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Original Article

Is preoperative chemoradiation in rectal cancer patients modulated by ACE inhibitors? Results from the Dutch Cancer Registry

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ABSTRACT

Background and purpose: The aim of this study was to assess the effect of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) on tumor response to preoperative chemoradiation for rectal cancer.
Materials and methods: Data on patients who received chemoradiation prior to surgery for rectal cancer between 2010 and 2015 were retrieved from linkage between the PHARMO Database Network, Dutch Pathology Registry and Netherlands Cancer Registry. Pathological complete response rates (pCR) were compared between patients who did or did not use ACEIs/ARBs during treatment. Multivariable analysis was performed using logistic regression.
Results: Out of 345 patients, 92 patients (26.7%) used ACEIs/ARBs during treatment. Median age was 65 years (range 30–85). Older and male patients were more likely to use ACEIs/ARBs. pCR (ypT0N0) was observed in 17.4% of patients using ACEIs/ARBs compared to 14.6% of patients who did not use ACEIs/ARBs ($p = 0.595$). A good response (ypT0-1N0) was observed in 21.7% of ACEIs/ARBs patients vs. 19.4% of patients who did not use ACEIs/ARBs ($p = 0.724$). Multivariable analysis, taking into account background variables and co-medication, showed increased pCR in patients using beta-blockers (odds ratio 2.3, 95% confidence interval 1.0–5.4).
Conclusion: In this retrospective cohort, the use of ACEIs/ARBs was not associated with tumor response to preoperative chemoradiation in rectal cancer patients. Thereby, the suggested potentiating effect of ACEIS/ARBs could not be confirmed in our study. Further research could be directed to investigate a possible benefit of beta-blockers or other anti-hypertensive drugs.

Rectal cancer is one of the most common cancers worldwide and accounts for one third of colorectal cancer cases [1]. Rectal cancer patients are treated by surgery with or without (chemo)radiation, depending on tumor stage, location and size [2]. Preoperative chemoradiation (CRT) is used to downstage the tumor, which is associated with improved oncological outcomes [3,4]. Unfortunately, only 50% of patients respond to preoperative treatment and a minority of patients even show progression during treatment [5,6]. Therefore, it is important to identify factors that could potentially influence tumor response to CRT in rectal cancer.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are inhibitors of the renin-angiotensin system and are commonly subscribed as antihypertensive treatment [7]. In addition to a blood pressure regulatory effect, ACEIs are thought to block angiogenesis and have been hypothesized to have a mediating effect on the immune response associated with cancer [8]. Several recent studies have reported a potential beneficial effect of the use of ACEIs and ARBs during anti-cancer treatment. Some studies reported a decreased cancer risk in patients using ACEIs or ARBs [9,10], others reported a reduction in cancer recurrence [11,12] or improved cancer survival [13–15]. However, a beneficial effect of the use of ACEIs or ARBs was not confirmed in all studies [16–18].

Morris et al. recently published data from two independent small databases of rectal cancer patients in which 25 and 49 patients respectively used ACEIs or ARBs. The authors found a threefold increase in pathological complete response rates following preoperative (chemo)radiation in patients using ACEIs or ARBs [19]. This was the first study to suggest a relation between the incidental use of ACEIs and ARBs and tumor response in rectal cancer patients.

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We hypothesized that the use of ACEIs/ARBs could potentiate the effects of CRT on rectal cancer thanks to an effect on angiogenesis, thereby possibly improving tumor perfusion and chemotherapeutic delivery. With the current study, we aimed to investigate the effect of ACEIs and ARBs on tumor response to preoperative CRT in rectal cancer patients in a large population based cohort.

Pharmacological mechanism of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) act as inhibitors on the renin-angiotensin system. Renin (produced in the kidney) stimulates the conversion of angiotensinogen into Angiotensin I. Angiotensin-converting enzyme (ACE) subsequently converts the hormone angiotensin I to the active vasoconstrictor angiotensin II. Angiotensin II has a direct effect on vascular smooth muscle and induces vasoconstriction. By blocking the formation of angiotensin II ACEIs and ARBs induce the following effects:

- vasodilatation and inhibition of the bradykinin metabolism.
- down regulation of the sympathetic adrenergic activity.
- induction of natriuretic and diuretic effects, reducing blood volume, venous pressure and arterial pressure.

