ISSN 1948-5204 (online)

# World Journal of *Gastrointestinal Oncology*

*World J Gastrointest Oncol* 2015 January 15; 7(1): 1-5

Published by Baishideng Publishing Group Inc

WJGO World Journal of Gastrointestinal Oncology

A peer-reviewed, online, open-access journal of gastrointestinal oncology

# Editorial Board

2011-2015

The *World Journal of Gastrointestinal Oncology* Editorial Board consists of 428 members, representing a team of worldwide experts in gastrointestinal oncology. They are from 40 countries, including Argentina (2), Australia (10), Belgium (5), Brazil (2), Canada (4), Chile (2), China (56), Czech Republic (1), Denmark (1), Finland (3), France (7), Germany (24), Greece (13), Hungary (2), India (9), Iran (2), Ireland (2), Israel (4), Italy (41), Japan (47), Kuwait (2), Mexico (1), Netherlands (7), New Zealand (2), Norway (1), Poland (3), Portugal (5), Romania (1), Saudi Arabia (1), Serbia (2), Singapore (4), South Korea (27), Spain (10), Sweden (5), Switzerland (2), Syria (1), Thailand (1), Turkey (6), United Kingdom (15), and United States (95).

Siu Tsan Yuen, *Hong Kong*
Wei-Hui Zhang, *Harbin*
Li Zhou, *Beijing*
Yong-Ning Zhou, *Lanzhou*

**Czech Republic**

Ondrej Slaby, *Brno*

**Denmark**

Hans Jørgen Nielsen, *Hvidovre*

**Finland**

Riyad Bendardaf, *Turku*
Pentti Ilmari Sipponen, *Espoo*
Markku Voutilainen, *Jyväskylä*

**France**

Bouvier Anne-Marie, *Cedex*
Stéphane Benoist, *Boulogne*
Ouaissi Mehdi, *Marseille*
Jean-François Rey, *Jean-François Rey*
Karem Slim, *Clermont-Ferrand*
David Tougeron, *Poitiers*
Isabelle Van Seuningen, *Lille*

**Germany**

Hajri Amor, *Freiburg*
Han-Xiang An, *Marburg*
Karl-Friedrich Becker, *München*
Stefan Boeck, *Munich*
Dietrich Doll, *Marburg*
Joachim Drevs, *Freiburg*
Volker Ellenrieder, *Marburg*
Ines Gütgemann, *Bonn*
Jakob Robert Izbicki, *Hamburg*
Gisela Keller, *München*
Jörg H Kleeff, *Munich*
Axel Kleespies, *Munich*
Hans-Joachim Meyer, *Solingen*
Lars Mueller, *Kiel*
Martina Müller-Schilling, *Heidelberg*
Joachim Pfannschmidt, *Heidelberg*
Marc André Reymond, *Bielefeld*
Robert Rosenberg, *München*
Ralph Schneider, *Marburg*
Helmut K Seitz, *Heidelberg*
Nikolas Hendrik Stoecklein, *Düsseldorf*
Oliver Stoeltzing, *Mainz*
Ludwig G Strauss, *Heidelberg*

**Greece**

Ekaterini Chatzaki, *Alexandroupolis*
Eelco de Bree, *Heraklion*
Maria Gazouli, *Athens*
Vassilis Georgoulias, *Heraklion*
John Griniatsos, *Athens*
Ioannis D Kanellos, *Thessaloniki*
Vaios Karanikas, *Larissa*
Georgios Koukourakis, *Athens*
Michael I Koukourakis, *Alexandroupolis*
Gregory Kouraklis, *Athens*
Kostas Syrigos, *Athens*
Ioannis A Voutsadakis, *Larissa*

**Hungary**

László Herszényi, *Budapest*
Zsuzsa Schaff, *Budapest*

**India**

Uday Chand Ghoshal, *Lucknow*
Ruchika Gupta, *New Delhi*
Kalpesh Jani, *Vadodara*
Ashwani Koul, *Chandigarh*
Balraj Mittal, *Lucknow*
Rama Devi Mittal, *Lucknow*
Susanta Roychoudhury, *Kolkata*
Yogeshwer Shukla, *Lucknow*
Imtiaz Ahmed Wani, *Kashmir*

**Iran**

Reza Malekezdeh, *Tehran*
Mohamad Amin Pourhoseingholi, *Tehran*

**Ireland**

Aileen Maria Houston, *Cork*
Colm Ó'Moráin, *Dublin*

**Israel**

Nadir Arber, *Tel Aviv*
Eytan Domany, *Rehovot*
Dan David Hershko, *Haifa*
Yaron Niv, *Patch Tikva*

