32,5 cc. Whole liver median Dmean was 23,57±3,79 Gy. Right and left kidney median Dmean were respectively 11,1±5,68 Gy and 12,83±2,12 Gy. Both kidneys median V20 was 18%, median V23 was 15,08% and median V28 was 9,3%.

All data are summarized in table 2.

An example of treatment planning is represented in figure 1.

Patients' characteristic		Number of patients
Gender	Male	13
	Female	7
Age	Average (years)	65
Tumor localization	Proximal	9
	Middle	6
	Distal	5
AJCC stage	IB	1
	IIA	4
	IIB	6
	IIIA	6
	IIIB	2
	IIIC	1
Surgery type	Sub-total gastrectomy	4
	Total gastrectomy	16
Nodal dissection	D1	8
	D2	10
	Not recorded	2
Margin status	Negative	14
	Positive	5
	Not recorded	1

Table 1. Characteristics of enrolled patients. This table reports patient characteristics classification: gender, age, tumor localization, AJCC stage, surgery type, nodal dissection, and margin status.

Organ at risk	Constraints	Median value	Standard deviation
Heart	Dmean	5.57	±3.52 Gy
	V30	10.55%	-
Right Lung	Dmean	2.68	±1.45 Gy
Left Lung	Dmean	3.21	±1.16 Gy
Both Lungs	V20	5.3%	-
Spinal Cord	Dmean	24.1	±7.43 Gy
	Dmax	39.37	±4.24 Gy
Small Bowel	Dmean	26.97	±8.95 Gy
	V45	32.5 cc	-
Whole Liver	Dmean	23.57	±3.79 Gy
Right Kidney	Dmean	11.1	±5.68 Gy
Left Kidney	Dmean	12.83	±2.12 Gy
Both Kidneys	V20	18%	-
	V23	15.08%	-
	V28	9.3%	-

Table 2. IMRT plans dosimetric analysis. In this table we report: Dmean (mean dose), Dmax (maximal dose), V20 (volume receiving at least 20 Gy), V23 (volume receiving at least 23 Gy), V28 (volume receiving at least 28 Gy), V30 (volume receiving at least 30 Gy), V45 (volume receiving at least 45 Gy).

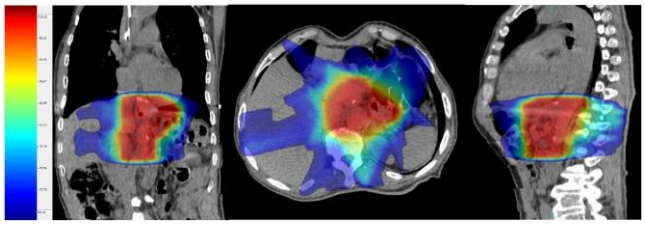

Figure 1. IMRT treatment plan isodoses (coronal, axial, sagittal axis) of a patient treated at our center. In this image we report: 30% isodose (deep blue), 60% isodose (light blue), 85% isodose (orange), 100% isodose (red).

Safety and feasibility

To evaluate if IMRT dosimetric advantages corresponding to clinical benefits, acute and late adverse events were investigated and collected according to CTCAE 5.0. During CRT, all patients received weekly clinical and hematological evaluations to analyze acute toxicities. The most frequent mild-moderate adverse events were gastrointestinal disorders, such as G1 nausea and vomiting (4 patients), G1 abdominal pain (4 patients) and G1 diarrhea (2 patients). The most challenging adverse events were nutrition disorders, including G2 anorexia (3 patients) and G2 hypoalbuminemia (2 patients).

During CRT, these disorders were partially offset by parenteral nutrition and hydration, nutritional supplements, and albumin infusion. Mean weight loss was 3.4 kg. Few patients developed blood disorders (probably relating to IMRT ability to obtain a better dose sparing of the spinal cord), such as G1 anemia (3 patients). No patients showed relevant kidney injury or liver disfunction: G1 creatinine increased occurred in 2 patients, G1 hypertransaminasemia occurred in 3 patients. After the end of CRT, every patient received clinical, hematological, and radiological examinations to analyze late toxicity and treatment efficacy. Median follow-up was 36 months. The most frequent chronic adverse event was gastrointestinal disorders such as G1 abdominal pain (3 patients) G2 esophagitis (2 patients). No patients manifested signs of nephrotoxicity, radiation induced liver disease, coronary events, or heart failure.

