Association Between Radiation Dose and Pathological Complete Response After Preoperative Radiochemotherapy in Esophageal Squamous Cell Cancer

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Abstract. *Aim: This study was undertaken to examine the impact of radiation dose on pathological complete response (pCR) rates following neoadjuvant radiochemotherapy (N-RCT) for squamous cell esophageal cancer (ESCC). Patients and Methods: From 1988 to 2011, 218 patients were treated with 30–30.6 Gy (1.8-2 Gy per fraction), 39.6-40 Gy (1.8-2 Gy per fraction) or 44-45 Gy (1.8-2 Gy per fraction) and concomitant cisplatin ± 5-fluorouracil (5-FU), oxaliplatin + 5-FU or 5-FU alone. The most commonly used concomitant chemotherapy was continuous infusion of 5-FU-alone with a dose of 300 mg/m^2/day during the whole course of treatment (n=111). To eliminate the dispersing effect of potentially different efficacy levels of these drug regimens on pCR, we excluded patients with regimens other than 5-FU-alone. Results: Histomorphological regression grade 1a (0% residual tumor), 1b (<10% residual tumor), 2 (10-50% residual tumor) and 3 (>50% residual tumor) was observed in 26 (23%), 24 (22%), 36 (32%) and 25 (23%) patients, respectively. pCR was observed in 9 out of 71 (13%) patients treated with 30 Gy–30.6 Gy, 13 of 34 (38%) patients treated with 39.6–40 Gy and 4 of 6 (67%) patients treated with 44-45 Gy (p=0.001). Median follow-up time from the start of N-RCT was 191 months (range=2-262 months). The estimated 5-year overall survival (OS) was 33% for the whole cohort. OS at 5 years was 58% for patients with pCR compared to 25% for patients with less favorable response to N-RCT (p=0.009), respectively. Conclusion: The dose of radiation correlates significantly with the likelihood of achieving a pCR in stage II/III squamous cell esophageal cancer patients. Prospective randomized trials are required to definitively evaluate the impact of application of higher radiation doses on efficacy and safety/tolerability in the context of N-RCT on the clinical outcomes.*

Neoadjuvant radiochemotherapy (N-RCT) followed by surgical resection is now considered the preferable standard-of-care in the management of stage II/III squamous cell esophageal cancer (ESCC). The goal of N-RCT is to obtain maximum tumor down-staging, facilitate complete resection with negative surgical margins for improved local control, as well as to target micrometastatic disease, thereby decreasing the risk of distant spread and increasing the probability of survival (OS). Several authors have reported pathological complete response (pCR) after N-RCT as prognostic factor for OS and/or disease-free survival (DFS) (1-3). Clinical data comparing the effect of different radiation doses in N-RCT of ESCC are rare. The present study was undertaken to examine the impact of radiation dose on pCR rates following N-RCT for ESCC.

Patients and Methods

Patient population. From 1988 to 2011, 218 patients were treated with 30-30.6 Gy (1.8-2 Gy per fraction), 39.6-40 Gy (1.8-2 Gy per fraction) or 44-45 Gy (1.8-2 Gy per fraction) and concomitant cisplatin ± 5-fluorouracil (5-FU), oxaliplatin + 5-FU or 5-FU alone.

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The most commonly used concomitant chemotherapy was 5-FU-alone (n=113). To eliminate the dispersing effect of potentially different efficacy levels of these drug regimens on pCR, we excluded patients with regimens other than 5-FU-alone. 5-FU was generally applied as a continuous infusion with a dose of 300 mg/m^2/day during the whole course of treatment including weekends. To further reduce heterogeneity, two additional patients with an application schedule of 500 mg/m^2/day on days 1-5 and 29-33 were excluded from the study.

Considering the radiation dose and the drug regimens, the remaining patients (n=111) were divided into 3 different groups, which were treated in different time periods: (i) Early N-RCT with 30-30.6 Gy (1.8-2 Gy per fraction) and 5-FU (300 mg/m^2/day) (n=71 patients); (ii) N-RCT with 39.6-40 Gy (1.8-2 Gy per fraction) and 5-FU (300 mg/m^2/day) (n=34 patients); (iii) Recent N-RCT with 44-45 Gy (1.8-2 Gy per fraction) and 5-FU (300 mg/m^2/day) (n=6).

