Ann Surg Oncol (2013) 20:1985–1992
DOI 10.1245/s10434-012-2824-2

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – THORACIC ONCOLOGY

Survival after Definitive (Chemo)Radiotherapy in Esophageal Cancer Patients: A Population-Based Study in the North-East Netherlands

Justin K. Smit, MD[1], Christina T. Muijs, MD[2], Johannes G. M. Burgerhof, MSc[3], Gabriel Paardekooper, MD[4], Paul R. Timmer, MD, PhD[4], Karin Muller, MD[5], Dankert Woutersen, MD[6], Véronique E. Mul, MD[2], Jannet C. Beukema, MD[2], Geke A. P. Hospers, MD, PhD[7], Boukje A. C. van Dijk, PhD[8], Johannes A. Langendijk, MD, PhD[2], and John Th. M. Plukker, MD, PhD[1]

[1]Surgical Oncology of the University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [2]Radiation Oncology of the University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [3]Epidemiology of the University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [4]Radiation Oncology, Isala Klinieken, Zwolle, The Netherlands; [5]Radiotherapy Institute Stedendriehoek en Omstreken, Deventer, The Netherlands; [6]Medisch Spectrum Twente, Enschede, The Netherlands; [7]Medical Oncology of the University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [8]Section of Epidemiology, Comprehensive Cancer Centers, Utrecht, The Netherlands

ABSTRACT

Background. Definitive (chemo)radiotherapy is employed in esophageal cancer patients as an alternative for patients considered medically unfit for surgery or having unresectable tumors. We evaluated a population-based cohort to improve the selection for intensified nonsurgical strategies and to identify prognostic factors.

Methods. Patients who had squamous cell carcinoma (SCC) or adenocarcinoma (AC) were treated in four referral centers in the north-east Netherlands with definitive chemoradiotherapy (dCRT) or radiotherapy (dRT) between 1996 and 2008.

Results. Of the 287 included patients, 110 were treated with dCRT and 177 with dRT. Median overall survival (OS) was 11 months (95 % confidence interval: 10–12 months), with OS of 22 and 8 % and disease-free survival (DFS) of 16 and 5 % at 2 and 5 years, respectively. DFS at 2 and 5 years was 24 and 9 % for SCC versus 10 and 2 % for AC patients ($P = 0.006$). OS after 2 and 5 years was 29 and 14 % for SCC patients versus 17 and 3 % for AC patients ($P = 0.044$). On multivariate Cox regression, SCC was an independent prognostic factor for DFS [$P = 0.020$, hazard ratio (HR) = 0.71] and OS ($P = 0.047$, HR = 0.76). On matched cohort analysis, DFS was higher in the dCRT group compared with dRT patients ($P = 0.016$). The locoregional failure rate was lower in the dCRT group and in SCC patients ($P = 0.001$ and 0.046).

Conclusions. Long-term results and the local control rate in SCC patients were better after definitive (chemo)radiotherapy compared with in AC patients. SCC was an independent prognostic factor for survival. Definitive chemoradiotherapy leads to improved local control rate and DFS.

Presented as an oral presentation at the Society of Surgical Oncology's 65th Annual Cancer Symposium, March 21–24, 2012, Orlando, FL, USA.

First Received: 17 March 2012;
Published Online: 29 December 2012

J. Th. M. Plukker, MD, PhD
e-mail: j.t.m.plukker@umcg.nl

As in many Western countries, the annual incidence of esophageal carcinoma in The Netherlands markedly increased from 1,100 to 2,000 newly diagnosed patients in the last decade.[1–3] Unfortunately, around half of these patients were considered to be incurable due to the extent of the primary tumor and/or the presence of distant metastases at the time of presentation.[4] Radical resection remains the mainstay of treatment. However, many patients have unresectable tumors or are medically unfit for surgery due to severe comorbidity

and/or poor general condition, often related to the relatively high-aged population.[4,5] Only 30–40 % of patients with nonmetastatic esophageal cancer are considered eligible for radical resection with curative intent, and generally the 5-year survival in these patients is between 35 and 38 %.[6,7] At present, preoperative chemoradiotherapy (CRT) is given as standard care in this patient category. This is based on the results of a number of randomized controlled trials showing an improvement of 10–15 % in 5-year survival as compared with surgery alone.[8–10] For patients with nonmetastatic localized unresectable tumors or those not amenable for surgery, definitive CRT (dCRT) or definitive radiotherapy (dRT) are viable options for curatively intended strategies.[4,11–14] Currently, the most frequently used concurrent CRT regimens in the neoadjuvant setting are also on occasion applied for dCRT and include radiation dosages of 40–50 Gy/4–6 weeks given concurrently with platinum-based chemotherapy combined with either paclitaxel or 5-fluorouracil (5-FU).[8–12,15] Although the long-term results of these regimens are encouraging with 3-year survival rates up to 25 %, especially among patients treated with dCRT, these treatment regimens are generally associated with significant acute and late treatment-related morbidity.[11,13,16–18] Identification of prognostic factors is warranted to optimize future treatment approaches and/or to identify patient categories that may not benefit from these treatments.

