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Original Research

Adjuvant androgen deprivation therapy for poor-risk, androgen receptor–positive salivary duct carcinoma☆

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KEYWORDS
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Abstract ***Aim:*** Salivary duct carcinoma (SDC), an aggressive subtype of salivary gland cancer, is androgen receptor (AR)–positive in 67–96% of cases. In patients with locally recurrent and metastatic (R/M) AR-positive SDC, androgen deprivation therapy (ADT) has an overall response rate of 18–64.7%. In this study, we describe the efficacy of adjuvant ADT in patients with poor-risk (stage 4a) AR-positive SDC.

Methods: This is a retrospective cohort study in which patients with stage 4a AR-positive SDC were offered adjuvant ADT, i.e. bicalutamide, luteinizing hormone-releasing hormone (LHRH) analogue or a combination of these after tumour resection. In the control group,

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Pharmaceutical;
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data were collected on patients with stage 4a SDC who underwent a tumour resection but did not receive adjuvant ADT.

Results: Twenty-two AR-positive SDC patients were treated with adjuvant ADT for a median duration of 12 months. The control group consisted of 111 SDC patients. After a median follow-up of 20 months in the ADT-treated patients and 26 months in the control group, the 3-year disease-free survival (DFS) was estimated as 48.2% (95% confidence interval [CI] 14.0–82.4%) and 27.7% (95% CI 18.5–36.9%) ($P = 0.037$). Multivariable Cox regression analysis showed a hazard ratio of 0.138 (95% CI 0.025–0.751, $P = 0.022$) for DFS and 0.064 (95% CI 0.005–0.764, $P = 0.030$) for overall survival (OS) in favour of the ADT-treated patients.

Conclusion: Poor-risk, AR-positive SDC patients who received adjuvant ADT have a significantly longer DFS compared with patients in the control group, who did not receive adjuvant ADT. For OS, this was just below and above the significance level, in case there was or was no correction for confounders.

1. Introduction

Salivary gland cancer is a rare cancer, with a global annual incidence of 0.4–2.6/100.000 people [1] and an annual incidence of 0.73/100.000 people in the European Union [2]. Salivary duct carcinoma (SDC) accounts for 9% of all salivary gland cancers and is a very aggressive subtype with a median overall survival (OS) of 3–5 years after primary diagnosis [3–6]. SDCs are androgen receptor (AR)–positive in 67–96% cases [3,7,8], and the male-to-female ratio is at least 4:1 [1]. Primary treatment includes resection of the affected salivary gland plus neck dissection, followed by postoperative radiotherapy. In case of recurrent and/or metastatic (R/M) disease, no standard treatment options are available.

In R/M disease, ADT demonstrated an impressive response rate of 18–64.7% and an increased OS compared to best supportive care in retrospective studies [9,10]. A recently conducted prospective phase 2 trial showed an overall response rate of 42% and a clinical benefit rate of 75% [11]. Currently, a randomised phase II European Organisation for Research and Treatment of Cancer (EORTC) trial comparing the effect of palliative ADT (triptorelin + bicalutamide) with that of palliative chemotherapy (cisplatin + doxorubicin or carboplatin + paclitaxel) on AR-positive, advanced salivary gland cancer is recruiting (ClinicalTrials.gov Identifier: NCT01969578).

SDC patients often present with advanced disease. At initial presentation, 37.7–67.2% of patients are diagnosed with stage 4a/b disease (T4 or N2/N3 without distant metastases) and 5.8–12.8% of patients are diagnosed with stage 4c disease (distant metastatic disease) [3,14,15]. In case of stage 4a/b disease, patients are treated with curative intent, but 3-year disease-free survival (DFS) is 32.5% and 3-year OS is 52.5% [16]. Therefore, in this study, patients with stage 4a/b disease were defined as the poor-risk group, and improving the efficacy of primary treatment to reduce the recurrence risk is urgently warranted.

