JOURNAL OF GERIATRIC ONCOLOGY 7 (2016) 176–186

Available online at www.sciencedirect.com

ScienceDirect

Comparative effectiveness of postoperative chemotherapy among older patients with non-metastatic rectal cancer treated with preoperative chemoradiotherapy

Jennifer L. Lund[a,c,*], *Til Sturmer*[a,c], *Hanna K. Sanoff*[b,c]

[a]*Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA*
[b]*Department of Medicine, University of North Carolina, Chapel Hill, NC, USA*
[c]*Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA*

ARTICLE INFO

Article history:
Received 23 October 2015
Received in revised form
14 January 2016
Accepted 29 January 2016
Available online 23 February 2016

Keywords:
Rectal cancer
Chemotherapy
Aging
Comparative effectiveness research

ABSTRACT

Objective: Postoperative chemotherapy is standard following preoperative chemoradiation therapy (CRT) and curative resection for clinically staged II/III rectal cancer. Recent trials have questioned whether postoperative chemotherapy improves overall survival. The objective of the study was to evaluate the comparative effectiveness of postoperative chemotherapy following CRT or radiation therapy (RT) with specific attention to the impact of age on postoperative chemotherapy effectiveness.

Materials and Methods: Patients treated with CRT or RT then resection of pathologically staged 0-III rectal cancer diagnosed from 2004 to 2009 were identified from the Surveillance, Epidemiology and End Results program-Medicare database. Propensity score weighted Cox proportional hazards models and Kaplan Meier methods were used to compare the effectiveness of 1) postoperative 5-fluorouracil (5-FU) or capecitabine to no treatment and 2) postoperative oxaliplatin + 5-FU/capecitabine to 5-FU/capecitabine alone on mortality. Results were stratified by age.

Results: We identified 1316 patients; 49% received postoperative chemotherapy, 341 (52%) included oxaliplatin. After weighting, postoperative 5-FU/capecitabine alone was associated with decreased mortality in patients aged 66–74 (adjusted hazard ratio (aHR) = 0.46, 95% CI: 0.30, 0.72), corresponding to a 5-year risk difference of −0.23, (95% CI: −0.33, −0.12). No further mortality reduction from adding oxaliplatin to 5-FU/capecitabine was seen in patients aged 66–74 (aHR = 1.57, 95% CI: 0.93, 2.65). No mortality reduction for 5-FU/capecitabine alone was observed among patients aged 75+ (aHR = 1.11, 95% CI: 0.76, 1.63).

Conclusions: Among patients <75 years, postoperative 5-FU/capecitabine was associated with reduced mortality after preoperative CRT/RT and surgical resection; however, the addition of oxaliplatin was not associated with further mortality reduction. Decisions regarding postoperative chemotherapy after age 75 warrant consideration of individual patient risks and preferences, as benefits may be limited.

* *Corresponding author at:* Department of Epidemiology, 2102-D McGavran-Greenberg Hall, Gillings School of Global Public Health, CB#7435, University of North Carolina, Chapel Hill, NC 27599-7435, USA. Tel.: +1 919 966 7440; fax: +1 919 966 2089.
E-mail address: Jennifer.Lund@unc.edu (J.L. Lund).

http://dx.doi.org/10.1016/j.jgo.2016.01.011
1879-4068/

1. Introduction

For over 30 years the standard curative approach for stage II and III rectal cancer has included surgical resection, chemoradiotherapy (CRT), and 5-fluoruracil (5-FU)-based postoperative chemotherapy. This approach is based on results of randomized controlled trials (RCTs) conducted in the 1980s–90s where patients treated with all three modalities had the lowest rates of local and distant recurrence and the longest survival.[1,2] Rectal cancer treatment has since evolved. Total mesorectal excision is now standard with resultant lower rates of local recurrence.[3–6] CRT is administered preoperatively, providing better functional outcomes and possibly better local control and DFS.[7,8] In 2004, the addition of oxaliplatin to 5-FU or capecitabine was shown to offer incremental survival benefit for patients with stage III colon cancer,[9–12] and its use was rapidly incorporated into treatment guidelines for rectal cancer and disseminated into routine clinical practice.[13]