**Italy**

Massimo Aglietta, *Turin*
Domenico Alvaro, *Rome*
Azzariti Amalia, *Bari*
Marco Braga, *Milan*
Federico Cappuzzo, *Rozzano*
Lorenzo Capussotti, *Torino*
Fabio Carboni, *Rome*
Vincenzo Cardinale, *Rome*
Luigi Cavanna, *Piacenza*
Massimo Colombo, *Milan*
Valli De Re, *Pordenone*
Ferdinando De Vita, *Naples*
Riccardo Dolcetti, *Aviano*
Pier Francesco Ferrucci, *Milano*
Francesco Fiorica, *Ferrara*
Gennaro Galizia, *Naples*
Silvano Gallus, *Milano*
Milena Gusella, *Trecenta*
Carlo La Vecchia, *Milano*
Roberto Francesco Labianca, *Bergamo*
Massimo Libra, *Catania*
Roberto Manfredi, *Bologna*
Gabriele Masselli, *Viale del Policlinico*
Simone Mocellin, *Padova*
Gianni Mura, *Arezzo*
Gerardo Nardone, *Napoli*
Gabriella Nesi, *Florence*
Francesco Perri, *San Giovanni Rotondo*
Francesco Recchia, *Avezzano*
Vittorio Ricci, *Pavia*
Fabrizio Romano, *Monza*
Antonio Russo, *Palermo*
Daniele Santini, *Rome*
Claudio Sorio, *Verona*
Cosimo Sperti, *Padova*
Gianni Testino, *Genova*
Giuseppe Tonini, *Rome*
Bruno Vincenzi, *Rome*
Zoli Wainer, *Forlì*
Angelo Zullo, *Rome*

**Japan**

Suminori Akiba, *Kagoshima*
Keishiro Aoyagi, *Kurume*
Narikazu Boku, *Shizuoka*
Yataro Daigo, *Tokyo*
Itaru Endo, *Yokohama*
Mitsuhiro Fujishiro, *Tokyo*
Osamu Handa, *Kyoto*
Kenji Hibi, *Yokohama*
Asahi Hishida, *Nagoya*
Eiso Hiyama, *Hiroshima*
Atsushi Imagawa, *Okayama*
Johji Inazawa, *Tokyo*
Terumi Kamisawa, *Tokyo*
Tatsuo Kanda, *Niigata*
Masaru Katoh, *Tokyo*
Takayoshi Kiba, *Hyogo*
Hajime Kubo, *Kyoto*
Hiroki Kuniyasu, *Kashihara*
Yukinori Kurokawa, *Osaka*
Chihaya Maesawa, *Morioka*
Yoshinori Marunaka, *Kyoto*
Osam Mazda, *Kyoto*
Shinichi Miyagawa, *Matsumoto*
Eiji Miyoshi, *Suita*
Toshiyuki Nakayama, *Nagasaki*
Masahiko Nishiyama, *Saitama*
Koji Oba, *Kyoto*
Masayuki Ohtsuka, *Chiba*
Masao Seto, *Aichi*
Tomoyuki Shibata, *Aichi*
Mitsugi Shimoda, *Tochigi*
Haruhiko Sugimura, *Hamamatsu*
Tomomitsu Tahara, *Aichi*
Shinji Takai, *Osaka*
Satoru Takayama, *Nagoya*
Akio Tomoda, *Tokyo*
Akihiko Tsuchida, *Tokyo*
Yasuo Tsuchiya, *Niigata*
Takuya Watanabe, *Niigata*
Toshiaki Watanabe, *Tokyo*
Yo-ichi Yamashita, *Hiroshima*
Hiroki Yamaue, *Wakayama*
Hiroshi Yasuda, *Kanagawa*
Hiroshi Yokomizo, *Kumamoto*
Yutaka Yonemura, *Osaka*
Reigetsu Yoshikawa, *Hyogo*

**Kuwait**

Fahd Al-Mulla, *Safat*

Salem Alshemmari, *Safat*

**Mexico**

Oscar G Arrieta Rodriguez, *Mexico City*

**Netherlands**

Jan Paul De Boer, *Amsterdam*
Bloemena Elisabeth, *Bloemena Elisabeth*
Peter JK Kuppen, *Leiden*
Gerrit Albert Meijer, *Amsterdam*
Anya N Milne, *Utrecht*
Godefridus J Peters, *Amsterdam*
Cornelis FM Sier, *Leiden*

**New Zealand**

Lynnette Robin Ferguson, *Auckland*
Jonathan Barnes Koea, *Auckland*

**Norway**

Kjetil Søreide, *Stavanger*

**Poland**

Andrzej Szkaradkiewicz, *Poznan*
Michal Tenderenda, *Polskiego*
Jerzy Wydmański, *Gliwice*

**Portugal**

Maria de Fátima Moutinho Gärtner, *Porto*
Celso Albuquerque Reis, *Porto*
Lucio Lara Santos, *Porto*
Maria Raquel Campos Seruca, *Porto*
Manuel António Rodrigues Teixeira, *Porto*