Differences in biologically effective dose within each of the three groups were minimal, *e.g.* 46.7 Gy$_{10}$ for the 39.6 Gy schedule as compared to 48 Gy10 for the 40 Gy schedule (calculation according to the linear-quadratic model with α/β value of 10 Gy for ESCC) (4). Such small differences were considered clinically irrelevant. The patients' characteristics are summarized in Table I.

RT technique. In the late 1980's and early 1990's, 2-dimensional radiotherapy was delivered. The treated area extended 5 cm beyond the longitudinal margins of the tumor, as defined by endoscopic and radiologic examination, and 2 cm beyond the radial margins. The radiation portals also included the locoregional lymph nodes plus a safety margin for patient positioning. A total dose of 30-40 Gy was delivered with two opposed a.p./p.a. fields and/or with a 3-field technique using 10 or 15 MeV photons. From the mid 1990's on, conformal external-beam radiotherapy with 6-15 MeV photons was delivered using 3- and 4-field techniques. The clinical target volume (CTV) comprised the primary tumor with a margin of 4 cm in the craniocaudal direction and regional lymph nodes. The margin of the planning target volume added to the CTV was 8-10 mm in all directions, taking internal organ movements, as well as setup errors into account.

Surgical resection. After identical restaging, all patients underwent radical resection with reconstruction according to the primary tumor location approximately 4-6 weeks after the last day of N-RCT, with radical 2-field lymphadenectomy in a high-volume tertiary referral center.

Pathological analysis. The tumor stage was defined according to the classification of the UICC 2002 (5). To grade the response to N-RCT, the degree of histomorphological regression was classified as described by Becker *et al*. (6) into the following categories: Complete regression (0% residual tumor; grade 1a), subtotal tumor regression (<10% residual tumor per tumor bed; grade 1b), partial tumor regression (10-50% residual tumor per tumor bed; grade 2) and minimal or no tumor regression (>50% residual tumor per tumor bed; grade 3). If a vital tumor was present at 1 mm or less from the proximal, distal or circumferential resection margin, it was considered microscopically positive (R1). If the surgeon reported an unresectable residual macroscopic tumor, it was considered an R2 resection.

Statistical methods. OS was analyzed according to the Kaplan-Meier method. Survival curves were compared between different subgroups by the log-rank test. Comparison of cumulative incidence functions was performed using Gray's test. Assumed linear relationships between radiation dose and the probability to achieve pathological complete response were assessed by linear regression analysis. Based on the fitted regression models, predicted probabilities with 95% confidence bands were calculated and displayed. Baseline characteristics were compared between subgroups by chi-square test. A two-sided level of significance of α=5% was used for all statistical tests. No correction of *p*-values was applied to adjust for multiple testing. However, results of all statistical tests being conducted were thoroughly reported so that an informal adjustment of *p*-values can be performed while reviewing the data (7). Toxicity was assessed retrospectively according to CTC Version 3.0.

Results

Histomorphological regression grade 1a (pCR), 1b, 2 and 3 was observed in 26 (23%), 24 (22%), 36 (32%) and 25 (23%) patients, respectively. A pCR was observed in 9 of 71 (13%) patients treated with 30-30.6 Gy, 13 of 34 (38%) patients treated with 39.6-40 Gy and 4 of 6 (67%) patients treated with 44-45 Gy (*p*=0.001). No statistically significant differences were observed between the groups treated with different radiation doses regarding factors that might have influenced pCR rate, *e.g.* T stage or tumor length (Table I). Estimated linear dose-response relationships are displayed in Figure 1.

Median follow-up time from the start of N-RCT was 191 months (range=2-262 months). The 5-year OS was 33±5% for the whole cohort with a median OS of 29 months (Table II). The OS at 5 years was 58±10% for patients with pCR compared to 25±5% for patients with less favorable response to N-RCT (*p*=0.009), respectively (Figure 2).