While the best outcomes have been observed in patients treated with all modalities, early trials were not designed to test the individual contribution of each component of the preoperative CRT and postoperative chemotherapy platform on rectal cancer outcomes. The Cochrane Collaboration conducted a meta-analysis of 21 RCTs to examine whether the postoperative chemotherapy component in isolation reduces mortality over observation.[14] The meta-analysis reported a 17% reduction in the relative risk of all-cause mortality associated with postoperative chemotherapy; however, only a single trial, EORTC 22921, specifically evaluated chemotherapy following modern preoperative CRT. Now after 10 years of follow-up, 5-FU only marginally reduced mortality compared with observation (hazard ratio (HR) = 0.91, 95% CI: 0.77, 1.09); however, fewer than half of patients in EORTC 22921 were able to complete postoperative therapy at the planned dose and schedule.[15,16] A second multi-trial analysis in which individual patient data from EORTC 22921 were combined with that of three additional trials of chemotherapy following preoperative treatment showed no benefit of postoperative chemotherapy (HR = 0.97, 95% CI: 0.81, 1.17).[17]

The three recently completed randomized trials comparing postoperative 5-FU/capecitabine with and without oxaliplatin have done little to elucidate the role of postoperative oxaliplatin, as in two trials the addition of oxaliplatin resulted in an improvement in disease free survival (DFS) of a similar magnitude as is seen in stage III colon cancer, but the third reported no DFS benefit.[18–20] Though long-term follow-up is immature, it seems unlikely that these results will markedly change given the close relationship between DFS and overall survival in colorectal cancer.[21]

While expert guidelines from the National Comprehensive Cancer Network,[22] European Society of Medical Oncology,[23] and the National Institute for Health and Care Excellence[24] continue to include the recommendation to at least consider postoperative chemotherapy, there is insufficient data about the effectiveness of postoperative chemotherapy (with our without oxaliplatin) to reduce recurrence or cancer mortality in preoperatively-treated patients.[25,26] Because older adults tend to be underrepresented in trials,[27] there are even less data regarding the effectiveness of postoperative chemotherapy approaches in this population.

We evaluated the effectiveness of postoperative chemotherapy with 5-FU or capecitabine alone – and the incremental effectiveness of oxaliplatin – following preoperative CRT and surgery for rectal cancer in routine care settings in the USA. With over half of all patients with rectal cancer diagnosed over the age of 65,[28] we also specifically evaluated the impact of age on the comparative effectiveness of postoperative chemotherapy approaches.

2. Methods

2.1. Data Sources

Cancer cases were obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program which collects demographic and tumor data for individuals diagnosed with cancer residing within one of the 18 SEER regions.[29] The linkage of persons in SEER with their Medicare enrollment and claims data allows for the identification of cancer treatments[30,31] and extended mortality follow-up.

2.2. Study Population

We included patients diagnosed with pathologically confirmed, first primary cancer of the rectum/rectosigmoid junction from 2004 to 2009, with continuous Medicare parts A and B fee-for-service and no managed care enrollment for the 12-months before and 6-months following the cancer diagnosis date, ensuring complete claims capture and to define covariates and treatments. Patients with American Joint Commission on Cancer (AJCC) 6th Edition stage 0-III were included to ensure inclusion of patients with clinical stage II and III rectal cancer (for which CRT is standard) who were down staged by preoperative therapy because pathologic stage (e.g. ypT and ypN stage) supersedes clinical stage in SEER. Patients who underwent complete surgical resection within 180 days from diagnosis and received preoperative CRT or radiation therapy alone (RT) between the date of diagnosis and surgery date were included in the study.

2.3. Ascertainment of Treatment

Administrative codes identified cancer-directed treatments (Appendix A) and have high validity for identifying specific chemotherapy agents.[30–32] Postoperative chemotherapy was assessed from the date of surgery through the following 122 days (4 months). Specific chemotherapeutic agents administered within the 60 days of the first chemotherapy administration were used to define the initial postoperative chemotherapy group (i.e., 5-FU/capecitabine alone or in combination with oxaliplatin).[30,33–35]

2.4. Ascertainment of All-Cause and Cancer-Specific Mortality

The primary outcome of interest was all-cause mortality ascertained through December 2011 from the Medicare enrollment database.[36] Follow-up began 122 days from the surgery date (i.e., the landmark). The secondary outcome of cancer-