**Romania**

Marius Raica, *Timisoara*

**Saudi Arabia**

Ragab Hani Donkol, *Abha*

**Serbia**

Milos M Bjelovic, *Belgrade*
Goran Zoran Stanojevic, *Nis*

**Singapore**

Peh Yean Cheah, *Singapore*
Si-Shen Feng, *Singapore*
Zhi-Wei Huang, *Singapore*
Qi Zeng, *Singapore*

**South Korea**

Seungmin Bang, *Seoul*
Daeho Cho, *Seoul*
Byung Ihn Choi, *Seoul*
Hyun Cheol Chung, *Seoul*
Sang-Uk Han, *Suwon*
Jun-Hyeog Jang, *Incheon*
Seong Woo Jeon, *Daegu*
Dae Hwan Kang, *Mulgeum-Gigu*
Gyeong Hoon Kang, *Seoul*
Dong Yi Kim, *Gwangju*
Jae J Kim, *Seoul*
Jin Cheon Kim, *Seoul*
Jong Gwang Kim, *Daegu*
Min Chan Kim, *Busan*
Samyong Kim, *Daejeon*
Inchul Lee, *Seoul*
Jung Weon Lee, *Seoul*
Kyu Taek Lee, *Seoul*
Kyung Hee Lee, *Daegu*
Na Gyong Lee, *Seoul*
Suk Kyeong Lee, *Seoul*
Jong-Baeck Lim, *Seoul*
Young Joo Min, *Ulsan*
Sung-Soo Park, *Seoul*
Young Kee Shin, *Seoul*
Hee Jung Son, *Seoul*
Si Young Song, *Seoul*

**Spain**

Manuel Benito, *Madrid*
Ignacio Casal, *Madrid*
Antoni Castells, *Barcelona*
Jose JG Marin, *Salamanca*
Joan Maurel, *Barcelona*
Emma Folch Puy, *Barcelona*
Jose Manuel Ramia, *Guadalajara*
Margarita Sanchez-Beato, *Madrid*
Laura Valle, *Barcelona*
Jesus Vioque, *San Juan*

**Sweden**

Nils Albiin, *Stockholm*
Samuel Lundin, *Göteborg*
Haile Mahteme, *Uppsala*
Richard Palmqvist, *Umea*
Ning Xu, *Lund*

**Switzerland**

Paul M Schneider, *Zurich*
Luigi Tornillo, *Basel*

**Syria**

Zuhir Alshehabi, *Lattakia*

**Thailand**

Sopit Wongkham, *Khon Kaen*

**Turkey**

Uğur Coşkun, *Ankara*
Sukru Mehmet Erturk, *Istanbul*
Vedat Goral, *Diyarbakir*
Yavuz Selim Sari, *Istanbul*
Mesut Tez, *Ankara*
Murat H Yener, *Istanbul*

**United Kingdom**

Shrikant Anant, *Oklahoma City*
Runjan Chetty, *Scotland*
Chris Deans, *Edinburgh*
Dipok Kumar Dhar, *London*
Thomas Ronald Jeffry Evans, *Glasgow*
Giuseppe Garcea, *Leicester*
Oleg Gerasimenko, *Liverpool*
Neena Kalia, *Birmingham*
Anthony Maraveyas, *East Yorkshire*
Andrew Maw, *North Wales*
Kymberley Thorne, *Swansea*
Chris Tselepis, *Birmingham*
Nicholas Francis Scot Watson, *Nottingham*
Ling-Sen Wong, *Coventry*
Lu-Gang Yu, *Liverpool*

**United States**

Mohammad Reza Abbaszadegan, *Phoenix*
Gianfranco Alpini, *Temple*
Seung Joon Baek, *Knoxville*
Jamie S Barkin, *Miami Beach*
Carol Bernstein, *Arizona*
Paolo Boffetta, *New York*
Kimberly Maureen Brown, *Kansas City*
De-Liang Cao, *Springfield*
Weibiao Cao, *Providence*
Chris N Conteas, *Los Angeles*
Pelayo Correa, *Nashville*
Joseph John Cullen, *JCP*
James Campbell Cusack, *Boston*
Ananya Das, *Scottsdale*
Juan Dominguez-Bendala, *Miami*
Wafik S El-Deiry, *Philadelphia*
Laura Elnitski, *Rockville*
Guy Douglas Eslick, *Boston*
Thomas Joseph Fahey III, *New York*
James W Freeman, *San Antonio*
Bruce Joseph Giantonio, *Philadelphia*
Ajay Goel, *Dallas*
Karen Gould, *Omaha*
Nagana Gowda A Gowda, *West Lafayette*
Stephen Randolph Grobmyer, *Florida*
Young S Hahn, *Charlottesville*
John W Harmon, *Maryland*
Paul J Higgins, *New York*
Steven Norbit Hochwald, *Gainesville*
Jason L Hornick, *Boston*
Qin Huang, *Duarte*
Su-Yun Huang, *Houston*
Jamal A Ibdah, *Columbia*
Yihong Jiang-Cao Kaufmann, *Little Rock*
Temitope Olubunmilayo Keku, *Chapel Hill*
Saeed Khan, *Silver Spring*
Vijay Pranjivan Khatri, *Sacramento*

