J Cancer Res Clin Oncol (2017) 143:313–320
DOI 10.1007/s00432-016-2289-y

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

The recommended treatment strategy for locally advanced gastric cancer in elderly patients aged 75 years and older: a Surveillance, Epidemiology, and End Results database analysis

Kai-tai Liu[1] · Jue-feng Wan[2,3] · Gen-hua Yu[4] · Yan-ping Bei[1] · Xue Chen[1] · Miao-zhen Lu[1]

Received: 6 September 2016 / Accepted: 10 October 2016 / Published online: 18 October 2016

Background As patients aged 75 years and older are often underrepresented in randomized clinical trials, the external validity of clinical trials-based recommendations in older gastric patients was still controversial. The aim of this study is to explore the recommended treatment strategy for locally advanced gastric cancer in elderly patients.
Methods We designed our study to specifically evaluate the cancer-specific survival (CSS) of four subgroups of patients according to four different treatment modalities: adjuvant radiation (RT), surgery only, RT only and no surgery/no RT by analyzing the Surveillance, Epidemiology, and End Results (SEER)-registered database. Kaplan–Meier methods were adopted and multivariable Cox regression models were built for the analysis of survival outcomes and risk factors.
Results The 5-year CSS was 43.8 % in adjuvant RT, 28.5 % in surgery only, 14.9 % in RT only and 1.4 % in no surgery/no RT, which had significant difference in univariate log-rank test ($P < 0.001$) and multivariate Cox regression ($P < 0.001$). Moreover, we observed significant survival benefits in adjuvant RT group in all age categories, including age 75–79 years, age 80–84 years and age ≥85 years (all $P < 0.001$).
Conclusions Surgery and adjuvant RT may be the recommended treatment strategy in elderly patients with locally advanced gastric cancer, especially for patients medically fit for the combined modality therapy.

Keywords Gastric cancer · Elderly · Treatment · SEER

Introduction

By some estimates, gastric cancer is the fifth most frequently diagnosed cancer and the third leading cause of death from cancer worldwide (Ferlay et al. 2013). Gastric cancer is often diagnosed at an advanced stage and has a poor outcome (Macdonald 2006). Postoperative chemoradiation therapy has been established as a standard of care in patients with locally advanced gastric cancer (Macdonald et al. 2001; Lee et al. 2006, 2012; Leong et al. 2011). In general, patients were excluded if they were older than 75 years of age in most clinical trials, for the reason that elderly patients are more likely to have other concomitant chronic illnesses, which may increase the risk of complications and even death during treatment. Indeed, older patients with gastric cancer are less likely to receive standard treatment compared to younger patients, even when such treatments are potentially curative (Hundahl et al. 1997). Thus, the optimal treatment strategies in elderly patients are still controversial.

We designed our study to specifically evaluate the cancer-specific survival of four subgroups of elderly patients with locally advanced gastric cancer (T3, T4 Any N or Any T, N+) according to four different treatment modalities:

Kai-tai Liu, Jue-feng Wan and Gen-hua Yu have contributed equally to this work.

✉ Miao-zhen Lu
lmz2005@yeah.net

[1] Department of Radiation Oncology, Lihuili Hospital, Ningbo Medical Center, No. 57, Xing'Ning Road, Ningbo 315041, China

[2] Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

[3] Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

[4] Department of Radiation Oncology, Huzhou Central Hospital, Huzhou, Zhejiang Province, China

adjuvant radiation (RT), surgery only, RT only and no surgery/no RT by analyzing the Surveillance, Epidemiology, and End Results (SEER)-registered database.

Results

Patient characteristics

We identified 3218 patients in SEER database during the 8-year study period (between 2004 and 2011) who met inclusion criteria. There were 499 patients in adjuvant RT, 2012 patients in surgery only, 305 patients in RT only and 402 patients in no surgery/no RT. There were 1783 (55.4 %) males and 1435 (44.6 %) females. The median diagnosis age was 87 years (range 75–100), and the majority of patients were white (71.1 %). Patient demographics and pathological features are summarized in Table 1. Although the proportion fell every year from 2004 to 2011, patients aged 75 years and older still made up more than one-third of the population of gastric cancer (Fig. 1). Compared with the slight decreasing pattern of surgery only, the increasing trends of RT only and no surgery/no RT were observed in elderly patients. Moreover, the adjuvant RT accounted for <20 % of care patterns for elderly patients with locally advanced gastric cancer, of which the trend changed little from 2004 to 2011 (Fig. 2). But in patients younger than 75 years with locally advanced gastric cancer, the adjuvant RT accounted for almost 40 % of care patterns (Fig. 3).