In cancer patients, the use of AIEs/ARBs has been hypothesized to block tumor angiogenesis, thereby lowering the risk of cancer. However, findings in the literature have not been consistent. Small retrospective clinical studies have suggested a possible potentiating effect of the use of ACEIs/ARBs concurrent with (chemo)radiation therapy.

Materials and methods

Data from patients with histologically confirmed rectal cancer between 2010 and 2015 were obtained from PALGA, the nationwide network and registry of histo- and cytopathology in the Netherlands which contains data of all histological, cytological, and autopsy examinations[20]. PALGA achieves complete national coverage since 1990 and is the basis for the Netherlands Cancer Registry (NCR). Records from PALGA were linked to the PHARMO Database Network. The PHARMO Database Network is a population-based network of electronic healthcare databases and combines data from different primary and secondary healthcare settings in the Netherlands, covering more than 4 million (25%) residents of a well-defined population in the Netherlands [21,22]. For this study, the Out-patient Pharmacy Database was used to obtain information on dispensed medication. The Out-patient Pharmacy Database comprises GP or specialist prescribed healthcare products dispensed by the out-patient pharmacy. The dispersion records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty and costs. Drug dispersions are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System. Data from the NCR was used to obtain clinical information and information on the administration of preoperative therapy. In total, data were available for 5002 patients, of which data were complete in all 3 registries for 971 patients.

In the Netherlands, between CRT and surgery a treatment interval of >6 weeks is respected, whereas short course radiation therapy (5×5 Gy) is generally followed by surgery within one week. Because pathological response of rectal cancer is dependent on the time interval between (chemo)radiation and surgery [5,23], we decided to include patients who received CRT only.

Statistics

Statistical analyses were performed using SPSS software version 22. The use of ACEIs/ARBs was collected for the six months prior to the diagnosis and for the three months after rectal cancer diagnosis (i.e. during preoperative treatment). Baseline characteristics were analyzed using the chi^2-test, or, in case of an expected cell count <5, the Fisher exact test or a Monte Carlo simulation (number of samples 10,000) was used. Primary outcomes were a complete (pCR) or good pathological response, defined as ypT0N0 and ypT0-T1N0 respectively. Tumor downsizing and nodal downstaging were also studied. Downsizing was defined as a lower pathological tumor category when compared to clinical tumor category. Nodal downstaging was defined as a pN0 in patients with a clinical cN1 or cN2 category. Outcomes were compared between the group of rectal cancer patients who used ACEIs/ARBs and the group of rectal cancer patients who did not use these medications. Multivariable analysis was performed to correct for possible confounding effects. The following frequently used co-medications of ACEIs/ARBs have been described to potentially influence tumor response in rectal cancer patients: statins, metformin, aspirin, and were therefore evaluated as potentially confounders [24]. Variables were entered into the multivariable model based on clinical significance and/or *p*-value of <0.1 during univariable analysis.

Results

A total of 971 rectal cancer patients were identified, of whom 345 received CRT. Baseline characteristics for rectal cancer patients are displayed in Table 1. Median age was 65 years (range 30–85). Ninety-two patients of the 345 patients (26.7%) used ACEIs/ARBs. The type of ACEIs/ARBs used is presented in Supplementary Table I. Older patients and male patients used ACEIs/ARBs significantly more often than younger and female rectal cancer patients. The mean age for patients using ACEI/ARBs was 67 years compared to 62 years in patients who did not use those drugs ($p < 0.001$). Out of all male patients, 32.4% used ACEI/ARBs compared with 17.4% of female patients ($p = 0.002$). ACEI/ARB use was related to the use of aspirin ($p < 0.001$), acenocoumarol ($p < 0.001$), metformin ($p < 0.001$), statin ($p < 0.001$) and beta-blockers ($p < 0.001$).