The primary objectives of this population-based study are to evaluate the results after primary (chemo)radiation and to identify prognostic factors for tumor control and survival.

PATIENTS AND METHODS

Patients

This historical cohort study initially composed 312 patients treated between 1996 and 2008 in four radiotherapy referral centers in the north-eastern part of The Netherlands for nonmetastatic esophageal cancer with curative intent by dRT (≥50 Gy) or dCRT (≥50 Gy combined with platinum-based chemotherapy, see below). Thirteen patients were excluded because of missing data, such as incomplete staging information, discontinuation of treatment, and inadequate follow-up. Twelve other patients were excluded because of histology other than adenocarcinoma (AC) or squamous cell carcinoma (SCC). Therefore, after exclusion, 287 patients were analyzed, including 110 (38.3 %) patients treated with dCRT and 177 (61.7 %) patients treated with dRT alone. The indications for employing definitive CRT or RT were locoregionally unresectable tumors, medically unfit or inoperable patients based on either severe comorbidity or high-age-based frailty and/or patient's own choice.

Methods

Staging Procedure The pretreatment workup generally consisted of endoscopic ultrasonography (EUS) with fine-needle aspiration (FNA) of suspected lymph nodes, 16-64 multidetector computed tomography (md-CT) scans of the neck, chest, and abdomen, and cervical echographic examination. EUS information could be obtained in 90 % of the patients. When available, 18-F-fluorodeoxyglucose positron emission tomography (FDG-PET) was also applied. FDG-PET was standard procedure from 2002 onwards. Bronchoscopy was required when the tumor was tethered to the trachea or main stem bronchus. Patients were staged according to the Union for International Cancer Control tumor–node–metastasis (TNM) 6th edition, which was the most current TNM classification at time of staging.[19]

Treatment Regimen Radiotherapy planning was carried out after direct simulation, based on diagnostic CT images, or by use of treatment planning CT images. During direct simulation patients had to swallow barium contrast to facilitate identification and localization of the primary tumor. For the treatment planning CT scan, patients received oral contrast.

The gross tumor volume (GTV), defined as the macroscopic primary tumor and regional lymph node metastases, was reconstructed using all available information derived from endoscopy, EUS, CT, and from FDG-PET if available.

At direct simulation, margins from GTV to field margin were 5 cm in caudal–cranial direction and 2 cm in transversal plane. If treatment planning was based on planning CT, the clinical target volume (CTV) was obtained by adding a 3 cm margin in cranial–caudal direction and 1 cm margin in transversal plane. A 1 cm margin was used around the pathological lymph nodes. The planning target volume (PTV) was generated by expanding the CTV with a margin of 1 cm in all directions to account for setup uncertainties and organ motion.

The dRT regime consisted of external-beam radiotherapy (EBRT), which was combined with intraluminal brachytherapy (ILBT) in 93 % of the patients. A total dose of 50–70 Gy (median dose 60 Gy) was given in fractions of 2 Gy, five times per week, and was generally delivered by three-dimensional conformal radiotherapy (3D-CRT) with at least 6-MV photons. The ILBT was given in two fractions of 6 Gy or a single fraction of 10 Gy. The treated length was equal to the tumor length estimated at endoscopy plus 1–2 cm margins in cranial and caudal directions. The required dose was specified at 1 cm from the radiation source or 0.5 cm under the mucosa surface.

Due to positive results in favor of dCRT in prospective randomized studies comparing dCRT with dRT, for example, the Radiation Therapy Oncology Group (RTOG)

85–01 study, dCRT was gradually introduced from 2005 onwards as standard treatment in the four radiotherapy referral centers.[11]

Patients who underwent dCRT received a total radiation dose of 50–54 Gy (median dose 50.4 Gy) in daily fractions of 1.8–2 Gy.