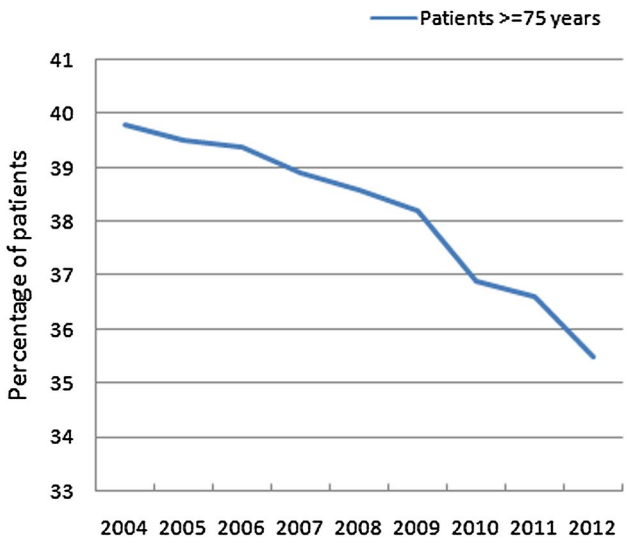

Fig. 1 Trend of the proportion of patients with gastric cancer aged 75 years and older from 2004 to 2011

Impact of different treatment strategies on survival outcomes in elderly patients with gastric cancer

The 5-year CSS was 43.8 % in adjuvant RT, 28.5 % in surgery only, 14.9 % in RT only and 1.4 % in no surgery/no RT, which had significant difference in univariate log-rank test ($P < 0.001$) (Fig. 4). Furthermore, the survival analyses were stratified by different age groups (age 75–79 years, age 80–84 years, age ≥85 years, Figs. 5, 6, 7). It demonstrated

Table 1 Patient characteristics

Variable	Total $n = 3218$	Adjuvant RT $n = 499$ (%)	Surgery only $n = 2012$ (%)	RT only $n = 305$ (%)	No surgery/no RT $n = 402$ (%)	*P* value
Sex						<0.001
Male	1783	314 (62.9)	1043 (51.8)	213 (69.8)	213 (53.0)	
Female	1435	185 (37.1)	969 (48.2)	92 (30.2)	189 (47.0)	
Race						<0.001
White	2288	329 (65.9)	1400 (69.6)	255 (83.6)	304 (75.6)	
Black	343	57 (11.4)	221 (11.0)	22 (7.2)	43 (10.7)	
Other	587	113 (22.7)	391 (19.4)	28 (9.2)	55 (13.7)	
Pathological grading						<0.001
Grade I	74	11 (2.2)	46 (2.3)	10 (3.3)	7 (1.8)	
Grade II	903	138 (27.7)	604 (30.0)	87 (28.5)	74 (18.4)	
Grade III	1974	330 (66.1)	1271 (63.2)	151 (49.5)	222 (55.2)	
Grade IV	67	12 (2.4)	44 (2.2)	5 (1.6)	6 (1.5)	
Unknown	200	8 (1.6)	47 (2.3)	52 (17.1)	93 (23.1)	
Histological type						0.022
Adenocarcinoma	2613	392 (78.6)	1648 (81.9)	253 (83.0)	320 (79.6)	
Mucinous	114	16 (3.2)	82 (4.1)	9 (3.0)	7 (1.7)	
Signet ring cell	491	91 (18.2)	282 (14.0)	43 (14.0)	75 (18.7)	