There was no significant difference between the three radiation dose levels considering hematological acute toxicity ≥ grade 3 (*p*=0.360) (Table III). Dysphagia (n=14, 13%) and hoarseness (n=14, 13%) were the most frequent grade 3-4 acute toxicities. The risk of grade 3-4 non-hematological acute toxicity was higher in patients who were treated with higher radiation doses (40% *vs.* 24% for doses of at least 39.6 Gy *vs.* 30-30.6 Gy) but this difference did not reach statistical significance (*p*=0.052). Postoperative 30-day mortality was high (10%) in the beginning of the study, when the radiation dose was limited to 30-30.6 Gy. It declined to 3% when 39.6-40 Gy were the Institutional standard and 0% in the most recent time period when 44-45 Gy were administered. Other complications are summarized in Table IV.

Discussion

The use of neoadjuvant radiochemotherapy is based on the premise of preoperative devitalization, reduction of the tumor bulk, eradication of lymph node metastases and distant microscopic involvement, if systemically active drug

Table I. *Patients' and subgroups' characteristics*.

Characteristics	All patients n=111	Group 1 n=71	Group 2 n=34	Group 3 n=6	*p*-Value
Age, median (range), y	55 (37-76)	52 (37-74)	61 (44-76)	62 (53-70)	<0.001
Gender, No. (%)					0.183
Female	21 (19)	10 (14)	10 (29)	1 (17)	
Male	90 (81)	61 (86)	24 (71)	5 (83)	
ECOG-PS, No. (%)					0.701
0-1	97 (87)	63 (89)	29 (85)	5 (83)	
2	14 (13)	8 (11)	5 (15)	1 (17)	
Weight loss, No. (%)					0.655
<10%	82 (74)	51 (72)	27 (79)	4 (67)	
≥10%	29 (26)	20 (28)	7 (21)	2 (33)	
T-Stage, No. (%)					0.599
1	2 (2)	2 (3)	0	0	
2	7 (6)	5 (7)	2 (6)	0	
3	92 (83)	55 (78)	31 (91)	6 (100)	
4	10 (9)	9 (13)	1 (3)	0	
N-Stage, No. (%)					0.403
N0	16 (14)	13 (18)	3 (9)	0	
N+	95 (86)	58 (72)	31 (91)	6 (100)	
Clinical stage*, No. (%)					0.578
2	21 (19)	16 (23)	5 (15)	0	
3	89 (80)	54 (76)	29 (85)	6 (100)	
4a	1 (1)	1 (1)	0	0	
Grading, No. (%)					0.260
G1-2	53 (48)	38 (54)	13 (38)	2 (33)	
G3-4	58 (52)	33 (47)	21 (62)	4 (67)	
Localization, No. (%)					0.368
Upper thoracic	16 (14)	10 (14)	6 (17)	0	
Mid thoracal	30 (27)	20 (28)	7 (21)	3 (50)	
Lower thoracal	8 (7)	3 (4)	4 12)	1 (17)	
Overlapping	57 (51)	38 (54)	17 (50)	2 (33)	
Length, median (range), cm	5 (2-15)	5 (2-15)	6 (3-13)	6 (3-10)	0.645
Length, No. (%)					0.665
≤8 cm	99 (89)	64 (90)	30 (88)	5 (83)	
>8 cm	12 (11)	7 (10)	4 (12)	1 (17)	
RT-Tech., No. (%)					0.001
2-D	56 (50)	32 (45)	24 (71)	0	
3-D	55 (50)	39 (55)	10 (29)	6 (100)	
R-Status, No. (%)					0.580
R0	86 (78)	52 (73)	29 (85)	5 (83)	
R1/R2	22 (20)	17 (24)	4 (12)	1 (17)	
No data available	3 (3)	2 (3)	1 (3)	0	
Path. reg. grade, No. (%)					0.001
pCR	26 (23)	9 (13)	13 (38)	4 (67)	
non-pCR	85 (77)	62 (87)	21 (62)	2 (33)	

PS, Performance status; y, years; RT-Tech, radiotherapy technique; Path. reg. grade, pathological regression grade; pCR, pathological complete response. *According to UICC 2002 (6th edition).

regimens are utilized. Theoretically, this should increase the resectability, particularly for tumors located in the proximal half of the esophagus, and diminish intraoperative spread of tumor cells. The possible increase of the resection rate and reduction of local recurrences with this approach, however, have to be balanced against a potentially increased perioperative morbidity and, in the small minority of patients who do not respond to radiation, an unjustifiable delay of potentially curative surgery (8).