One chemotherapy regime consisted of cisplatin/5-fluorouracil (FU) at week 1 and 5 during RT, with two additional courses at week 8 and 11 (RTOG 85-01 scheme), employed in 64 patients (64/110 patients).[11] The other employed chemotherapy scheme consisted of carboplatin/paclitaxel at week 1, 8, 15, 22, 29, and 35 during RT, employed in 46 patients (46/110 patients).[20]

In the dCRT group, ILBT was employed in 36 % of patients.

Data Acquisition Data were obtained using the medical records of the four radiotherapy referral centers. Additionally, information from comprehensive cancer centers was also acquired. From these two datasets a database was constructed.

Data were collected anonymously and were only known to the principle investigators (J.K.S., C.T.M., and J.T.P.). According to national guidelines and ethics codes, no institutional board review was required for this study.

Follow-Up In general, patients were seen for regular follow-up according to national guidelines at 4–8 weeks after completion of treatment, every 3 months in the first year, every 4–6 months in the second and third year, and annually up to 5 years or until death. Only one center routinely performed CT scans during follow-up; the other centers performed radiological examinations solely based on clinical grounds. A recurrence site was defined as either local (esophageal bed), regional (lymph nodes) or distant metastasis.

Statistics Overall survival (OS) was defined as the time interval between the starting date of the (chemo)radiotherapy treatment and documentation of the day of death or last follow-up. Disease-free survival (DFS) and locoregional recurrence-free survival (LRFS) were determined from the starting date of treatment to documented date of first recurrence, last follow-up, or death of any cause. OS, DFS, and LRFS rates were calculated according to the Kaplan–Meier method and compared using the log-rank test. Cox regression analyses were performed to identify independent prognostic factors. Groups were compared using *t*-tests or Mann–Whitney tests in the case of a continuous response variable, and with Fisher's exact test in the case of a categorical outcome. Because of the nonrandomized nature of this study, we also compared the dCRT and dRT groups matched on possible confounding variables (TNM stage and age). Matched cohorts were created according to the propensity score, which is a balancing score implemented in our statistical package.[21,22] The matching procedure was performed with the help of an experienced biostatistician (J.G.M.B.). First, we randomly selected 75 dCRT patients from the 110 in the total dCRT group. Then, a matched group of 75 patients was formed from the 177 in the total dRT group based on age and T, N, and M stage. Matching with a larger population instead of 75 patients corrected less based on the propensity score. Importantly, the characteristics listed in Tables 1 and 2 between the 75 randomly selected patients and the initial 110 were not different.

TABLE 1 Clinicopathological characteristics between adenocarcinoma (AC) and squamous cell carcinoma (SCC) patients

Characteristics	AC $N = 164$	SCC $N = 123$	P value
Gender			
Male/female	136/28	88/35	0.030
Age (years)			
Mean (range)	72 (37–88)	65 (32–87)	<0.001
Localization primary tumor			
Mid/upper	11 %	49 %	<0.001
Distal/GEJ	88 %	51 %	
T stage			
T1	7 %	5 %	0.838 (NS)
T2	16 %	14 %	
T3	59 %	63 %	
T4	18 %	18 %	
N stage			0.682 (NS)
N1	65 %	65 %	
M stage			0.107 (NS)
M1a	10 %	4 %	
Treatment			
dCRT	34 %	44 %	0.111 (NS)
dRT	66 %	56 %	
Dose			
Median	54 Gy	54 Gy	0.877 (NS)
ILBT			
Yes	74 %	65 %	0.091 (NS)
90-Day mortality	3.0 %	4.9 %	0.538 (NS)

GEJ gastroesophageal junction, *SCC* squamous cell carcinoma, *AC* adenocarcinoma, *NS* not significant, *ILBT* intraluminal brachytherapy

P value <0.05 [95 % confidence interval (CI)] was considered significant. The statistical analyses were performed by using the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA) software, version 18.0.

RESULTS

Comparison of Clinical Characteristics

Characteristics are compared between AC and SCC patients in Table 1. Male-to-female ratio (136/28 versus

TABLE 2 Clinicopathological characteristics between patients treated with dCRT and dRT, before and after matching