RT radiation

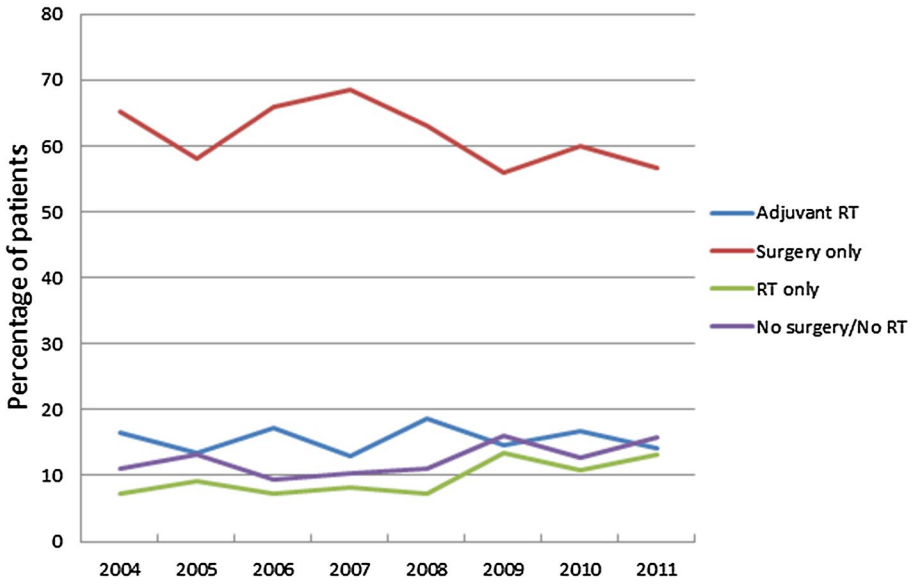

Fig. 2 Patterns of care are illustrated for elderly patients (≥75) with locally advanced gastric cancer from 2004 to 2011 according to treatment modality. RT indicates radiation

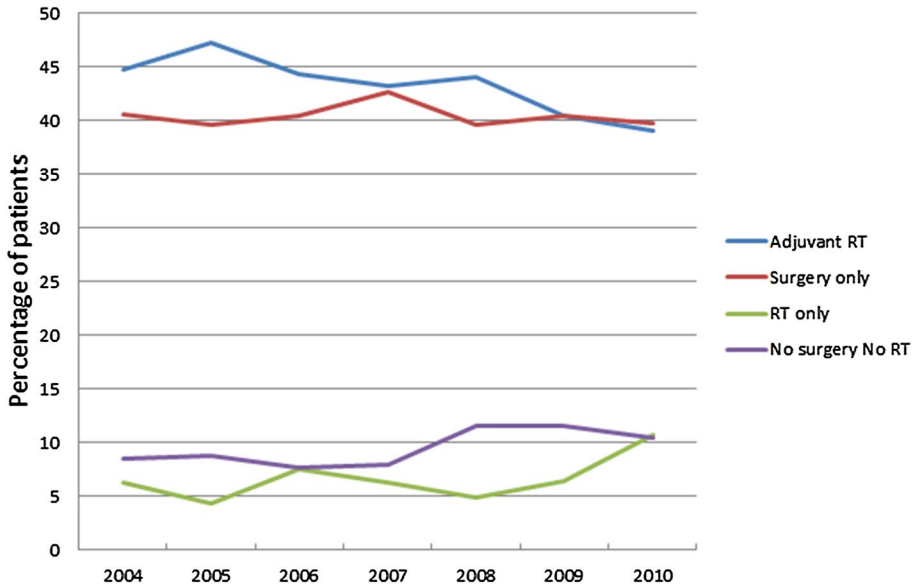

Fig. 3 Patterns of care are illustrated for patients (<75) with locally advanced gastric cancer from 2004 to 2011 according to treatment modality. RT indicates radiation

that adjuvant RT significantly increase survival in all age categories, including age 75–79 years, age 80–84 years and age ≥85 years (all $P < 0.001$). Besides, signet ring cancer, white and black race, higher tumor grade were identified as significant risk factors for poor survival on univariate analysis (all $P < 0.001$) (Table 2). When multivariate analysis with Cox regression was performed, we convinced these factors as independent prognostic factors (Table 2).