Pathological complete response in rectal cancer patients

The overall pCR rate (ypT0N0) in rectal cancer patients following CRT was 15.4%. A pCR was found in 17.4% ($N = 16$) of patients who used ACEIs/ARBs during treatment (Fig. 1 and Supplementary Table I). This was not statistically different from patients who did not use ACEIs/ARBs (14.6% [$N = 37$], $p = 0.529$). Multivariable analysis confirmed that there was no significant difference between the use of ACEIs/ARBs and the pCR rate in rectal cancer patients undergoing CRT (Table 2). However, the use of beta-blockers was associated with an increased pCR: the PCR rate was 22.0% in patients using beta-blockers vs. 13.3% in beta-blocker naïve patients (OR 2.4 [95%CI 1.0–5.4]). Other drugs did not show a significant relation with pCR.

Pathological good response in rectal cancer patients

A good response (ypT0-1N0) was found in 20.0% of patients. Among patients who used ACEIs/ARBs during treatment, 21.7% ($N = 20$) had a good response (Fig. 1). This was not statistically different from patients who did not use ACEIs/ARBs during preoperative CRT (19.4% [$N = 49$], $p = 0.626$). Multivariable analysis confirmed that there was no significant relation (Table 3).

Table 1
Characteristics for rectal cancer grouped according to ACE/ARB use.

	ACE/ARB *N* 92 (%)	No ACE/ARB *N* 253 (%)	*p*-value
Age, years; mean (95% CI)	67 (66–69)	62 (60–63)	<0.001
0–59	12 (13.0)	94 (37.2)	
60–74	58 (63.0)	130 (51.4)	
>75	22 (23.9)	29 (11.5)	
Sex			0.002
Male	69 (75.0)	144 (56.9)	
Female	23 (25.0)	109 (43.1)	
Year of diagnosis			0.525
2010–2012	47 (51.1)	139 (54.9)	
2013–2015	45 (48.9)	114 (45.1)	
Histology			0.203
AC	73 (94.8)	193 (89.8)	
MC	3 (3.9)	21 (9.8)	
Other	1 (1.3)	1 (0.5)	
Unknown	15	38	
cT			0.458
cT1	–	2 (0.8)	
cT2	11 (12.8)	20 (8.2)	
cT3	68 (79.1)	194 (79.5)	
cT4	7 (8.1)	28 (11.5)	
cTx	6	9	
ypT			0.294
ypT0	16 (17.4)	39 (15.5)	
ypT1	4 (4.3)	16 (6.3)	
ypT2	36 (39.1)	72 (28.6)	
ypT3	33 (35.9)	118 (46.8)	
ypT4	3 (3.3)	7 (2.8)	
ypTx	–	1	
cN			0.715
cN0	15 (18.5)	44 (18.1)	
cN1	34 (42.0)	91 (37.4)	
cN2	32 (39.5)	108 (44.4)	
cNx	11	10	
ypN			0.597
ypN0	64 (69.6)	174 (68.8)	
ypN1	21 (22.8)	51 (20.2)	
ypN2	7 (7.6)	28 (11.1)	
Drug use during CRT			
Acenocoumarol			<0.001
Yes	14 (15.2)	9 (3.6)	
No	78 (84.8)	244 (96.4)	
Aspirin			<0.001
Yes	32 (34.8)	24 (9.5)	
No	60 (65.2)	229 (90.5)	
Statins			<0.001
Yes	49 (53.3)	35 (13.8)	
No	44 (46.7)	218 (86.2)	
Metformin			<0.001
Yes	17 (18.5)	11 (4.3)	
No	75 (81.5)	242 (95.7)	
Glitazones			1.000
Yes	–	1 (0.4)	
No	92 (100)	252 (99.6)	
Beta-blockers			<0.001
Yes	49 (53.3)	33 (13.0)	
No	43 (46.7)	220 (87.0)	
Corticosteroids			0.213
Yes	9 (9.8)	15 (5.9)	
No	83 (90.2)	238 (94.1)	

CRT, chemoradiation; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; OR, odds ratio; CI, confidence interval.

Tumor downsizing and nodal downstaging in rectal cancer patients

There were no differences in tumor downsizing or nodal downstaging between rectal cancer patients who did or did not use ACEIs/ARBs during treatment. Tumor downsizing was present in 41.3% of patient who used ACE/ARBs, and in 48.8% of patients who did not ($p = 0.162$). Nodal downstaging was present in 28.8% of ACE/ARB patients vs. 35.7% ($p = 0.306$).