The concept of N-RCT has evolved over time, as also demonstrated in the present study, which looked at different consecutive treatment protocols. Different
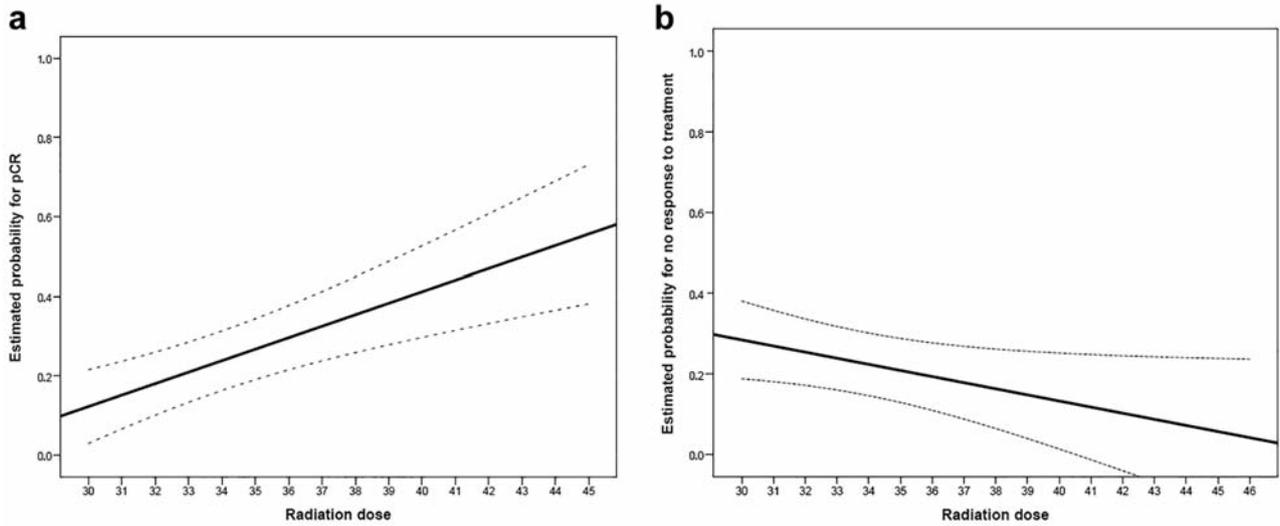
Figure 1. *a: Estimated probability for pathological complete response (Becker 1a) represented as solid line with 95% confidence bands (dashed lines). b: Estimated probability for no response to treatment (Becker 3) represented as solid line with 95% confidence bands (dashed lines).*

radiation doses and drug regimens were also used in previous studies that demonstrated large inter- and intra-institutional variability (9-12). Not all theoretically possible combinations have been explored in a systematic fashion, resulting in uncertainty about efficacy and optimal balance between response and side-effects (therapeutic window). The ideal N-RCT regimen is yet to be defined. The most beneficial effect of N-RCT is found in patients with potentially resectable tumors with favorable clinical or complete histopathological response to preoperative therapy. Esophageal cancer patients who achieved a pCR after N-CRT had superior outcomes compared to patients who achieved a partial response or non-response. In the study reported by Donahue *et al*. (13), in which 194 patients who received N-CRT were retrospectively reviewed, the pCR group experienced superior results compared to results in other patients with respect to OS ($p=0.013$) and DFS ($p=0.035$). Berger *et al*. (14) also reported confirmatory data insofar as the pCR group had superior OS ($p=0.02$) and DFS ($p=0.015$). This is in line with our recently published series, which showed that patients with pCR (Becker grade 1a) had 5-year OS of 65% compared to 50% for pathological remission grade 1b and 21% for minimal or no response to treatment ($p=0.006$) (1). Important questions arise from these observations. Is the rate of pCR mainly determined by tumor biology and fixed at a certain level or will it improve linearly with increasingly aggressive N-RCT? In the latter case, is it safe to combine such treatment with surgery? In other words, studies examining dose-response relationships are necessary (15-18).
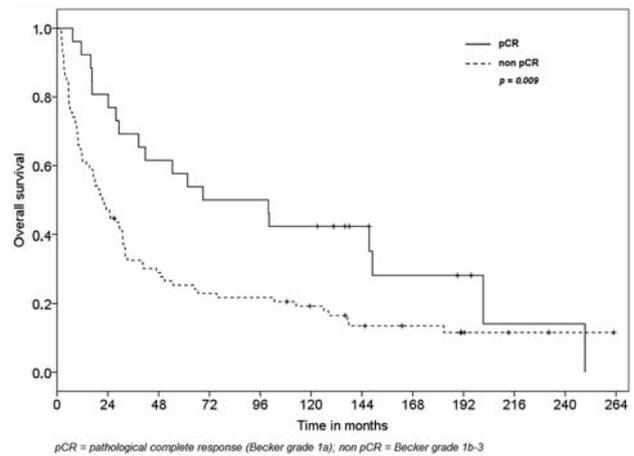