Discussion

Gastric cancer is rampant in many countries around the world. In 2015, an estimated 24,590 people will be diagnosed and 10,720 people will eventually die of their disease in the USA (Siegel et al. 2015). The average age at diagnosis is 71 years, and almost two-thirds of those diagnosed with gastric cancer are above 65 (Howlader et al. 2015). In the present study, we found patients aged 75 years and older made up more than one-third of the population of gastric cancer, even though the proportion fell every year from 2004 to 2011. As patients aged 75 years and older are often underrepresented in the US National Cancer Institute (NCI) randomized clinical trials (Murthy et al. 2004), the external validity of clinical trials-based recommendations in older persons was still controversial. Studies have demonstrated that older patients are less likely to receive standard cancer treatment than younger patients

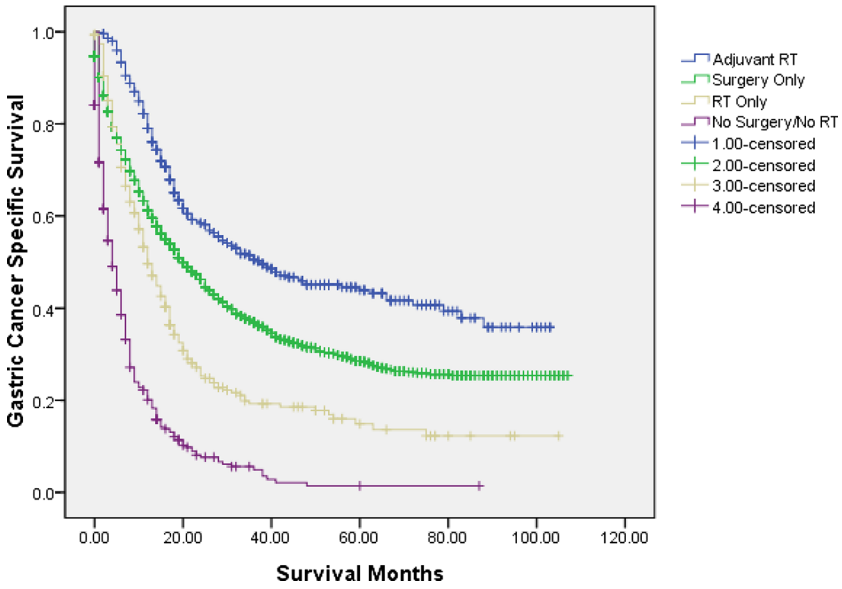

Fig. 4 Survival curves in elderly patients with gastric cancer according to four subgroups. The 5-year cancer-specific survival was 43.8 % in adjuvant RT, 28.5 % in surgery only, 14.9 % in RT only and 1.4 % in no surgery/no RT, which had significant difference ($P < 0.001$). RT indicates radiation

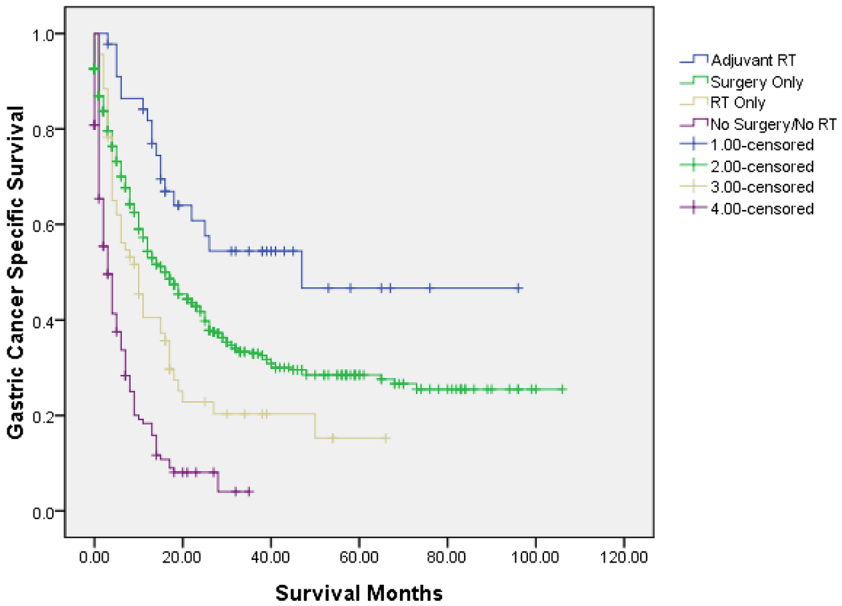

Fig. 5 Survival curves in patients with gastric cancer according to four subgroups in age 75–79 years ($P < 0.001$). RT indicates radiation

in breast cancer and prostate cancer, even when such treatments are potentially curative (Greenfield et al. 1987; Bennett et al. 1991). As such, it is not clear whether results of gastric cancer studies are equally applicable to elderly patients. Extrapolation of results of younger patients may not be appropriate.