4. Discussion

Even if margin negative gastrectomy with proper lymphadenectomy is considered the cornerstone of treatment for potentially curable gastric cancer, the overall effects after curative surgery alone remain far from satisfactory. With the goal of reducing the high locoregional recurrence rates, during the last decades the role of a multidisciplinary approach, including radiotherapy and chemotherapy, has been widely investigated. Early publications on the use of adjuvant CRT for gastric cancer date back to the early 1980s and report series of patients treated postoperatively with radiation therapy from 20 Gy to 50 Gy with concurrent 5-fluorouracil (5FU). (15-17)

In 2001, the phase III SWOG INT-0116 trial was published by MacDonald et al. It was the first large-scale controlled study to provide significant benefits in terms of overall survival and relapse free survival in patients with gastric or gastroesophageal junction cancer who underwent complete resection followed by postoperative CRT, with radiation therapy dose of 45 Gy in 25 fractions for 5 weeks. (18,19)

Even if this trial has been criticized by many Asian researchers because of the low rates of D2 lymph node dissection, this treatment approach has been considered the standard adjuvant treatment of resected gastric adenocarcinoma for the following years. Nowadays, the "Macdonald regimen" is widely used in the United States, though it has not gained wide acceptance in Europe. In 2006, the UK phase III MAGIC trial was published. This study showed that perioperative adjuvant chemotherapy based on three cycles of ECF (epirubicin, cisplatin, 5FU), pre-surgery and post-surgery, produced a successful result by improving survival rates in patients with gastric cancer. Since then, this regimen has become the standard of care in Europe, eclipsing adjuvant CRT. (20) Nowadays, FLOT regimen, consisting of docetaxel, oxaliplatin, leucovorin and 5-fluorouracil is considered the standard of care for patients who can tolerate a triple cytotoxic drug regimen, while for patients unfit for triplet ChT, a combination of a fluoropyrimidine with cisplatin or oxaliplatin is recommended. While for other gastrointestinal tumors, the crucial role of neoadjuvant radiotherapy has already been demonstrated; in gastric cancer the potential benefit of additional preoperative radiotherapy to perioperative ChT is currently undefined, and it still is being explored in clinical trials. (21-23) In Asian countries, adjuvant chemotherapy alone, without neoadjuvant therapy, is preferred.

The efficacy of this approach has been demonstrated by several large-randomized trials. Among these, the ACTS-GC trial, which reported better survival rates with S-1 monotherapy, and the CLASSIC trial showing the beneficial effect of adjuvant capecitabine plus oxaliplatin chemotherapy regimen (XELOX). (24,25) Furthermore, the ARTIST trial demonstrated that chemoradiotherapy did not significantly reduce recurrence compared to adjuvant chemotherapy alone after curative resection and D2 lymph node dissection. (26)

With regards to postoperative chemoradiotherapy, a retrospective Dutch registry study suggested that this approach was associated with improved survival compared with no further treatment in patients who had undergone a resection with microscopic tumor at the margin (R1). (27)

In fact, radiation therapy is estimated to reduce the risk of local relapse, decreasing tumor spreading to the peritoneum, small omentum or large omentum, pancreas, and duodenum, as well as lymphatic or hematogenic dissemination, especially to the liver.

Nowadays, except in the US, adjuvant CRT is recommended in patients who haven’t received preoperative ChT and haven’t undergone an appropriate D2 lymphadenectomy, or who have undergone gastrectomy with involved margins and are not candidates for more extended surgery. Radiotherapy should preferably be given as a concomitant regimen of fluoropyrimidine based ChT to a total dose of 45-50.4 Gy in 25-28 fractions of 1.8 Gy (five fractions per week) by 3D-CRT or IMRT techniques.

Many dosimetric studies compared 3D-CRT with IMRT treatment plans, showing a reduction in the dose received by the organs at risk: IMRT has shown to be able to decrease the dose received by the left kidney, resulting in a statistically significant preservation of renal function. (28,29) Furthermore, a comparison of treatment plans by IMRT, single arc VMAT and double arc VMAT published in 2014, suggested that treatment with double arc VMAT improved the coverage of the target volume but it did not reduce the dose received by the liver compared to IMRT with 5 beams. (30)

In summary, it can be said that radiation oncologists have at their disposal different delivery techniques to use in gastric cancer adjuvant settings, and each one of them has different characteristics in terms of target volume coverage and organs at risk dose sparing.

IMRT has demonstrated to achieve excellent target coverage while reducing the mean liver dose and volume above threshold dose, allowing at the same time to deliver a higher than standard dose (50.4 Gy vs 45.0 Gy). Even if IMRT plans are considered more complex due to difficulties with beam arrangements, this technique should be recommended in every institution.