WJGO

World Journal of Gastrointestinal Oncology

Contents

Monthly Volume 7 Number 1 January 15, 2015

## MINIREVIEWS

**Contents**

*World Journal of Gastrointestinal Oncology*
**Volume 7 Number 1 January 15, 2015**





NAME OF JOURNAL
*World Journal of Gastrointestinal Oncology*

ISSN
ISSN 1948-5204 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly



EDITORIAL OFFICE
Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
*World Journal of Gastrointestinal Oncology*
Room 903, Building D, Ocean International Center, No. 62 Dongsihuan Zhonglu, Chaoyang District, Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLISHER
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

PUBLICATION DATE
January 15, 2015



INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2222-0682/g_info_20100722180909.htm.

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Gastrointestinal Oncology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4251/wjgo.v7.i1.1

*World J Gastrointest Oncol* 2015 January 15; 7(1): 1-5
ISSN 1948-5204 (online)


MINIREVIEWS

# Role of radiotherapy in the pre-operative management of carcinoma of the esophagus

Bryan H Burmeister

Bryan H Burmeister, Division of Cancer Services, Princess Alexandra Hospital, University of Queensland, Brisbane 4012, Australia
Author contributions: Burmeister BH solely contributed to this manuscript.
Conflict-of-interest: I have no other conflicts of interest to declare.

Correspondence to: Bryan H Burmeister, MD, Division of Cancer Services, Princess Alexandra Hospital, University of Queensland, 199 Ipswich Road, Brisbane 4102, Australia. bryan.burmeister@health.qld.gov.au
Telephone: +61-7-31766581
Fax: +61-7-31761983
Received: June 30, 2014
Peer-review started: June 30, 2014
First decision: October 28, 2014
Revised: December 16, 2014
Accepted: December 29, 2014
Article in press: December 31, 2014
Published online: January 15, 2015

## Abstract

The use of radiotherapy in the management of carcinoma of the esophagus and gastro-esophageal junction has undergone much evolution over the past 2 decades. Advances to define its role have been slow with meta-analyses often providing the most useful data. In spite of this many institutions around the world are divided about the role of radiotherapy in this disease and attribute different roles to radiotherapy based on clinical stage, tumor site and histology. The purpose of this review is to try to define the role of radiotherapy given our current knowledge base and to review which current and future trials may fill the gaps of knowledge that we currently have. It will also highlight the difficulties in making firm recommendations about the use of radiotherapy especially in a time when technology and treatments are rapidly evolving.

**Key words:** Esophageal cancer; Preoperative therapy; Neoadjuvant therapy; Chemoradiotherapy; Surgery



**Core tip:** This review describes the history and development of radiotherapy in the pre-operative setting for resectable esophageal cancer. In particular it focuses on data from multicenter phase Ⅱ and phase Ⅲ trials as well as meta-analyses from across the world. The review concludes with a discussion about the role of new radiation technologies in the management of esophageal cancer.

Burmeister BH. Role of radiotherapy in the pre-operative management of carcinoma of the esophagus. *World J Gastrointest Oncol* 2015; 7(1): 1-5 Available from: URL: http://www.wjgnet.com/1948-5204/full/v7/i1/1.htm DOI: http://dx.doi.org/10.4251/wjgo.v7.i1.1

## INTRODUCTION

The issue of improving loco-regional control and possibly survival for resectable esophageal cancer has been a subject of interest for about the last 3 decades. Prior to 1980 radiotherapy was used mostly as sole modality for therapy when patients were not suitable for surgery. Response rates and survival however were low and it was only when chemotherapy was added to radiotherapy that response rates improved and long term remissions

from the disease were noted. At the time, squamous cell carcinoma (SCC) was the predominant cell type and being a relatively responsive disease, most early clinical trials involving pre-operative therapy were confined to that histology. It was only in the late 1990s that some investigators began to include adenocarcinoma (AC) in neoadjuvant clinical trials on the basis that if surgery was to be the major treatment modality, histological subtype might not play a major role in outcomes. In this review I trace the progress of the early trials involving SCC only, the combined histology trials and finally some of the meta-analyses, most of which have included both histological subtypes. The dilemma however is far from resolved with the issue of whether radiotherapy adds real benefit to systemic therapy in terms of survival and loco-regional control yet to be determined in a randomized trial.