Older patients may be at risk of overtreatment or undertreatment because of several competing factors such as comorbidities, frailty, clinician perceptions and decreased life expectancy. Some studies showed that elderly patients have a higher incidence of postoperative complications that are caused by reduced physiological function (Audisio et al. 1997; Page et al. 2002). Additionally, rates of underlying diseases are higher among elderly patients, meaning that complications may tend to be more serious. Yamada et al. (2013) found preoperative lymphocyte count, hemoglobin level, serum albumin levels and percent vital capacity were significantly lower in the ≥85 years group than in the 75–84 years group. Patients over 85 years old are more likely to suffer postoperative pneumonia after gastrectomy than younger old patients. Takama et al. (2015) found preoperative serum albumin level and prognostic nutritional index are significant predictors of postoperative complications in patients with gastric cancer who were 85 years or older. Although the INT-0116 trial demonstrated postoperative chemoradiation improved survival for patients with locally advanced resected gastric adenocarcinoma, the acute toxicity of adjuvant chemoradiation reported was

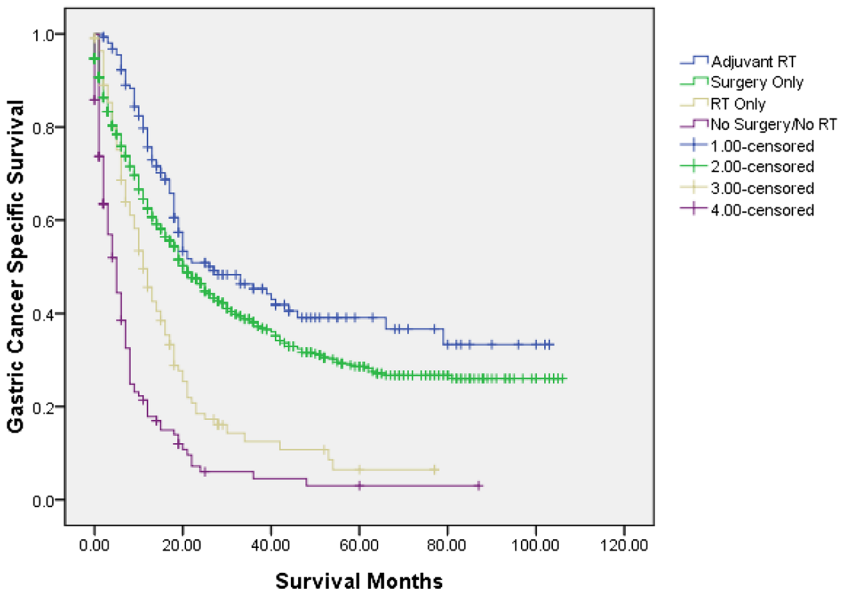

Fig. 6 Survival curves in patients with gastric cancer according to four subgroups in age 80–84 years ($P < 0.001$). RT indicates radiation

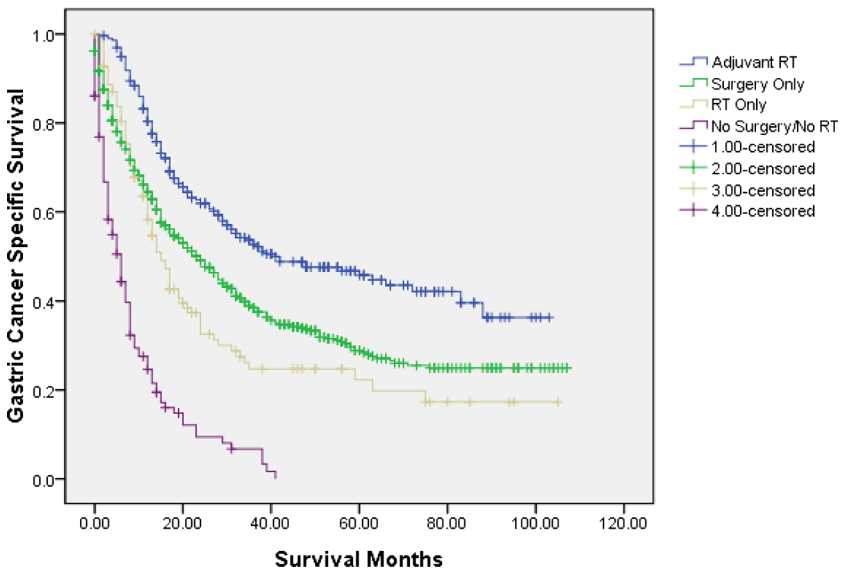

Fig. 7 Survival curves in patients with gastric cancer according to four subgroups in age ≥85 years ($P < 0.001$). RT indicates radiation