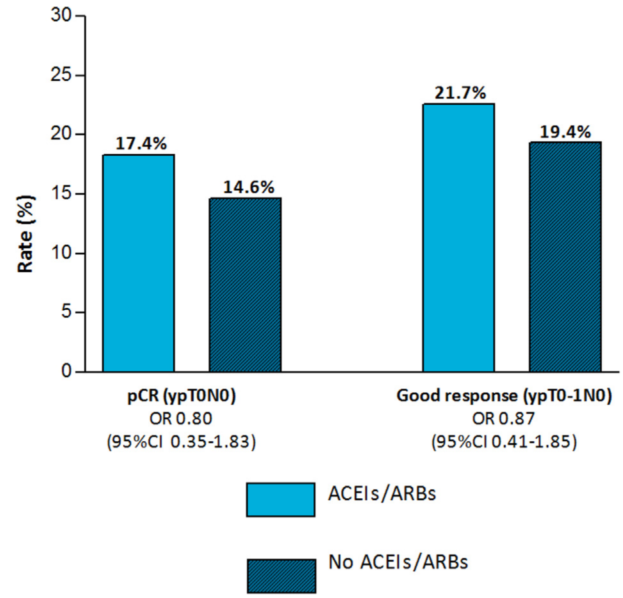

Fig. 1. Comparison of complete and good pathological response in rectal cancer patients using ACEI/ARB vs. a control group of ACEI/ARB naive patients. *ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; OR, odds ratio; CI, confidence interval.*

Discussion

This retrospective cohort study demonstrated that the use of ACEIs/ARBs is not related to tumor response to CRT in rectal cancer patients. In the current era of organ sparing strategies in rectal cancer, there is an ongoing search for factors that may improve tumor response to preoperative therapy [2]. Radiation therapy sorts its effect through a deposit of energy in the tissue that induces DNA damage directly or via degeneration of free radicals. The effect of RT is different in tumor and normal tissues due to better DNA repair mechanisms of the latter. The biological effect of RT is dependent on several factors. The availability of anti-oxidants that can disarm free radicals, the site and number of energy deposits that take place in the cells and in the surrounding microenvironment, the DNA recovery processes, and the time between two cell divisions all have been demonstrated to influence the efficacy of RT [25,26]. Previous research has shown that RT is up to three times less effective in poorly oxygenized tissues, indicating that improving oxygenation of the tumor tissue can aid the chemical reactions that induce DNA damage and/or prevent its repair [25,27]. The importance of tumor oxygenation is supported by a multitude of studies that have looked into methods such as the use of hyperthermia, oxygen-mimetic radiosensitizers, or induction of tumor angiogenesis [25]. Recent reports in the literature have suggested a beneficial effect of ACEIs/ARBs on colorectal cancer treatment by improving angiogenesis, and therefore we hypothesized that the use of ACEIs/ARBs might also potentiate the effects of CRT in rectal cancer. Results from the current population-based study, however, did not confirm this hypothesis since there was no significant correlation between the use of ACEIs/ARBs and pathological response rates.

The outcomes of the present study contradict findings of a recent pilot study by Morris et al. [19]. Results from that study demonstrated a three-fold increase in the rate of pCR to

Table 2
Multivariable analysis complete pathological response (pCR; ypT0N0).