## PRE-OPERATIVE RADIATION THERAPY

Following the suggestion that radiotherapy may lead to a complete pathological response (pCR) in some patients prior to surgery in esophageal cancer, some investigators did report non-randomized retrospective comparisons of surgery alone *vs* pre-operative radiotherapy followed by surgery. Radiation doses ranged from 20-60 Gy and there were some reports of a survival improvement in those treated with both radiotherapy and surgery, although these studies were non-randomized and clearly a possibility of better performance status patients having combined modality therapy existed. It was not long however before randomized trials were devised to assess outcomes following pre-operative radiotherapy. Between 1981 and 1992 five randomized trials were reported[1-5]. All of these involved SCC and radiation doses varied from 20-40 Gy. Survival outcomes were inconsistent with 3 trials reporting improved survival with pre-operative radiotherapy[2,3,5] and 2 had better survival in the surgery alone arm[1,4]. None of these results however reached statistical significance. Nevertheless an average of 15% of patients did achieve a pCR and local failure rates ranged from 20%-58%. Since that time radiotherapy as a single modality is seldom used as a sole modality in the pre-operative setting.

## PRE-OPERATIVE CHEMORADIOTHERAPY

The use of pre-operative chemoradiotherapy in esophageal cancer was first used in 2 phase Ⅱ studies based in the United States[6,7]. The Southwestern Oncology Group trial accrued 113 patients treated with pre-operative chemoradiotherapy using concurrent cisplatin, fluorouracil and 30 Gy. Median survival was 12 mo and 3 year survival 16%[7]. The RTOG study had even poorer survival[6]. Several other phase Ⅱ trials incorporating tri-modality therapy have been done, including some incorporating newer chemotherapy agents including paclitaxel, carboplatin and oxaliplatin. Most show similar median survival times of 20%-58% although the selection criteria for these studies vary and may well affect the different outcomes.

There have been numerous randomized trials comparing surgery alone with pre-operative chemoradiotherapy followed by surgery[8-14]. The earlier studies only involved patients with SCC but more recent ones included both histologies. The first to report a positive outcome in favor of tri-modality therapy was that by Walsh *et al*[12] who only reported the outcomes of a subset of AC patients despite the fact that both subtypes were included in the trial[12]. Although the outcome was significantly beneficial in terms of survival for those receiving chemoradiotherapy, the trial has been criticized as the workup imaging did not include computed tomography (CT) scanning of the chest and abdomen and the outcomes of the surgery alone arm were exceptionally poor. More recently the trials by Tepper *et al*[15] and the CROSS study by van Hagen *et al*[16] have clearly shown benefits in survival and these have both been based on high tumor response rates including pCR rates in the experimental arm. Some of the other chemoradiotherapy trials have shown benefits for subgroups. The Australian trial by Burmeister *et al*[14] showed a benefit for patients with SCC but not AC and then because AC constituted the majority of patients recruited to the trial, there was no overall survival benefit. In the trial by Urba, the benefit was seen in overall survival at 3 years but the difference did not reach statistical significance[13]. Other trials in this area have been negative in terms of survival but have also been criticized because of having low doses of radiotherapy and split courses of treatment.

## OUTCOMES OF META-ANALYSES

Meta-analyses (MAs) are frequently used to reach conclusions about absolute trial endpoint such as survival when individual trials don't have enough numbers to provide statistically significant outcomes. The problem is that when trials are included in MAs the sample populations may be different with different eligibility criteria, requirements for clinical staging and in esophageal cancer, different histological subtypes. Requirements for clinical staging may be evolutionary in that earlier trial investigators may not have had access to more contemporary forms of imaging such as CT or positron emission tomography (PET). This means that some of the earlier trials may have included patients with more advanced disease that would be excluded by more modern forms of imaging. Another issue with MAs is that they often fail to address secondary endpoints such as loco-regional control, pCR rates, resectability rates, toxicity and quality of life, unless all the trials included these endpoints and the same methodology in assessing them was used.

### *Radiotherapy plus surgery vs surgery alone*

For patients having pre-operative radiotherapy alone, there is only one MA which has been published on multiple occasions as a Cochrane review[17]. This review involved all 5 randomized trials comparing surgery alone with pre-operative radiotherapy followed by surgery. The dominant histology was SCC although some trials

did include AC. The outcomes was an improvement in survival in those patients receiving combined therapy although this did not reach statistical significance ($P$ = 0.06).

### Chemoradiotherapy plus surgery vs surgery alone

There are multiple MAs involving a comparison of surgery alone with pre-operative chemoradiotherapy[18-23]. These have evolved with the completed trials. The first of these to be published was by Urschel *et al*[18] in 2003 and involved more than 1000 patients from 9 randomized trials[18]. They concluded there was a benefit for pre-operative chemoradiotherapy in terms of survival at 3 years. The most widely quoted meta-analysis was published by Gebski *et al*[22] in 2007 combining results of 10 trials and more than 1200 patients. They found a significant benefit in terms of all-cause mortality for those patients receiving pre-operative chemoradiotherapy with a hazard ratio of 0.81 (95%CI: 0.70-0.93; $P$ = 0.002). Three years later the same group updated their results with outcomes from 12 trials and 1854 patients[23]. The hazard ratio for all-cause mortality with patients receiving pre-operative chemoradiotherapy was 0.78 (95%CI: 0.70-0.88, $P$ < 0.0001), indicating a more definite result in favor of neoadjuvant therapy.