We hypothesised efficacy of adjuvatn ADT in poor-risk patients with SDC because of the efficacy of ADT in R/M SDC and results on adjuvant ADT in poor-risk prostate cancer patients [17]. Therefore, adjuvant ADT was started on these patients on an individual basis. By combining the data of patients treated in the Radboud University Medical Center (Nijmegen, the Netherlands) and the Istituto Nazionale dei Tumori (Milan, Italy), we were able to describe the efficacy of adjuvant ADT in poor-risk, AR-positive patients with SDC. Outcomes were compared to those of a Dutch historical cohort.

2. Patients and methods

2.1. Study design

A retrospective cohort study was performed in which patients with stage 4a/b AR-positive SDC were offered off-label adjuvant ADT after tumour resection. In the control group, data were collected on patients with stage 4a/b SDC who underwent a tumour resection but did not receive adjuvant ADT. Although this study was a retrospective analysis and not a prospective trial, this study has been reviewed by the ethics committee as institutional guidelines dictate to ensure responsible use of human tissue and data protection in health research. The ethics committee has passed a positive judgement on the study. All patients gave informed consent stating that they were aware of the goal of treatment and lack of scientific evidence for this treatment (off-label use).

2.2. Adjuvant ADT-treated patients

Data on patients who underwent a surgical tumour resection and received off-label adjuvant ADT between

2007 and 2018 for stage 4a/b AR-positive SDC at the Radboud University Medical Center (Nijmegen, the Netherlands) or the Istituto Nazionale dei Tumori (Milan, Italy) were collected. Tumours of the major glands were staged according to the 7th edition of the tumour/node/metastasis (TNM) classification for cancer of major salivary glands. Tumours of the minor salivary glands were staged similar to squamous cell carcinoma, according to the 7th edition of the TNM classification for head and neck cancers.

ADT consisted of bicalutamide monotherapy 150 mg once daily (OD), a LHRH analogue (10.8 mg of goserelin per 3 months or 3.25 mg of triptorelin per 28 days) or a combination of these (goserelin or triptorelin plus bicalutamide 50 mg OD). The planned duration of ADT differed between 1 and 2 years (Milan) and 5 years (Nijmegen). An experienced pathologist reviewed all SDC tumours to confirm the diagnosis. In Nijmegen, the androgen receptor was determined using the androgen receptor polyclonal antibody of Santa Cruz, dilution 1:200, after pretreatment with citrate (pH 6.0) for 10 min in a pretreatment module. Immunostaining was carried out using the Powervision method (Immunologic). In Milan, the androgen receptor was determined using the AR antibody AR441 of Dako, dilution 1:25, after pretreatment with ethylene diamine tetra-acetic acid for 15 min at 96 °C. The androgen receptor was scored positive based on strong nuclear staining in at least 70% of tumour cells.

2.3. Control group

Patients diagnosed with SDC in the Netherlands between 1990 and 2014 were anonymously collected from the Nationwide Network and Registry of Histo- and Cytopathology (PALGA) [18]. One hundred seventy-seven patients were included [3]. This cohort was expanded by including SDC patients visiting the Radboud University Medical Center between 2014 and 2018, resulting in 207 patients. An experienced pathologist reviewed all 207 SDC tumours to confirm the diagnosis. Of these patients, surgically resected patients diagnosed with stage 4a/b SDC and who did not receive adjuvant ADT were selected as the control group. Subsequently, we decided to remove stage 4b SDC patients ($n = 3$) from the control group, because all ADT-treated patients had stage 4a SDC. As stage 4b SDC patients have a worse prognosis, these patients were removed to have, a priori, more similar groups (in terms of prognosis) at baseline. See Fig. 1 for the flowchart of the inclusion of ADT-treated patients and the control group.

2.4. Analyses

Baseline characteristics were described using descriptive statistics. DFS was defined as the time from the date of diagnosis until the date of recurrence or death. Patients without recurrence or death at the last follow-up were censored. OS was defined as the time from diagnosis until