Figure 2. *OS considering pCR after N-RCT.*

Our present attempt towards analyses of potential associations between radiation dose and likelihood of pCR has methodological advantages and disadvantages. On the one hand, we eliminated sources of bias and heterogeneity, such as different tumor histology or drug regimens. On the other hand, residual imbalances still might be present in retrospective studies with limited numbers of patients. Especially the sub-group treated with 44-45 Gy was very small. This might explain the unusually high rate of pCR in this sub-group. There was no statistically significant difference in baseline parameters explaining the observed increase of pCR rate with radiation dose. Factors such as T

Table II. *Results of univariate analyses for OS.*

Factor	Group	No.	5-year OS (%)	*p*-Value
Age	<59	64	34±6	0.895
	≥59	47	32±7	
Gender	Male	90	30±5	0.132
	Female	21	46±11	
ECOG-PS	0-1	97	36±5	0.007
	2	14	14±9	
Weight loss	<10%	82	35±5	0.376
	≥10%	29	26±8	
T-Stage	T1/T2	9	33±16	0.796
	T3/T4	102	33±5	
N-Stage	N0	16	31±12	0.967
	N+	95	33±5	
Grading	G1/2	53	34±7	0.714
	G3/4	58	32±6	
Localization	Upper thoracal	16	44±12	0.382
	Mid thoracal	30	37±9	
	Lower thoracal	8	38±17	
	Overlapping	57	27±6	
Length	≤8cm	99	33±5	0.553
	>8cm	12	33±14	
Dose levels	30 Gy	71	33±6	0.947
	40 Gy	34	32±8	
	45 Gy	6	33±19	
R- Status	0	86	39±5	0.003
	1/2	22	14±7	
	No data	3	0	
Path. reg. grade	pCR	26	58±10	0.009
	non pCR	85	25±5	
pT-Stage	T0/T1	37	46±8	0.071
	T2/T3/T4	74	27±5	
pN-Stage	N0	72	37±6	0.161
	N+	39	26±7	

Abbreviations: PS, performance status; Path. reg. grade, pathological regression grade; pCR, pathological complete response; pT-Stage, pathological T-Stage; pN-Stage, pathological N-Stage.

Table III. *Acute toxicity grade ≥3 after N-RCT.*

Acute toxicities Grade ≥3	All patients (n=111) No. (%)	Group 1 (n=71) No. (%)	Group 2 (n=34) No. (%)	Group 3 (n=6) No. (%)
Non-hematologic	35 (32)	18 (25)	13 (38)	4 (67)
Abscess	1 (1)	0	0	1 (17)
Cough	0	0	0	0
Reduced kidney function	1 (1)	0	1 (3)	0
Dermatitis	2 (2)	2 (3)	0	0
Dysphagia	14 (13)	5 (7)	8 (24)	1 (17)
Esophagitis and mucositis	11 (10)	3 (4)	5 (15)	3 (50)
Hoarseness	14 (13)	12 (17)	1 (3)	1 (17)
Nausea	4 (4)	1 (1)	2 (6)	1 (17)
Pulmonary symptoms	4 (4)	0	3 (9)	1 (17)
Severe fever	5 (5)	1 (1)	3 (9)	1 (17)
Hematologic	5 (5)	3 (4)	2 (6)	0
Neutropenia	5 (5)	3 (4)	2 (6)	0
Thrombocytopenia	1 (1)	1 (1)	0	0