Factor	Univariable			Multivariable		
	N	pCR (%)	*p*-value	OR	95% CI	Adjusted *p*-value
Age, years			0.380			
0–59	106	11.3				
60–74	188	17.0				
>75	51	17.6				
Sex			0.314			
Male	213	16.9				
Female	132	12.9				
Year of diagnosis			0.864			
2010–2012	186	15.1				
2013–2015	159	15.7				
cT			0.371			0.402
cT1-cT2	33	21.2		1.00		
cT3	262	14.9		0.67	0.25–1.80	
cT4	35	8.6		0.36	0.08–1.60	
cN			0.324			0.392
cN0	59	22.0		1.00		
cN1	125	13.6		0.54	0.22–1.33	
cN2	140	15.0		0.63	0.27–1.48	
Drug use during CRT						
ACEIs/ARBs			0.529	0.80	0.35–1.83	0.595
Yes	92	17.4				
No	253	14.6				
Acenocoumarol			0.550			
Yes	23	8.7				
No	322	15.8				
Aspirin			0.075	2.08	0.75–5.82	0.161
Yes	56	23.2				
No	289	13.8				
Statins			0.703	0.58	0.20–1.64	0.303
Yes	84	16.7				
No	261	14.9				
Metformin			0.594	0.64	0.13–3.16	0.586
Yes	28	10.7				
No	317	15.8				
Glitazones			0.154			
Yes	1	100				
No	344	15.1				
Beta-blockers			0.058	2.34	1.01–5.41	0.047
Yes	82	22.0				
No	263	13.3				
Corticosteroids			0.773			
Yes	24	16.7				
No	321	15.3				

CRT, chemoradiation; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; OR, odds ratio; CI, confidence interval.

preoperative (chemo)radiation in patients using ACEIs/ARBs (52% vs. 17%). These findings were confirmed in an independent cohort of patients, in which a two-fold increase in pCR was found (24% vs. 12%). There are several explanations for the discrepancy with our findings. Firstly, clinical stage was lower in their study with a greater proportion of patients being node negative (43.5–61.2% vs. 18% in our study). Another discrepancy between the studies concerns patient selection. We only selected patients who received CRT, whereas Morris et al. also included patients undergoing radiation therapy without concurrent chemotherapy. We have previously shown that CRT is associated with favorable pCR rates compared with short-course radiation therapy followed by a long treatment interval [5]. Since Morris et al. did not differentiate between CRT and short-course radiation therapy, a lower instead of higher pCR rate would be expected. Notably, the pCR rates of 52% in the subgroup of 25 patients as reported by Morris et al. are higher than those reported in the literature [6], and cannot be explained apart from chance due to low numbers. Finally, Morris et al. selected patients from two hospitals only, and the number of patients was smaller: 25 out of 115 patients used ACEI/ARB in the first cohort of patients and 49 out of 186 patients in the second cohort vs. 92 out of 345 in the current study. In the present study, data were derived from large population-based datasets, which might be less susceptible to selection bias.

Frequently used drugs were included in the multivariable model to correct for possible confounding effects. pCR was found more often in patients who used beta-blockers compared with patients who did not (22.0% vs. 13.3%, $p = 0.022$). However, the use of beta-blockers was not equally distributed between the groups: 53% of patients using ACEIs/ARBs used beta-blockers vs. 13% in the ACEIs/ARBs naive group ($p < 0.001$). A recent Swedish population-based study showed improved survival outcomes and less postoperative complications in patients using beta-blockers prior to rectal cancer surgery [28]. That study, however did not study the effect of preoperative therapy or tumor response, but mainly demonstrated a reduction in perioperative complications.

Table 3
Multivariable analysis good pathological response (ypT0-1N0) in rectal cancer patients.

Factor	Univariable N	ypT0-1N0 (%)	*p*-value	Multivariable OR	95% CI	Adjusted *p*-value
Age, years			0.646			
0–59	106	17.0				
60–74	188	21.3				
>75	51	21.6				
Sex			0.223			
Male	213	22.1				
Female	132	16.7				
Year of diagnosis			0.552			
2010–2012	186	18.8				
2013–2015	159	21.4				
cT			0.078			0.129
cT1-cT2	33	30.3		1.00		
cT3	262	19.8		0.65	0.27–1.56	
cT4	35	8.6		0.23	0.05–0.96	
cN			0.119			0.159
cN0	59	30.5		1.00		
cN1	125	18.4		0.50	0.23–1.11	
cN2	140	18.6		0.50	0.23–1.08	
Drug use during CRT						
ACEIs/ARBs			0.626	0.87	0.41–1.85	0.724
Yes	92	21.7				
No	253	19.4				
Acenocoumarol			0.589			
Yes	23	13.0				
No	322	20.5				
Aspirin			0.165	1.80	0.70–4.60	0.223
Yes	56	26.8				
No	289	18.7				
Statins			0.950	0.59	0.23–1.50	0.264
Yes	84	20.2				
No	261	19.9				
Metformin			0.430	0.70	0.18–2.73	0.609
Yes	28	14.3				
No	317	20.5				
Glitazones			0.200			
Yes	1	100				
No	344	19.8				
Beta-blockers			0.146	1.94	0.90–4.17	0.091
Yes	82	25.6				
No	263	18.3				
Corticosteroids			0.797			
Yes	24	16.7				
No	321	20.2				

CRT, chemoradiation; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; OR, odds ratio; CI, confidence interval.