In this retrospective/single center study, we collected data of patients with resected gastric cancer, who underwent CRT with IMRT to 50.4 Gy, concurrent with fluoropyrimidine based chemotherapy at our institution, between January 2016 and January 2022. With the goal of assessing safety and efficacy, we performed a dosimetric analysis of IMRT plan to examinate dose distribution to PTV and OARs, demonstrating safety and feasibility of this treatment. Furthermore, no significant acute or late toxicities were observed in this study sample, supporting the hypothesis that IMRT dosimetric advantages can translate into clinical benefits.

References

1. Ilic M, Ilic I. Epidemiology of stomach cancer. World journal of gastroenterology. 2022; 28(12): 1187–1203.
2. Li Y, Feng A, Zheng S, Chen C, Lyu J. Recent Estimates and Predictions of 5-Year Survival in Patients with Gastric Cancer: A Model-Based Period Analysis. Cancer control: journal of the Moffitt Cancer Center. 2022; 29: 10732748221099227.
3. Lordick F, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G, Vogel A, Smyth E C, & ESMO Guidelines Committee. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of oncology: official journal of the European Society for Medical Oncology. 2022; 33(10): 1005–1020.
4. Yoon H I, Chang J S, Lim J S, Noh S H, Hyung W J, An J Y, Lee Y C, Rha S Y, Kim K H, Koom W S. Defining the target volume for post-operative radiotherapy after D2 dissection in gastric cancer by CT-based vessel-guided delineation. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology. 2013; 108(1): 72–77.
5. Ren F, Li S, Zhang Y, Zhao Z, Wang H, Cui Y, Wang M. Efficacy and safety of intensity-modulated radiation therapy versus three-dimensional conformal radiation treatment for patients with gastric cancer: a systematic review and meta-analysis. Radiation oncology (London, England). 2019; 14(1): 84.
6. Freites-Martinez A, Santana N, Arias-Santiago S, Viera A. (2021). Using the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0) to Evaluate the Severity of Adverse Events of Anticancer Therapies. CTCAE versión 5.0. 2021; 112(1): 90–92.
7. Socha J, Wołąkiewicz G, Wasilewska-Teśluk E, Janiga P, Kondraciuk T, Majewska A, Olearski K, Kępka L. Clinical target volume in postoperative radiotherapy for gastric cancer: identification of major difficulties and controversies. Clinical & translational oncology: official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico. 2016; 18(5): 480–488.
8. Chen Y C, Lin J C, Liu W H, Huang S F, Chou Y C, Li M H, Tsai J T. Comparing treatment plans for proximal and middle/distal stomach cancer: intensity-modulated radiotherapy, volumetric-modulated arc therapy, and tomotherapy. Ther Radiol Oncol 2019; 3: 4.
9. Kapoor R, G Y S, Das N, Dracham C B, Khosla D, Oinam A S. Dosimetric Evaluation of 3-Dimensional Conformal Radiotherapy Technique in Postoperative Patients with Gastric Carcinoma: When Is IMRT Really Needed?. Asian Pacific Journal of Cancer Care. 2020; 5: 151-156.
10. Monti A F, Ostinelli A, Frigerio M, Cosentino D, Bossi A, Cazzaniga L F, Scandolaro L, Valli M C. An ICRU 50 radiotherapy treatment chart. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology. 1995; 35(2): 145–150.
11. Muren L P, Karlsdottir A, Kvinnsland Y, Wentzel-Larsen T, Dahl O. Testing the new ICRU 62 'Planning Organ at Risk Volume' concept for the rectum. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology. 2005; 75(3): 293–302.
12. Bentzen S M, Constine L S, Deasy J O, Eisbruch A, Jackson A, Marks L B, Ten Haken R K, Yorke E D. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. International journal of radiation oncology, biology, physics. 2010; 76(3 Suppl): 3–9.
13. Spatola C, Tocco A, Milazzotto R, Pagana A, Chillura I, Bevilacqua R, Militello C, Salamone V, Raffaele L, Migliore M, Privitera G. Role, timing and technique of radiotherapy in pediatric pleuropulmonary synovial sarcoma. Future oncology (London, England). 2016; 12(23s): 73–77.
14. Spatola C, Militello C, Tocco A, Salamone V, Luigi R, Migliore M, Marletta D, Cannizzaro A, Bevilacqua R, Milone P, Pergolizzi S, Privitera, G. Single-institution experience of intensity-modulated radiotherapy for malignant pleural mesothelioma at University of Catania. Future oncology (London, England). 2018; 14(6s): 17–21.
15. Moertel C G, Childs D S, O'Fallon J R, Holbrook M A, Schutt A J, Reitemeier R J. Combined 5-fluorouracil and radiation therapy as a surgical adjuvant for poor prognosis gastric carcinoma. J Clin Oncol. 1984; 2(11):1249–54.
16. Dent D M, Werner I D, Novis B, Cheverton P, Brice P. Prospective randomized trial of combined oncological therapy for gastric carcinoma. Cancer. 1979; 44(2): 385–91.
17. Allum W H, Hallissey M T, Ward L C, Hockey M S. A controlled, prospective, randomised trial of adjuvant chemotherapy or radiotherapy in resectable gastric cancer: interim report. British Stomach Cancer Group. Br J Cancer. 1989; 60(5): 739–44.
18. Macdonald J S, Smalley S R, Benedetti J, Hundahl S A, Estes N C, Stemmermann G N, Haller D G, Ajani J A, Gunderson L L, Jessup J M, Martenson J A. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. The New England journal of medicine. 2001; 345(10): 725–730.
19. Smalley S R, Benedetti J K, Haller D G, Hundahl S A, Estes N C, Ajani J A, Gunderson L L, Goldman B, Martenson J A, Jessup J M, Stemmermann G N, Blanke C D, Macdonald, J S. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2012; 30(19): 2327–2333.