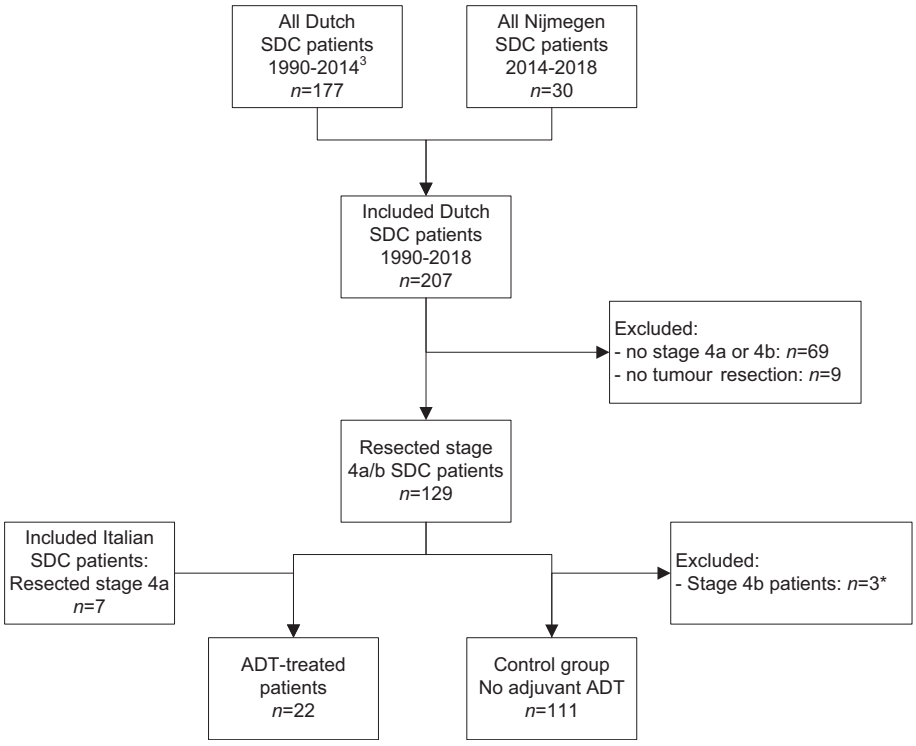

Fig. 1. Flowchart showing the inclusion of ADT-treated patients and the control group.*Because all ADT-treated patients were diagnosed with stage 4a SDC, we removed the patients with stage 4b SDC ($n = 3$) from our control group to have more similar groups at baseline. ADT, androgen deprivation therapy.

death. Patients who remained alive at the last follow-up were censored. DFS and OS were estimated by Kaplan–Meier survival curves. The log-rank test was used to compare DFS and OS between adjuvant ADT-treated patients and the control group. *P*-values <0.05 were considered statistically significant. In addition, associations between treatment and DFS and OS were estimated in a univariable Cox regression analysis. Next, in a multivariable Cox regression model, we accounted for possible confounders for the association between treatment and DFS and OS: gender, age, treatment centre, location of primary tumour, T-stage, N-stage, expleomorphic adenoma (yes/no), resection margins, number of positive lymph nodes, postoperative radiotherapy (yes/no), adjuvant chemotherapy (yes/no), AR status and year of diagnosis. Patients with missing values in one or more of the variables were excluded from the analysis. HER2 was not included in the Cox regression analysis because of a high number of missing values. Instead, DFS and OS were estimated for HER2-positive and HER2-negative controls to assess the influence of HER2 status on treatment outcome. Analyses were performed using SPSS, version 25.0.

3. Results

3.1. Patient characteristics

Twenty-two AR-positive SDC patients with stage 4a SDC received ADT as adjuvant treatment. All patients underwent a tumour resection, combined with a neck dissection (21 patients, 95.5%), and a majority of patients (21 patients, 95.5%) underwent postoperative radiotherapy. Median age was 60 years (range 29–84 years). See Table 1 for patient characteristics. All patients had a nuclear AR-staining pattern in >70% of the tumour cells. Patients were treated with bicalutamide monotherapy ($n = 12$), an LHRH analogue ($n = 1$) or a combination of these ($n = 9$). All (postmenopausal) women ($n = 3$) were treated with combined androgen blockade. Fifteen patients were treated at the Radboud University Medical Center, and seven patients were treated at the Istituto Nazionale dei Tumori. All patients received treatment between 2007 and 2018. Median duration of ADT was 12 months (range 1–31 + months), and the median follow-up was 20 months (range 1–114 months). ADT was usually well tolerated, and none of the patients stopped therapy or switched to another form of therapy because of toxicity, but some patients reported gynaecomastia or itching as adverse events, and for one patient, the reason for stopping is unknown. Currently, of 22 ADT-treated patients, 11 patients are still under treatment, six patients stopped because of disease recurrence, i.e. one patient with a local and distant recurrence and five patients with a distant recurrence, four patients stopped because of planned end of treatment (three patients after 1 year, one patient after 2 years) and one patient stopped for an unknown reason.