considerable: 54 % of patients experienced grade 3 or 4 hematological toxicity 33 % of patients experienced grade 3 or 4 gastrointestinal toxicity. Among the chemoradiation group, only 64 % of patients completed treatment and 17 % discontinued treatment due to toxicity (Macdonald et al. 2001). The median age of INT-0116 trial was 60 years. The rates of treatment deviation may be even higher among individuals 75 years or older. If elderly patients had a decrease in functional status due to surgery, they may no longer be good candidates for adjuvant therapy. Coburn et al. (2008) found that that age was a significant predictor of receipt of adjuvant radiation therapy after gastrectomy for nonmetastatic gastric adenocarcinoma: 44.5 % of patients received adjuvant RT in 18–59 years, 31.0 % in 60–74 years and 12.6 % in 75–85 years. Similarly, others have observed that more than 60 % of gastric cancer operations were performed in those aged 65 years and older, while only 30.8 and 23.3 % of elderly patients received adequate nodal evaluation and adjuvant RT, respectively (Dudeja et al. 2011). Specifically, age groups 80 years and older were at fivefold risk of receiving no adjuvant RT. Thus, older patients with gastric cancer are less likely to receive any type of treatment for their cancer compared to younger patients. In agreement with these findings, our study demonstrated the adjuvant RT accounted for <20 % of care patterns in elderly patients with locally advanced gastric cancer, compared with the proportion of almost 40 % in patients younger than 75 years.

Table 2 Univariate and multivariate survival analyses of patients with gastric cancer according to various clinicopathological variables

Variable	*n*	5-year CSS (%)	Univariate *P*	Multivariate *P*
Sex			0.709	0.793
Male	1783	27.0		
Female	1453	26.2		
Race			<0.001	0.001
White	2288	24.9		
Black	343	21.6		
Other	587	35.9		
Treatment pattern			<0.001	<0.001
Adjuvant RT	499	43.8		
Surgery only	2012	28.5		
RT only	305	14.9		
No surgery/no RT	402	1.4		
Histological type			<0.001	0.001
Adenocarcinoma	2613	28.5		
Mucinous	114	30.5		
Signet ring cell	491	15.7		
Pathological grading			<0.001	<0.001
Grade I	74	38.4		
Grade II	903	36.1		
Grade III	1974	23.9		
Grade IV	67	10.7		
Unknown	200	11.1		

CSS cancer-specific survival, *RT* radiation

Data in the literature regarding elderly patients with gastric cancer seem to be limited and sometimes conflicting. Hoffman et al. (2012) examined the survival benefit of postoperative chemoradiation therapy for elderly patients with resected gastric adenocarcinoma. They identified 1023 patients aged 65 years and older (median, 76) who underwent gastrectomy for non-metastatic stage IB–IV gastric adenocarcinoma diagnosed between 2000 and 2002 in the linked Surveillance, Epidemiology, and End Results–Medicare database. In this study, thirty percent of patients received adjuvant chemoradiation and receipt of adjuvant chemoradiation therapy did not significantly increase survival. In contrast, Strauss et al. (2010) analyzed patients aged 65 years or older with stage IB through stage IV (M0) gastric cancer, from 1991 to 2002, who underwent gastric resection in the Surveillance, Epidemiology, and End Results–Medicare database and found adjuvant therapy significantly reduced the mortality rate for stages III and IV (M0), trended toward improved survival for stage II, and showed no benefit for stage IB. Besides, they observed trends toward improved survival in all age categories except 80–85 years. In our opinion, these studies identified patients based on the old edition of the AJCC staging manual and from old times of diagnosis. In our study, all cases were identified from diagnosed time between 2004 and 2011 and restaged according to the criteria described in the seventh edition AJCC staging manual released in 2010. We found elderly patients in adjuvant RT had the significantly best CSS and detected survival benefits from the administration of adjuvant RT in all age categories, including age 75–79 years, age 80–84 years and age ≥85 years.