20. Cunningham D, Allum W H, Stenning S P, Thompson J N, Van de Velde C J, Nicolson M, Scarffe J H, Lofts F J, Falk S J, Iveson T J, Smith D B, Langley R E, Verma M, Weeden, S, Chua Y J, MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. The New England journal of medicine. 2006; 355(1): 11–20.
21. Lo Greco M C, La Rocca M, Marano G, Finocchiaro I, Liardo R L E, Milazzotto R, Acquaviva G, Basile A, Palmucci S, Foti P V, Pergolizzi S, Pontoriero A, Parisi S, Spatola C. Integrated Intensified Chemoradiation in the Setting of Total Neoadjuvant Therapy (TNT) in Patients with Locally Advanced Rectal Cancer: A Retrospective Single-Arm Study on Feasibility and Efficacy. Cancers. 2023; 15(3): 921.
22. Milazzotto R, Spatola C, Tocco A, Raffaele L, Salamone V, Aglieco A, Trombatore C, Di Cataldo A, Privitera G: Metastatic esophagogastric junction cancer: case report of a complete long-term response after combined chemoradiotherapy. EuroMediterranean Biomedical Journal. 2018; 13: 082–084
23. Li N, Xiang X, Zhao D, Wang X, Tang Y, Chi Y, Yang L, Jiang L, Jiang J, Shi J, Liu W, Fang H, Tang Y, Chen B, Lu N, Jing H, Qi S, Wang S, Liu Y, Song, Y, … Jin, J. Preoperative versus postoperative chemo-radiotherapy for locally advanced gastric cancer: a multicenter propensity score-matched analysis. BMC cancer. 2022; 22(1): 212.
24. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K, ACTS-GC Group. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. The New England journal of medicine. 2007; 357(18): 1810–1820.
25. Bang Y J, Kim Y W, Yang H K, Chung H C, Park Y K, Lee K H, Lee K W, Kim Y H, Noh S I, Cho J Y, Mok Y J, Kim Y H, Ji J, Yeh T S, Button P, Sirzén F, Noh S H, CLASSIC trial investigators. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet (London, England). 2012 379(9813): 315–321.
26. Lee J, Lim D H, Kim S, Park S H, Park J O, Park Y S, Lim H Y, Choi M G, Sohn T S, Noh J H, Bae J M, Ahn Y C, Sohn I, Jung S H, Park C K, Kim K M, Kang W K. 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. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2012, 30(3): 268–273.
27. Schernberg A, Rivin Del Campo E, Rousseau B, Matzinger O, Loi M, Maingon P, Huguet F. Adjuvant chemoradiation for gastric carcinoma: State of the art and perspectives. Clinical and translational radiation oncology. 2018; 10: 13–22.
28. Trip A K, Nijkamp J, Van Tinteren H, Cats A, Boot H, Jansen E P, Verheij M. IMRT limits nephrotoxicity after chemoradiotherapy for gastric cancer. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology. 2014; 112(2): 289–294.
29. Spatola C, Tocco A, Pagana A, Milazzotto R, Luigi R, Salamone V, Militello C, Migliore M, Foti P V, Cataldo A D, Acquaviva G, Privitera G (2018). Combined taxane-based chemotherapy and intensity-modulated radiotherapy with simultaneous integrated boost for gastroesophageal junction adenocarcinoma. Future oncology (London, England). 2018; 14(6s): 47–51.
30. Li Z, Zeng J, Wang Z, Zhu H and Wei Y. Dosimetric comparison of intensity modulated and volumetric arc radiation therapy for gastric cancer. Oncol Lett. 2014; 8: 1427-1434.