	Before matching		*P* value	After matching		*P* value
	dCRT $N = 110$	dRT $N = 177$		dCRT $N = 75$	dRT $N = 75$	
Gender						
Male/female	88/22	136/41	0.560 (NS)	59/16	57/18	0.846 (NS)
Age (years)						
Mean (range)	61.7 (32–82)	71.1 (36–88)	<0.001	61.5 (42–82)	65.7 (32–82)	0.005
Localization						
Mid/upper	35 %	25 %	0.072 (NS)	34 %	29 %	0.591 (NS)
Distal/GEJ	65 %	75 %		66 %	71 %	
Histology						
AC/SCC	51/49 %	61/39 %	0.111 (NS)	55/45 %	52/48 %	0.870 (NS)
T stage						
T1	1 %	9 %	<0.001	1 %	0 %	0.171 (NS)
T2	7 %	20 %		5 %	13 %	
T3	59 %	61 %		66 %	68 %	
T4	33 %	10 %		28 %	19 %	
N stage						
N1	84 %	52 %	<0.001	87 %	81 %	0.505 (NS)
M stage						
M1a	15 %	3 %	<0.001	16 %	7 %	0.120 (NS)
ILBT						
Yes	36 %	93 %	<0.001	32 %	91 %	<0.001
90-Day mortality	3.6 %	4.0 %	1.000 (NS)	2.6 %	5.3 %	0.681 (NS)

GEJ gastroesophageal junction, *SCC* squamous cell carcinoma, *AC* adenocarcinoma, *NS* not significant, *ILBT* intraluminal brachytherapy

88/35, $P = 0.030$), age (72 versus 65 years, $P < 0.001$), and localization [more distal/gastroesophageal junction (GEJ) tumors 88 % compared with 51 %, $P < 0.001$] differed between AC and SCC patients. Stage- and treatment-related characteristics did not differ between AC and SCC patients. Comorbidities and reasons not to perform primary resection were not routinely recorded in the data administration of the Comprehensive Cancer Centre, The Netherlands, but sufficient information could be obtained from patient records in referral centers (84 %, $n = 241$). A trend ($P = 0.06$) was observed in the distribution difference between the dCRT and dRT groups regarding these pre-treatment comorbidities (Table 3). To adequately evaluate the results between the dCRT and dRT groups and to reduce selection bias, we created matched groups with similar baseline characteristics (see "Methods" section and Table 2).

The characteristics of the matched patients treated with dCRT and dRT are displayed in Table 2. Patients treated with dCRT were relatively younger (61.5 versus 65.7 years) compared with dRT patients. The T, N, and M stage were comparable in the two groups.

Posttreatment 90-day mortality did not differ between the two groups ($P = 1.000$ and $P = 0.681$, Table 2).

TABLE 3 Comparison of comorbidity and primary reasons to abandon surgery between dCRT and dRT groups ($P = 0.06$)

Factor	dCRT $N = 89$	dRT $N = 152$
Pulmonary	6 %	9 %
Cardiovascular	16 %	30 %
Unresectable	57 %	45 %
Age	21 %	16 %

Disease-Free and Overall Survival

The median DFS and OS of the whole group ($n = 287$) were, respectively, 8 months (95 % CI: 7–9 months) and 11 months (95 % CI: 10–12 months). The 1-, 2-, and 5-year survival rates were 37, 16, and 5 % for DFS (Fig. 1a) and 49, 22, and 8 % for OS (Fig. 1b).

The DFS for patients with SCC was significantly better compared with patients with AC (1, 2, and 5 years: 40, 24, and 9 versus 34, 10, and 2 %; $P = 0.006$, log-rank test; Fig. 1c).

Similarly, the OS for SCC patients was significantly better than in AC patients, with 47, 29, and 14 % at 1, 2,