A total of 111 control patients with stage 4a SDC received regular treatment with curative intent without adjuvant ADT between 1990 and 2017, of which 81 patients (73.0%) were male. All patients had a tumour resection, and 99 patients, (89.2%) a neck dissection. Surgery was followed by postoperative radiotherapy in 103 patients (92.8%). Median age was 65 years (range 39–92 years), and the median follow-up was 26 months (range 0–197 months).

3.2. Disease-free survival

Three-year DFS was 48.2% (95% confidence interval [CI] 14.0–82.4%) in the adjuvant ADT-treated patients and 27.7% (95% CI 18.5–36.9%) in the control group ($P = 0.037$). Median DFS was 33 months (95% CI could not be calculated because of insufficient events) in the adjuvant ADT-treated patients and 21 months (95% CI 16.5–25.5 months) in the control group (Fig. 2). In the control group, median DFS in HER2-positive patients was 22 months (95% CI 15.5–28.5 months) and in HER2-negative patients was 21 months (95% CI 15.8–26.2 months) ($P = 0.952$). In the Cox regression analysis, 110 patients were included. In the univariable Cox regression analysis estimating the association between treatment and DFS, the hazard ratio for adjuvant ADT was 0.492 compared with the control group without adjuvant ADT(95% CI 0.213–1.139, $P = 0.098$). In the multivariable Cox regression analysis in which the association was adjusted for possible confounders, adjuvant ADT had a hazard ratio of 0.138 (95% CI 0.025–0.751, $P = 0.022$) for DFS. In Table 2, all results of the univariable and multivariable Cox regression analyses are shown. Next to adjuvant ADT, postoperative radiotherapy, female gender, lower T-stage and SDC expleiomorphic adenoma significantly improved DFS.

3.3. Overall survival

Three-year OS was 77.9% (95% CI 49.7–100%) in the adjuvant ADT-treated patients and 53.9% (95% CI 43.5–64.3%) in the control group ($P = 0.074$). Median OS was not reached in the adjuvant ADT-treated patients and was 46 months (95% CI 24.3–67.7 months) in the control group (Fig. 3). In the control group, median OS in HER2-positive patients was 48 months (95% CI 20.7–75.3 months) and in HER2-negative patients was 60 months (95% CI 18.8–101.1 months) ($P = 0.427$). In the univariable Cox regression model, the hazard ratio for adjuvant ADT-treated patients was 0.41 compared with patients in the control group (95% CI 0.127–1.326, $P = 0.137$). In the multivariable Cox regression analysis, adjuvant ADT–treated patients had a hazard ratio of 0.064 (95% CI 0.005–0.764, $P = 0.030$) for OS. In Table 2, all results of the univariable and multivariable Cox regression analyses are shown. Next to adjuvant ADT,

Table 1
Patient characteristics.