### Chemoradiotherapy plus surgery vs chemotherapy plus surgery

The meta-analysis by Sjoquist *et al*[23] also included a subgroup review of comparisons of pre-operative chemotherapy *vs* pre-operative chemoradiotherapy. Only 2 trials were able to be included. Both included only patients with AC and both were underpowered. The first one published by Stahl *et al*[24] included junctional tumours and a long extended course of neoadjuvant chemotherapy. The second by Burmeister *et al*[25] had a much shorter chemotherapy regimen and included only esophageal cancer patients. It did suggest that trimodality therapy did improve resectability rates. Neither trial showed a survival benefit for trimodality over bimodality therapy, both being concluded prematurely due to poor accrual. The hazard ratio for these 2 trials combined was 0.77 (95%CI: 0.53-1.12; $P$ = 0.17) in favor of neoadjuvant chemoradiotherapy. This however is clearly not significant and more trials comparing these 2 approaches are required and are currently being conducted.

### Individual patient data meta-analysis

In 2013 Ronellenfitsch *et al*[26] published a more detailed MA involving individual patient data (IPD). This is a more sophisticated form of MA in that it enables one to look at subgroups and secondary outcomes in more detail. Unfortunately this MA also did not include the CROSS trial, and some trial chairs refused to provide IPD. Not only did this MA confirm the survival benefit seen in patients receiving neoadjuvant chemotherapy and chemoradiotherapy, but it also detected an improved benefit for junctional tumours. Improved benefits were also noted for other subgroups, such as Eastern Co-operative Oncology Group performance status 0, male gender and age < 65 years. They were also able to look at disease-free survival in some trials which mirrored outcomes in overall survival, although not reaching statistical significance. They also found no difference in post-operative morbidity or mortality. They were however unable to further define the role of radiotherapy in the pre-operative management of esophageal cancer using the IPD that they managed to procure.

## NEW RADIOTHERAPY TECHNOLOGIES

Radiotherapy technology has been rapidly evolving over the past decade with most tumors and sites now being able to be treated with highly conformal therapies including intensity modulated radiotherapy and volumetric modulated arc therapy. These new technologies have enabled the oncologist to deliver high doses of radiation with more precision to the tumor and at the same time spare surrounding tissues and organs which has dramatically reduced morbidity. In esophageal cancer the uptake of these modalities has been slow but in currently imbedded in most new protocols involving definitive treatment. It is only a matter of time until they are routinely used in the neoadjuvant setting where the big gain will be in offsetting radiation related surgical morbidity with high doses. It also may enable one to delay surgery which is currently conducted 4-8 wk post radiotherapy to 10-12 wk post radiotherapy. This in turn may make it possible to avoid surgery in some patients where a complete endoscopic and PET related response has been achieved. This concept of "surgery as needed" is increasingly being adopted at other sites where neoadjuvant chemoradiotherapy is used and has the potential to not only reduce health costs but improve quality of life for patients during their cancer journey.

## DISCUSSION

One of the big issues around assessing the value of the local treatment modality is deciding on the magnitude of its benefit if there is indeed one. Local treatment modalities such as surgery and radiotherapy aim primarily to control tumors at the primary site and/or regional lymph nodes in order to reduce or eliminate the problems associated with uncontrolled tumor and the effects it may have function, cosmesis, and control of local symptoms. In the esophagus elimination of dysphagia is a principle aim of local treatment with surgery being able to do this effectively with all small tumors and radiotherapy with some small tumors especially SCC. Better control rates are theoretically obtained with these 2 modalities combined in more advanced tumors. Radiotherapy given in the pre-operative setting has the advantage of being able to downstage tumours and make resections easier with less chance of having involved margins.

However in order to have an impact on survival, comparisons of different local treatment modalities require large numbers of patients because improvements in local

control will only result in a survival benefit in a small proportion of those who experience a local control benefit. This means that most published randomized clinical trials comparing local modalities have not shown a survival benefit but rather one in terms of local control and improved resectability where surgery has been involved.

On the other hand trials that have added a systemic therapy such as chemotherapy to one arm of the trial could be expected to possibly confer a survival benefit. This is on the basis of many patients already having subclinical metastatic disease that a systemic agent may be able to control or delay converting to overt metastases. In addition the chemotherapy agents used in esophageal cancer have useful radio-sensitizing properties which may enhance the effects of radiotherapy and further improve local outcomes. It is however unknown whether an exceptionally good local outcome such as pCR at time of surgery is always associated with prolonged survival although many studies suggest that it does.