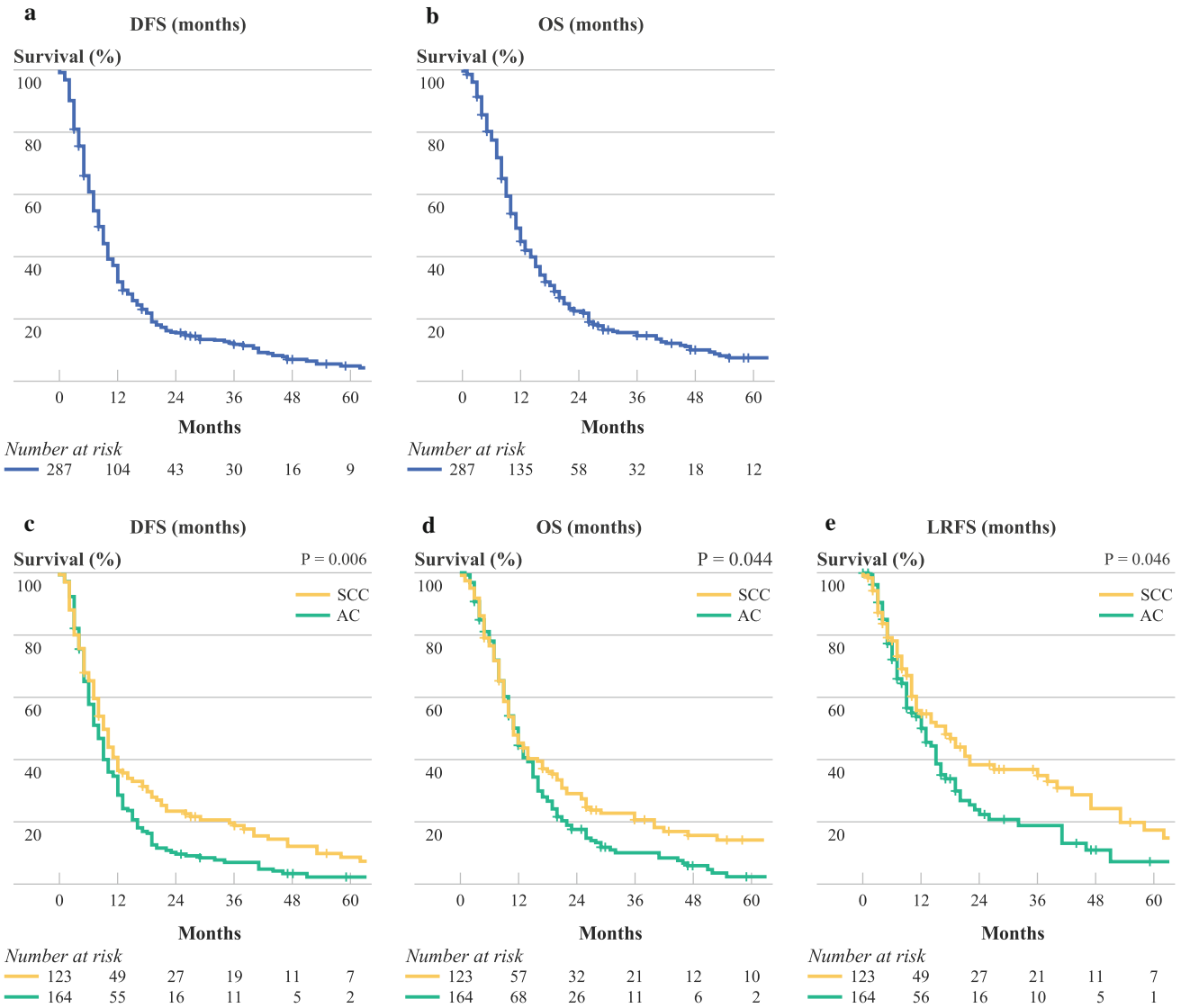

FIG. 1 Kaplan–Meier survival curves of (**a**) disease-free survival (DFS) and (**b**) overall survival (OS) in the total population ($n = 287$). Survival curves of (**c**) DFS and (**d**) OS between squamous cell carcinoma (SCC) versus adenocarcinoma (AC) patients. (**e**) Survival *curve* of locoregional recurrence-free survival (LRFS) between SCC and AC patients

and 5 years for SCC versus 50, 17 and 3 % for AC patients ($P = 0.044$, log-rank test) (Fig. 1d).

In the matched analysis, patients in the dCRT group showed better DFS compared with the dRT group ($P = 0.016$, log-rank test). The difference in OS did not reach significance, although there was a trend towards better survival in favor of the dCRT group ($P = 0.071$, log-rank test; Fig. 2b).

On multivariate Cox regression analysis of the whole group ($n = 287$), tumor histology was an independent prognostic factor for DFS with hazard ratio (HR) of 0.72 (95 % CI: 0.54–0.95) and for OS (HR of 0.76, 95 % CI: 0.58–0.99). The following factors were included in this analysis: T stage, N stage, M stage, histology (AC versus SCC), type of treatment (dCRT versus dRT), gender, and age. No other independent prognostic factors for OS and DFS could be identified.

Locoregional Recurrence-Free Survival

The median LRFS in the whole group ($n = 287$) was 13 months (95 % CI: 10–16 months) with 1-, 2-, and 5-year LRFS of 55, 31, and 12 %, respectively. The LRFS in SCC patients was significantly higher compared with AC patients, with 17 % at 5 years for SCC patients versus 7 % for AC patients ($P = 0.046$, log-rank test; Fig. 1e).

In the matched group analysis the dCRT group showed better LRFS compared with the dRT group, with 27 versus 9 % at 5 years ($P = 0.001$, log-rank test; Fig. 2c).