Although this is a large population-based study, it has several potential limitations. First, the SEER registry does not collect information on the comorbidities, nutritional status or performance status of the patients. One reason that the elderly patients may be undergoing less aggressive treatment may be due to comorbidities and poor performance status. Second, our study is the lack of data in the SEER registry on the use of chemotherapy and curability of surgery, resulting in a potentially significant confounder in the current study. It is possible that patients may have received adjuvant chemotherapy or preoperative chemotherapy. As for patients who are older than 75 years of age, they may receive less chemotherapy. Finally, the current analysis of the nonrandomized patient population could not exclude the possibility of selection bias. However, our study has its convincing power for its larger population-based study.

In conclusion, surgery and adjuvant RT may be the recommended treatment strategy in elderly patients with locally advanced gastric cancer, especially to patients medically fit for the combined modality therapy. Ideally, randomized studies for elderly patients should be performed.

Materials and methods

Patient selection in the SEER database

The SEER, a population-based reporting system, was surveyed for the retrospective collection of data used in the analysis. The SEER program collects and publishes cancer incidence and survival data from 18 population-based cancer registries, covering approximately 28 % of the population in the USA. The SEER data contain no identifiers and are publicly available for studies of cancer-based epidemiology and survival analysis.

Cases of gastric carcinoma (C16.0–16.9) diagnosed from 2004 to 2011 were extracted from the SEER database (SEER*Stat 8.2.1) according to the site recode classifications. All cases were restaged according to the criteria described in the American Joint Committee on Cancer (AJCC) staging manual (seventh edition, 2010). Histological type were limited to adenocarcinoma (ICD-03, 8140/3,

8144/3, 8210/3, 8211/3, 8221/3, 8255/3, 8260/3, 8261/3, 8262/3, 8263/3, 8310/3, 8323/3), mucinous adenocarcinoma (ICD-03, 8480/3, 8481/3) and signet ring cell carcinoma (ICD-03, 8490/3). Only patients aged 75 years and older with locally advanced gastric cancer (T3, T4 Any N or Any T, N+) and whose gastric cancer was a single primary tumor were included into the current study. We selected this range because AJCC TMN stage was available since 2004 and patients diagnosed after 2011 were excluded to ensure an adequate follow-up time. Patients were excluded if they were treated with either preoperative or intraoperative radiation, or were treated with both preoperative and postoperative radiation, and the sequence of radiation therapy and surgery was unknown. Other exclusion criteria were as follows: synchronous distance metastases, unknown TNM stage, unknown survival months and unknown treatment modality.

This study was based on the publicly available data from the SEER database, and we had got the permission to access these research data (Reference number: 10963-Nov 2014).

Statistical analysis

Age, sex, race, histological grade, histotype and cancer-specific survival (CSS) were extracted from SEER database. CSS was calculated from the date of diagnosis to the date of cancer-specific death. Deaths attributed to the rectal cancer were treated as events and deaths from other causes were treated as censored observations. The intergroup comparison of clinicopathologic variables was performed with the Chi-square test. Survival was analyzed using the Kaplan–Meier method (Kaplan 1958). The association between each of the potential prognostic factors and the estimated CSS was tested with the log–rank test (Mantel 1966). Multivariate analysis was performed using the Cox regression model (Gill 1992). The statistical test was two-sided, and $P < 0.05$ was considered statistically significant. PASW Statistics 13 (SPSS Inc., Chicago, USA) was used for the statistical analysis.

Acknowledgments The authors acknowledge the efforts of the Surveillance, Epidemiology, and End Results (SEER) program tumor registries in the creation of the SEER database. The interpretation and reporting of these data are the sole responsibility of the authors.