	Adjuvant ADT-treated patients (n = 22)	Control group (n = 111)	Difference between groups
	No. of patients (%)	No. of patients (%)	
Gender			
Male	19 (86.4%)	81 (73.0%)	0.280[b]
Female	3 (13.6%)	30 (27.0%)	
Age at diagnosis			
Median (range)	60 (29–84)	65 (39–92)	0.038[c]
Primary tumour			Parotid versus other
Parotid gland	20 (90.9%)	91 (82.0%)	0.529[b]
Submandibular gland	1 (4.5%)	13 (11.7%)	
Sublingual gland	0 (0.0%)	1 (0.9%)	
Minor salivary glands	1 (4.5%)	6 (5.4%)	
Surgery			
Tumour resection	1 (4.5%)	12 (10.8%)	0.694[b]
Tumour resection + neck dissection	21 (95.5%)	99 (89.2%)	
Resection margins			Free + close versus. not free
Free	0 (0.0%)	10 (9.0%)	1.000[b]
Close	3 (13.6%)	8 (7.2%)	
Not free	18 (81.8%)	89 (80.2%)	
Unknown	1 (4.5%)	4 (3.6%)	
TNM stage			
T1/T2/T3/T4/Tx	2/3/3/11/3[d]	9/29/11/58/4	T1-2 versus. T3-4
(%)	(9.1/13.6/13.6/50.0/13.6)	(8.1/26.1/9.9/52.3/3.6)	0.800[b]
N0/N1/N2/N3/Nx	3/0/16/0/3[d]	15/9/87/0/0	N0-1 versus. N2-3
(%)	(13.6/0.0/72.7/0.0/13.6)	(13.5/8.1/78.4/0.0/0.0)	0.762[b]
M0/M1	22/0	111/0	N.a.
(%)	(100.0/0.0)	(100.0/0.0	N.a.
Overall stage: IVa/IVb	22/0	111/0	
(%)	(100.0/0.0)	(100.0/0.0)	
Positive lymph nodes[a]	In 21 neck dissections	In 99 neck dissections	
0	3 (14.3%)	6 (6.1%)	
1–2	0 (0.0%)	19 (19.2%)	
3–15	9 (42.9%)	46 (46.5%)	
>15	9 (42.9%)	27 (27.3%)	
Unknown	0 (0.0%)	1 (1.0%)	
Ex-pleomorphic adenoma	5 (22.7%)	38 (34.2%)	0.331[b]
Androgen receptor status			
Positive	22 (100.0%)	102 (91.9%)	1.000[b]
Negative	0 (0.0%)	4 (3.6%)	
Not determined	0 (0.0%)	5 (4.5%)	
HER2 status			
Positive	3 (13.6%)	36 (32.4%)	0.380[b]
Negative	12 (54.5%)	66 (59.5)	
Not determined	7 (31.8%)	9 (8.1%)	
Other adjuvant treatments			(chemo)Radiotherapy versus none
Radiotherapy	17 (77.3%)	103 (92.8%)	1.000[b]
Concurrent chemoradiotherapy	4 (18.2%)	0 (0.0%)	
None	1 (4.5%)	8 (7.2%)	

ADT, androgen deprivation therapy; N.a., not applicable.
[a] These lymph node categories were used because these are prognostic categories for distant metastatic-free survival and overall survival [3].
[b] Fisher's exact test.
[c] Mann–Whitney U test.
[d] In three patients, TNM data were incomplete. They had stage 4a disease, but the exact T- and N-stage was unknown. Therefore, they were labelled as TxNx.

postoperative radiotherapy and a later year of diagnosis (a more recent diagnosis) significantly improved OS.

3.4. Palliative systemic treatments after disease recurrence

Four of the six ADT-treated patients (66.7%) with disease recurrence received a palliative systemic treatment: two patients received palliative ADT (LHRH analogue plus bicalutamide), one patient received vemurafenib plus cobimetinib because of a BRAF V600E mutation and one patient first received carboplatin plus docetaxel, and everolimus as second-line treatment.

In the control group, 26 of the 73 patients (35.6%) with disease recurrence received a palliative systemic treatment: 24 patients received palliative ADT (16