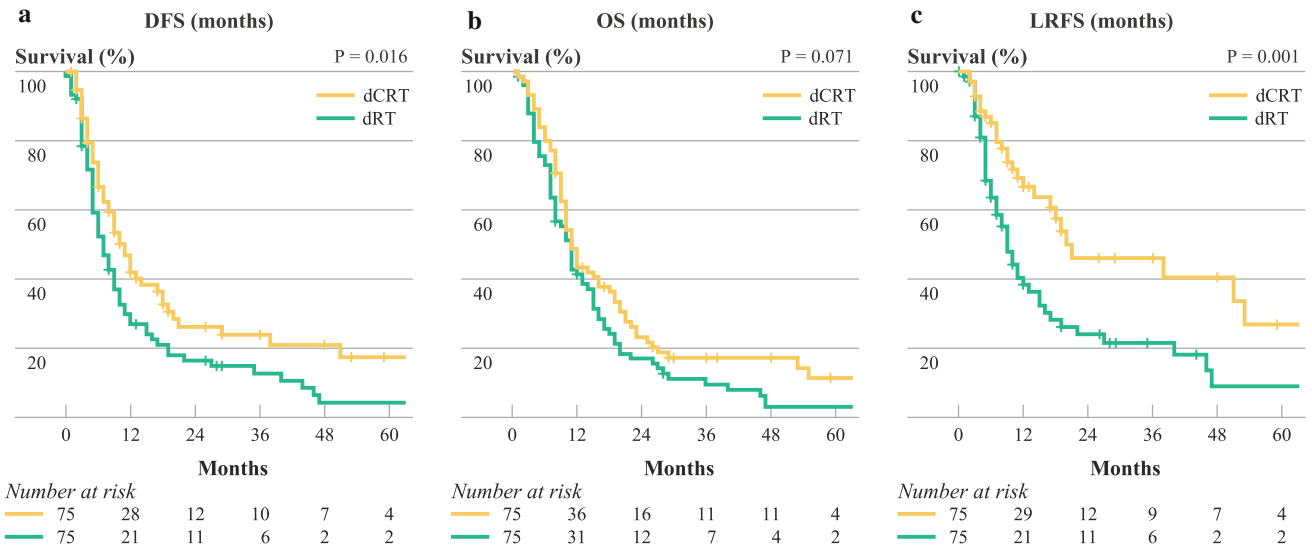

FIG. 2 Kaplan–Meier survival of (**a**) disease-free survival (DFS) and (**b**) overall survival (DFS) of the dCRT ($n = 75$) and dRT ($n = 75$) groups, according to matched cohorts. (**c**) Survival *curves* of locoregional recurrence-free survival (LRFS) between definitive chemoradiotherapy (dCRT) and radiotherapy (dRT) groups

Potential Staging Effect During the Study Period

To determine whether there was a different staging effect due to more appropriated staging procedures, patients were divided into two groups, namely group 1 treated before 2002 ($n = 92$) and group 2 treated from 2002 ($n = 195$). This time point coincided with the halfway point of the study period and the introduction of FDG-PET in the staging procedure (see "Methods" section). Both groups were well balanced with regard to T stage and N stage ($P = 0.21$ and 0.78). Patients in group 2 had relatively higher rates of M1a stage (according to the 6th TNM) patients compared with the group treated before 2002 (10 versus 1 %, $P = 0.005$). The OS and DFS between these two groups did not differ statistically.

DISCUSSION

The present study of a relatively large population-based cohort of patients treated with dCRT or dRT provides important prognostic information with possible consequences in current clinical practice.

The long-term DFS and OS at 5 years of the whole group were grim. Other centers have reported higher 5-year survival rates. One could speculate that the differences in survival are due to stricter selection criteria.[11,12,14,23] Therefore, direct comparison with these survival rates is difficult to make, since we included all curatively treatable stage categories, including a high percentage of T4 tumors and previously M1a-staged patients, compromising the survival rates.