Author contributions KTL, JFW and GHY conceived of and designed the study. KTL, JFW and YPB performed the analyses. GHY and XC prepared all tables. KTL and MZL wrote the main manuscript. All authors reviewed the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References

Audisio RA, Veronesi P, Ferrario L, Cipolla C, Andreoni B, Aapro M (1997) Elective surgery for gastrointestinal tumours in the elderly. Ann Oncol 8:317–326

Bennett CL, Greenfield S, Aronow H, Ganz P, Vogelzang NJ, Elashoff RM (1991) Patterns of care related to age of men with prostate cancer. Cancer 15(67):2633–2641

Coburn NG, Guller U, Baxter NN, Kiss A, Ringash J, Swallow CJ, Law CH (2008) Adjuvant therapy for resected gastric cancer-rapid, yet incomplete adoption following results of intergroup 0116 trial. Int J Radiat Oncol Biol Phys 70:1073–1080

Dudeja V, Habermann EB, Zhong W, Tuttle TM, Vickers SM, Jensen EH, Al-Refaie WB (2011) Guideline recommended gastric cancer care in the elderly: insights into the applicability of cancer trials to realworld. Ann Surg Oncol 18:26–33

Gill RD (1992) Multistate life-tables and regression models. Math Popul Stud 3:259–276

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2013) GLOBOCAN 2012 v1.0, Cancer Incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. International Agency for Research on Cancer, Lyon, France. http://globocan.iarc.fr/Default.aspx. Accessed 31 Aug 2014

Greenfield S, Blanco DM, Elashoff RM, Ganz PA (1987) Patterns of care related to age of breast cancer patients. JAMA 257:2766–2770

Hoffman KE, Neville BA, Mamon HJ, Kachnic LA, Katz MS, Earle CC, Punglia RS (2012) Adjuvant therapy for elderly patients with resected gastric adenocarcinoma: population-based practices and treatment effectiveness. Cancer 118:248–257

Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds) (2015) SEER Cancer Statistics Review, 1975–2012, National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site, April 2015

Hundahl SA, Menck HR, Mansour EG, Winchester DP (1997) The national cancer data base report on gastric carcinoma. Cancer 80:2333–2341

Kaplan EMP (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457–481

Lee HS, Choi Y, Hur WJ, Kim HJ, Kwon HC, Kim SH, Kim JS, Lee JH, Jung GJ, Kim MC (2006) Pilot study of postoperative adjuvant chemoradiation for advanced gastric cancer: adjuvant 5-FU/cisplatin and chemoradiation with capecitabine. World J Gastroenterol 12:603–607

Lee J, Lim DH, 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 (2012) 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 30:268–273

Leong T, Joon DL, Willis D, Jayamoham J, Spry N, Harvey J, Di Iulio J, Milner A, Mann GB, Michael M (2011) Adjuvant chemoradiation for gastric cancer using epirubicin, cisplatin, and 5-fluorouracil before and after three-dimensional conformal radiotherapy with concurrent infusional 5-fluorouracil: a multicenter study of the Trans-Tasman Radiation Oncology Group. Int J Radiat Oncol Biol Phys 79:690–695

Macdonald JS (2006) Gastric cancer—new therapeutic options. N Engl J Med 355:76–77

Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA (2001) Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach orgastroesophageal junction. N Engl J Med 345:725–730

Mantel N (1966) Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163–170

Murthy VH, Krumholz HM, Gross CP (2004) Participation in cancer clinical trials: race-, sex-, and age-based disparities. JAMA 291:2720–2726

Page MJ, Poritz LS, Kunselman SJ, Koltun WA (2002) Factors affecting surgical risk in elderly patients with inflammatory bowel disease. J Gastrointest Surg 6:606–613

Siegel RL, Miller KD, Jemal A (2015) Cancer statistics, 2015. CA Cancer J Clin 65:5–29

Strauss J, Hershman DL, Buono D, McBride R, Clark-Garvey S, Woodhouse SA, Abrams JA, Neugut AI (2010) Use of adjuvant 5-fluorouracil and radiation therapy after gastric cancer resection among the elderly and impacton survival. Int J Radiat Oncol Biol Phys 76:1404–1412

Takama T, Okano K, Kondo A, Akamoto S, Fujiwara M, Usuki H, Suzuki Y (2015) Predictors of postoperative complications in elderly and oldest old patients with gastric cancer. Gastric Cancer 18:653–661

Yamada H, Shinohara T, Takeshita M, Umesaki T, Fujimori Y, Yamagishi K (2013) Postoperative complications in the oldest old gastric cancer patients. Int J Surg 11:467–471