Table IV. *Surgery-related complications.*

Surgical complications	All patients (n=111) No. (%)	Group 1 (n=71) No. (%)	Group 2 (n=34) No. (%)	Group 3 (n=6) No. (%)
Clinical AL†	7 (6)	4 (6)	2 (6)	1 (17)
DVT/PE	4 (4)	4 (6)	0	0
Pneumonia	16 (14)	9 (13)	7 (21)	0
Severe fever	3 (1)	3 (4)	1 (3)	0
SVT	2 (2)	2 (3)	0	0
Vocal cord paresis	17 (15)	12 (17)	3 (9)	2 (33)
Wound infection	14 (13)	8 (11)	6 (18)	0

AL, Anastomotic leak; SVT, supraventricular tachycardia or atrial fibrillation; DVT/PE, deep vein thrombosis or pulmonary embolism requiring anticoagulation. †Clinical anastomotic leak, which required surgical intervention.

and N stage, tumor length or histological grade were equally distributed. The same interval between end of N-RCT and surgery was used throughout the study period. However, subtle imbalances resulting from improved staging methods and patient selection might have influenced the results. It should also be noted that introduction of 3-D conformal techniques might have reduced the risk of geographical miss. However, 2-D margins were generous and, therefore, we consider the influence of change in technique as less important compared to increase in dose. Our results are well compatible with radiobiological principles, suggesting that doses between 30 and 45 Gy are located on the steep part of the radiation-dose-response curve.

More advanced radiation treatment might also have contributed to better sparing of healthy lung tissue. Historical studies that reported high rates of postoperative morbidity

and mortality were carried-out in the 2-D era. Our own data suggest lower postoperative mortality in recently treated patients, despite higher radiation dose and increase in certain acute side-effects. Aside from improved treatment planning, this finding was likely influenced by advances in surgical technique and skills, as well as perioperative care and supportive therapy.

The optimal setting to study the present research question would require for randomization of patients between different radiation dose levels with identical staging and treatment planning, as well as stratification for factors, such as size of the gross tumor volume and amount of nodal involvement. Companion evaluation of predictive factors, including molecular features, would be desirable. In the absence of such data, our study adds relevant knowledge about the efficacy of higher radiation dose

considering the response to treatment in ESCC. One should note that we have excluded patients who received concomitant cisplatin for this dose-response analysis. Cisplatin-based radiochemotherapy has been shown to improve the response and outcomes in several *in vitro* and clinical studies and should not be replaced with 5-FU alone (10, 19). It is interesting to note that some tumors are very radioresponsive, shrinking rapidly after administration of only 30 Gy with concomitant 5-FU. Deciphering the mechanisms beyond this behavior would represent a major step forward in the development of individualized radiotherapy because a prior identification of these patients would allow for administration of well-tolerated moderate-dose treatment. As also demonstrated in our study, increasing radiation doses lead to increasing normal tissue side-effects (Tables III and IV). However, the differences were not dramatic and do not question the clinical safety of any of the studied regimens.

The complexity of N-RCT in esophageal cancer goes beyond schedule and dosing and several other issues need to be answered. What is the optimal clinical target volume? What is the optimal radiosensitizing agent or combination? Should chemotherapy be individualized based on histology? Is there a role for additional neoadjuvant chemotherapy prior to N-RCT? Is surgical resection mandatory in patients who have clinical complete response after N-RCT with a radiation dose in the curative range (50 – 54 Gy)? While a detailed discussion of these questions is beyond the scope of this article, it is important to stress that N-RCT with doses lower than 50 Gy is not a substitute for surgical resection, even in case of clinical complete response (20).

Conclusion

The dose of radiation correlates significantly with the likelihood of pCR, in line with radiobiological models. Prospective randomized trials are required to definitively evaluate the impact of higher radiation doses in the context of N-RCT on clinical outcomes and therapeutic window.

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