Many of the randomized trials involving chemotherapy have shown a survival benefit in their own right. Some such as the Walsh trial[12] have been interpreting as having a suboptimal result in the control arm whilst other more recent trials such as the CROSS trial clearly show a survival benefit for combined modality therapy and an improvement in local outcomes as well[16]. So in summary we still need to decide which patients require radiotherapy in addition to surgery plus platinum-based chemotherapy. The MAs and some trials suggest the all SCC patients may benefit. However the case in AC is far less clear, with possible more advanced tumors, those with ill defined resection margins on CT and those with nodal disease more likely to benefit in terms of local control. This hypothesis however is far from confirmed.

So what is clear right now is that although the most recent complete MA by Sjoquist *et al*[23] clearly demonstrates an improved survival advantage for neoadjuvant chemoradiotherapy when compared to neoadjuvant chemotherapy, this approach may not be required in all patients. More trials comparing these 2 modalities are being done but will take several years to analyze and may not have enough patients to give answer to all the endpoints apart from survival. Issues such as local control, respectability, toxicity and cost all are relevant in the current era. By doing more MAs involving IPD one has the potential to look at subgroups and secondary endpoints more rigorously and hopeful identify optimum therapies for patients.

## CONCLUSION

At the time of writing this review there remains controversy on the role of radiotherapy as part of a combined package with chemotherapy as a neoadjuvant therapy for operable esophageal cancer. Completion of the ongoing clinical trials investigating this role and sharing of the data as part of further MAs will add to our knowledge base in the management of esophageal cancer.

## REFERENCES


1 **Launois B**, Delarue D, Campion JP, Kerbaol M. Preoperative radiotherapy for carcinoma of the esophagus. *Surg Gynecol Obstet* 1981; **153**: 690-692 [PMID: 6794167]

2 **Huang G**, Gu X, Wang I. Experience with combined preoperative irradiation and surgery for carcinoma of the esophagus. *Gann Monogr Cancer Res* 1986; **31**: 159-164

3 **Gignoux M**, Roussel A, Paillot B, Gillet M, Schlag P, Favre JP, Dalesio O, Buyse M, Duez N. The value of preoperative radiotherapy in esophageal cancer: results of a study of the E.O.R.T.C. *World J Surg* 1987; **11**: 426-432 [PMID: 3630187 DOI: 10.1007/BF01655805]

4 **Arnott SJ**, Duncan W, Kerr GR, Walbaum PR, Cameron E, Jack WJ, Mackillop WJ. Low dose preoperative radiotherapy for carcinoma of the oesophagus: results of a randomized clinical trial. *Radiother Oncol* 1992; **24**: 108-113 [PMID: 1496141 DOI: 10.1016/0167-8140(92)90287-5]

5 **Nygaard K**, Hagen S, Hansen HS, Hatlevoll R, Hultborn R, Jakobsen A, Mäntyla M, Modig H, Munck-Wikland E, Rosengren B. Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. *World J Surg* 1992; **16**: 1104-1109; discussion 1110 [PMID: 1455880 DOI: 10.1007/BF02067069]

6 **Seydel HG**, Leichman L, Byhardt R, Cooper J, Herskovic A, Libnock J, Pazdur R, Speyer J, Tschan J. Preoperative radiation and chemotherapy for localized squamous cell carcinoma of the esophagus: a RTOG Study. *Int J Radiat Oncol Biol Phys* 1988; **14**: 33-35 [PMID: 3335460 DOI: 10.1016/0360-3016(88)90047-8]

7 **Poplin E**, Fleming T, Leichman L, Seydel HG, Steiger Z, Taylor S, Vance R, Stuckey WJ, Rivkin SE. Combined therapies for squamous-cell carcinoma of the esophagus, a Southwest Oncology Group Study (SWOG-8037). *J Clin Oncol* 1987; **5**: 622-628 [PMID: 3559653]

8 **Apinop C**, Puttisak P, Preecha N. A prospective study of combined therapy in esophageal cancer. *Hepatogastroenterology* 1994; **41**: 391-393 [PMID: 7959579]

9 **Le Prise E**, Etienne PL, Meunier B, Maddern G, Ben Hassel M, Gedouin D, Boutin D, Campion JP, Launois B. A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. *Cancer* 1994; **73**: 1779-1784 [PMID: 8137201 DOI: 10.1002/1097-0142(19940401)73]

10 **Bosset JF**, Gignoux M, Triboulet JP, Tiret E, Mantion G, Elias D, Lozach P, Ollier JC, Pavy JJ, Mercier M, Sahmoud T. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med* 1997; **337**: 161-167 [PMID: 9219702 DOI: 10.1056/NEJM199707173370304]