In the present study we found a difference in the DFS and OS rates between the SCC and AC groups. At 5 years, the OS rate in the AC group was 3 %, whereas in the SCC group this was 14 %. Furthermore, in this study, SCC tumors showed improved locoregional control compared with AC tumors. To date, little is known about the outcome of RT or CRT between SCC and AC tumors. Cooper et al. showed, in a prospective study, improved OS at 2 and 5 years for SCC compared with AC (38 and 21 versus 22 and 13 %) after dCRT treatment.[11] However, this difference was not statistically significant, arguably due to the small study population. Burmeister et al. also showed, in a histology subgroup analysis of a randomized controlled trial (RCT), that SCC is associated with better progression-free survival compared with non-SCC (HR of 0.47 versus HR of 1.02 in risk of death).[24] However, these patients underwent preoperative CRT instead of dCRT or dRT. Finally, a recent Dutch RCT, comparing surgery versus preoperative CRT, also showed better outcome of SCC patients compared with AC patients (HR of 0.34 and 0.82 in risk of death).[25] The improved outcome of preoperative CRT on SCC tumors in these studies generally increases the positive results of preoperative CRT in the whole group. However, this improvement in survival in the preoperative CRT arm for the SCC histology subtype could not be reproduced by a recent updated meta-analysis.[10] In contrast, Fiorica et al. described, in a meta-analysis, a benefit of preoperative CRT for AC compared with SCC.[26] Extent of surgery may be an important confounding factor in comparison of results of AC and SCC after preoperative CRT. SCC tumors are usually localized in the mid or upper esophagus and treated using a transthoracic approach, while AC tumors are located in the distal esophagus or gastroesophageal junction (GEJ), for which many surgeons

will opt for a transhiatal approach. However, there are indications that patients who were operated through a transthoracic approach have a better outcome compared with the transhiatal approach.[6,27] Large trials in the past have shown an advantage for preoperative chemotherapy compared with surgery alone for distal or GEJ esophageal AC tumors.[28,29] Therefore, some centers still opt for exclusion of radiotherapy from the preoperative regimen in case of distal or GEJ, AC tumors. This study adds further evidence that AC tumors have less survival benefit when RT is part of the treatment regimen. The choice to add RT to the treatment regimen, whether in the definitive or preoperative setting, should be considered carefully, as addition of RT may induce significant morbidity, such as life-threatening ulceration with perforation, fistula or stricture formation.[13,16–18]

In the matched analysis between dCRT and dRT in this study, DFS was better in the dCRT compared with the dRT group. We only observed a trend of significance in OS ($P = 0.07$) towards better survival for the dCRT group, which could be based on pretreatment existing differences in comorbidities between the two groups. Also, local control (LRFS), as a surrogate for response, in the dCRT group was better. A possible explanation is the radiosensitizing effect of concomitant chemotherapy. This is supported by previously published studies describing better outcome for dCRT compared with dRT patients.[11,12,14] The radiation dose is lower in the dCRT group since the chemotherapy will act as a radiosensitizer. Therefore, additional use of ILBT is mostly applied in the dRT group. Furthermore, the effect of dose escalation is still questionable. This was shown in the RTOG 94-05 study, in which a higher radiation dose did not translate into improved locoregional tumor control or overall survival.[30]

An important note is that, with increasing age and the presence of concomitant comorbidity, elderly patients usually receive dRT, while younger patients are generally treated with a combined modality of dCRT. Indeed, in our group, the dCRT patients were significantly younger with mean age of 61.7 versus 71.2 years in the dRT group. This age difference was reduced after matching to 61.5 versus 65.7 years. Moreover, there was no difference in the presence of pretreatment comorbidity and reasons to abandon surgery, as we here show in a subgroup analysis of 241 patients.

This study is subjected to some limitations. A possible drawback is that the information was limited to the data recorded in the patient and cancer registry files. Despite the long time interval in the current study, no staging-dependent effect was observed during the treatment period.

It was noted that patients with SCC were significantly younger than AC patients. This could be confounding when interpreting the survival data, but as shown in our multivariate analysis, patient age did not impact the DFS or OS.

CONCLUSIONS

In this study we show that SCC of the esophagus has better long-term results and local control rate than AC tumors after definitive (chemo)radiation. This histological subtype was demonstrated to be an independent prognostic factor for both OS and DFS in patients treated with (chemo)radiation. Although the OS difference between dRT and dCRT is small, the matched analysis showed that dCRT seems to offer better LRFS and DFS compared with dRT.

ACKNOWLEDGMENT Supported by GUIDE Post-graduate School of Medicine, University of Groningen. The authors would like to thank Michael G. Dickinson MD for editing our manuscript.