Recent pre-clinical studies found anti-proliferative effects of beta-blockers on human cancer cell lines from different origins, including colorectal cancer [29–31]. Also, retrospective studies have related the incidental use of beta-blockers to decreased tumor proliferation and/or improved response rates in breast cancer and meningioma patients [32,33]. The authors suggested that this beneficial effect could be due to improvement of angiogenesis (thereby improving tumor oxygenation and thus sensitivity for preoperative therapy), an increase of oxidative stress or the induction of an anti-tumor inflammatory response. However, as far as we are aware, no prospective data are available and no clinical studies have been performed to support these mechanisms for rectal cancer patients. The use of beta-blockers was not the primary focus of this study and further research is needed to evaluate the possible effect on tumor response in rectal cancer.

Other concomitantly taken therapeutic agents have also been described to have a potential effect on tumor response in rectal cancer patients [24]. A schematic overview of the literature on possible (chemo)radiation sensitizers is provided in Supplementary Table II. Retrospective studies have suggested that patients receiving statins during rectal cancer treatment can have a 1.5 to 4-fold increase in pCR rates [34–36]. However, no prospective data are available and other studies showed no benefit of statin use in rectal cancer patients [19,37,38]. Similarly, increased pCR rates have been reported in patients using metformin. A clinical study by Skinner et al. showed pCR rates up to 35% in diabetics taking metformin, which was significantly higher than in non-diabetic patients and in diabetics not using metformin (16.6% and 7.5% respectively) [39]. However, the number of patients using metformin was low ($N = 20$), and the results should therefore be interpreted with caution because of a high risk of selection bias. Again, other reports showed no increase in pCR [19,40]. In the current study, multivariable analysis showed no association between the use of metformin or statins and tumor response.

The use of aspirin is also being explored as a possible supplementary agent for rectal cancer treatment. Three clinical studies have been conducted analyzing pathological response in rectal cancer patients and showed no significant effect on pCR [19,38,41]. Even though there was no significant effect on pCR, in the prospective observational study by Restivo et al. the use of aspirin was related to an increased rate of tumor downstaging and good pathological responses (ypT0-1N0) [41]. The positive effects of aspirin, including improved survival following rectal cancer treatment, have been correlated to the presence of a PIK3CA mutation [42]. In the current study, an effect of aspirin on pathological response was not observed. However, the number of patients using aspirin might have been too small to demonstrate an effect, keeping in mind that the PIK3CA mutation occurs in only 10–20% of colorectal cancer patients [43].

In the current study, we investigated the effect of ACEIs and ARBs on tumor response to preoperative CRT in rectal cancer patients in a population based cohort. Data were derived from three large prospective registries, providing the opportunity to link data of drug dispersions to pathology and clinical data including preoperative treatment. Exploring commonly described drugs as possible RT sensitizers has the advantage that these medications have proven to be relatively safe when administered to large groups of patients and side effects are well-known. The present study does however have its limitations. First, a large number of patients ($N = 4031$) could not be analyzed because data were not available for all three registries. In addition, potential confounding could be present because of the retrospective nature of the analyses.

In conclusion, the use of ACEIs/ARBs was not related with tumor response to CRT in rectal cancer patients. The use of beta-blockers was not the primary focus of this study, but seemed to be related to tumor response. Further specific research is required to confirm whether the addition of beta-blockers to the standard treatment regimen would be safe and would lead to improvement of oncological outcomes.

Declaration of Competing Interest

None of the authors have conflicts of interests or funding to declare related to the work presented in this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.06.010.

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