11 **Lee JL**, Park SI, Kim SB, Jung HY, Lee GH, Kim JH, Song HY, Cho KJ, Kim WK, Lee JS, Kim SH, Min YI. A single institutional phase III trial of preoperative chemotherapy with hyperfractionation radiotherapy plus surgery versus surgery alone for resectable esophageal squamous cell carcinoma. *Ann Oncol* 2004; **15**: 947-954 [PMID: 15151953 DOI: 10.1093/annonc/mdh219]

12 **Walsh TN**, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 1996; **335**: 462-467 [PMID: 8672151 DOI: 10.1056/NEJM199608153350702]

13 **Urba SG**, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol* 2001; **19**: 305-313 [PMID: 11208820]

14 **Burmeister BH**, Smithers BM, Gebski V, Fitzgerald L,

Simes RJ, Devitt P, Ackland S, Gotley DC, Joseph D, Millar J, North J, Walpole ET, Denham JW. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. *Lancet Oncol* 2005; **6**: 659-668 [PMID: 16129366 DOI: 10.1016/S1470-2045(05)70288-6]

15 **Tepper J**, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, Kiel K, Willett C, Sugarbaker D, Mayer R. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J Clin Oncol* 2008; **26**: 1086-1092 [PMID: 18309943 DOI: 10.1200/JCO.2007.12.9593]

16 **van Hagen P**, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; **366**: 2074-2084 [PMID: 22646630 DOI: 10.1056/NEJMoa1112088]

17 **Arnott SJ**, Duncan W, Gignoux M, Hansen HS, Launois B, Nygaard K, Parmar MK, Rousell A, Spilopoulos G, Stewart G, Tierney JF, Wang M, Rhugang Z. Preoperative radiotherapy for esophageal carcinoma. *Cochrane Database Syst Rev* 2005; **(4)**: CD001799 [PMID: 16235286]

18 **Urschel JD**, Vasan H. A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. *Am J Surg* 2003; **185**: 538-543 [PMID: 12781882 DOI: 10.1016/S0002-9610(03)00066-7]

19 **Kaklamanos IG**, Walker GR, Ferry K, Franceschi D, Livingstone AS. Neoadjuvant treatment for resectable cancer of the esophagus and the gastroesophageal junction: a meta-analysis of randomized clinical trials. *Ann Surg Oncol* 2003; **10**: 754-761 [PMID: 12900366 DOI: 10.1245/ASO.2003.03.078]

20 **Fiorica F**, Di Bona D, Schepis F, Licata A, Shahied L, Venturi A, Falchi AM, Craxì A, Cammà C. Preoperative chemoradiotherapy for oesophageal cancer: a systematic review and meta-analysis. *Gut* 2004; **53**: 925-930 [PMID: 15194636 DOI: 10.1136/gut.2003.025080]

21 **Greer SE**, Goodney PP, Sutton JE, Birkmeyer JD. Neoadjuvant chemoradiotherapy for esophageal carcinoma: a meta-analysis. *Surgery* 2005; **137**: 172-177 [PMID: 15674197 DOI: 10.1016/j.surg.2004.06.033]

22 **Gebski V**, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol* 2007; **8**: 226-234 [PMID: 17329193 DOI: 10.1016/S1470-2045(07)70039-6]

23 **Sjoquist KM**, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, Gebski V. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011; **12**: 681-692 [PMID: 21684205 DOI: 10.1016/S1470-2045(11)70142-5]

24 **Stahl M**, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J, Langer P, Engenhart-Cabillic R, Bitzer M, Königsrainer A, Budach W, Wilke H. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol* 2009; **27**: 851-856 [PMID: 19139439 DOI: 10.1200/JCO.2008.17.0506]

25 **Burmeister BH**, Thomas JM, Burmeister EA, Walpole ET, Harvey JA, Thomson DB, Barbour AP, Gotley DC, Smithers BM. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. *Eur J Cancer* 2011; **47**: 354-360 [PMID: 21084184 DOI: 10.1016/j.ejca.2010.09.009]

26 **Ronellenfitsch U**, Schwarzbach M, Hofheinz R, Kienle P, Kieser M, Slanger TE, Burmeister B, Kelsen D, Niedzwiecki D, Schuhmacher C, Urba S, van de Velde C, Walsh TN, Ychou M, Jensen K. Preoperative chemo(radio)therapy versus primary surgery for gastroesophageal adenocarcinoma: systematic review with meta-analysis combining individual patient and aggregate data. *Eur J Cancer* 2013; **49**: 3149-3158 [PMID: 23800671 DOI: 10.1016/j.ejca.2013.05.029]

**P- Reviewer**: Milone M, Natsugoe S, Vieth M **S- Editor**: Ji FF
**L- Editor**: A **E- Editor**: Wu HL


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