REFERENCES

1. Brown LM, Devesa SS, Chow WH. Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. *J Natl Cancer Inst.* 2008;100:1184–7.
2. Crane LM, Schaapveld M, Visser O, Louwman MW, Plukker JT, van Dam GM. Oesophageal cancer in The Netherlands: increasing incidence and mortality but improving survival. *Eur J Cancer.* 2007;43:1445–51.
3. IKN. Available: http://www.cijfersoverkanker.nl/?language=en. Accessed 1 March 2012.
4. Smith GL, Smith BD, Buchholz TA, Liao Z, Jeter M, Swisher SG, et al. Patterns of care and locoregional treatment outcomes in older esophageal cancer patients: The SEER-Medicare Cohort. *Int J Radiat Oncol Biol Phys*. 2009;74:482–9.
5. Mariette C, Piessen G, Triboulet JP. Therapeutic strategies in oesophageal carcinoma: role of surgery and other modalities. *Lancet Oncol*. 2007;8:545–53.
6. Omloo JM, Lagarde SM, Hulscher JB, Reitsma JB, Fockens P, van Dekken H, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. *Ann Surg.* 2007;246:992–1000; discussion 1000–1.
7. Smit JK, Pultrum BB, van Dullemen HM, Van Dam GM, Groen H, Plukker JT. Prognostic factors and patterns of recurrence in esophageal cancer assert arguments for extended two-field transthoracic esophagectomy. *Am J Surg.* 2010;200:446–53.
8. 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;8:226–34.
9. 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;10:754–61.
10. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol.* 2011;12:681–92.
11. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA Jr, Al-Sarraf M, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective

randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA*. 1999;281:1623–7.
12. Herskovic A, Martz K, al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med*. 1992;326:1593–8.
13. Muijs CT, Beukema JC, Mul VE, Plukker JT, Sijtsema NM, Langendijk JA. External beam radiotherapy combined with intraluminal brachytherapy in esophageal carcinoma. *Radiother Oncol*. 2011;102(2):303–8.
14. Smith TJ, Ryan LM, Douglass HO Jr, Haller DG, Dayal Y, Kirkwood J, et al. Combined chemoradiotherapy vs. radiotherapy alone for early stage squamous cell carcinoma of the esophagus: a study of the Eastern Cooperative Oncology Group. *Int J Radiat Oncol Biol Phys.* 1998;42:269–76.
15. Geh JI, Bond SJ, Bentzen SM, Glynne-Jones R. Systematic overview of preoperative (neoadjuvant) chemoradiotherapy trials in oesophageal cancer: evidence of a radiation and chemotherapy dose response. *Radiother Oncol*. 2006;78:236–44.
16. Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol*. 2005;23:2310–17.
17. Bedenne L, Michel P, Bouche O, Milan C, Mariette C, Conroy T, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. *J Clin Oncol.* 2007;25:1160–8.
18. Gaspar LE, Winter K, Kocha WI, Coia LR, Herskovic A, Graham M. A phase I/II study of external beam radiation, brachytherapy, and concurrent chemotherapy for patients with localized carcinoma of the esophagus (Radiation Therapy Oncology Group study 9207): final report. *Cancer.* 2000;88:988–95.
19. Sobin LH. TNM, sixth edition: new developments in general concepts and rules. *Semin Surg Oncol*. 2003;21:19–22.
20. Wang H, Ryu J, Gandara D, Bold RJ, Urayama S, Tanaka M, et al. A phase II study of paclitaxel, carboplatin, and radiation with or without surgery for esophageal cancer. *J Thorac Oncol.* 2007;2:153–7.
21. D'Agostino RB,Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17:2265–81.
22. Weitzen S, Lapane KL, Toledano AY, Hume AL, Mor V. Principles for modeling propensity scores in medical research: a systematic literature review. *Pharmacoepidemiol Drug Saf*. 2004; 13:841–53.
23. Sykes AJ, Burt PA, Slevin NJ, Stout R, Marrs JE. Radical radiotherapy for carcinoma of the oesophagus: an effective alternative to surgery. *Radiother Oncol*. 1998;48:15–21.
24. Burmeister BH, Smithers BM, Gebski V, Fitzgerald L, Simes RJ, Devitt P, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. *Lancet Oncol*. 2005;6:659–68.
25. Gaast AV, van Hagen P, Hulshof M, Richel D, van Berge Henegouwen MI, Nieuwenhuijzen GA, et al. Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectable esophageal or esophagogastric junction cancer: results from a multicenter randomized phase III study. *J Clin Oncol*. 2010;(suppl; abstr 4004): 28:15.
26. Fiorica F, Di Bona D, Schepis F, Licata A, Shahied L, Venturi A, et al. Preoperative chemoradiotherapy for oesophageal cancer: a systematic review and meta-analysis. *Gut*. 2004;53:925–30.
27. Lee PC, Mirza FM, Port JL, Stiles BM, Paul S, Christos P, Altorki NK. Predictors of recurrence and disease-free survival in patients with completely resected esophageal carcinoma. *J Thorac Cardiovasc Surg*. 2011;141:1196–206.
28. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355:11–20.
29. Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol*. 2011;29:1715–21.
30. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol*. 2002;20:1167–74.