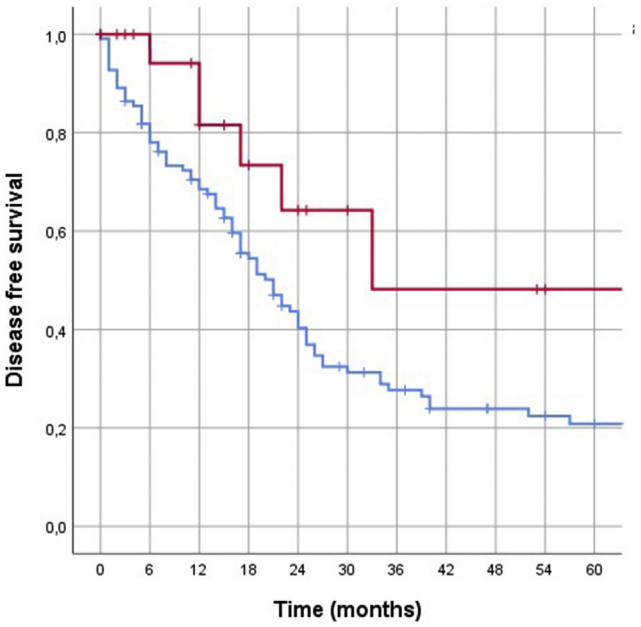

Fig. 2. Kaplan–Meier survival curves of the disease-free survival (DFS) of adjuvant ADT-treated patients (red) and the control group (blue). DFS was defined as the time from diagnosis until recurrence, death or last follow-up; $P = 0.037$. ADT, androgen deprivation therapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

patients received bicalutamide monotherapy, six patients received goserelin plus bicalutamide and two patients received triptoreline plus bicalutamide). Ten patients received palliative chemotherapy and/or targeted therapies (of which eight patients received palliative ADT before, resulting in a total of 26 patients receiving any systemic treatment): three patients received cyclophosphamide plus doxorubicin plus cisplatin, and two patients received docetaxel plus trastuzumab plus pertuzumab (because of HER2 amplification), and the following treatments were all received by one patient: carboplatin plus paclitaxel plus bevacizumab, capecitabine monotherapy, vemurafenib plus cobimetinib (BRAF V600E mutation), cetuximab monotherapy and trastuzumab plus pertuzumab (HER2 amplification).

4. Discussion

In this study, poor-risk AR-positive SDC patients receiving regular curative treatment *plus* adjuvant ADT were compared to poor-risk SDC patients receiving only regular curative treatment. We found a significantly longer DFS in the adjuvant ADT-treated patients. Differences in OS were just below and above significance level, depending on whether there was or no correction for confounders.

Patients were treated with androgen deprivation monotherapy (bicalutamide or an LHRH analogue) or a combination of these. In prostate cancer, combined androgen blockade shows a modest increase in OS but diminished quality of life in male patients [19]. In SDC, no such data exist although a higher response rate seems to be associated with combined androgen blockade, but they were not investigated in a randomised trial. Male patients were offered to choose between monotherapy and combined androgen blockade. All female patients were treated with combined androgen blockade.

The optimal duration of adjuvant ADT in SDC is unknown, and therefore, it differed between Nijmegen, 5 years, and Milan, 1–2 years. In this study, numbers are too small for a reliable suggestion on the optimal

Table 2
Cox regression analysis.

	Disease-free survival		Overall survival	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Univariable				
Treatment	0.492 (0.213–1.139)	0.098	0.410 (0.127–1.326)	0.137
Multivariable				
Treatment	0.138 (0.025–0.751)	0.022	0.064 (0.005–0.764)	0.030
Gender	0.502 (0.252–0.999)	0.050	0.581 (0.242–1.394)	0.224
Age	0.978 (0.954–1.003)	0.080	0.992 (0.963–1.022)	0.605
Treatment centre	0.997 (0.932–1.066)	0.922	1.045 (0.956–1.141)	0.334
Location of primary tumour	0.807 (0.482–1.350)	0.413	1.047 (0.594–1.846)	0.873
T-stage	1.259 (1.051–1.507)	0.012	1.164 (0.952–1.424)	0.138
N-stage	1.157 (0.880–1.522)	0.296	1.190 (0.812–1.746)	0.372
Ex-pleomorphic adenoma	0.554 (0.308–0.998)	0.049	0.943 (0.456–1.954)	0.876
Resection margins	1.060 (0.702–1.602)	0.781	1.285 (0.656–2.519)	0.465
Number of positive lymph nodes	1.002 (0.978–1.027)	0.847	1.026 (0.998–1.054)	0.067
Postoperative radiotherapy	0.053 (0.013–0.212)	0.000	0.071 (0.022–0.228)	0.000
Adjuvant chemotherapy	2.264 (0.223–22.952)	0.489	4.152 (0.151–114.119)	0.400
AR status	0.943 (0.067–13.244)	0.965	1.600 (0.083–30.725)	0.755
Year of diagnosis	1.010 (0.957–1.066)	0.714	0.910 (0.854–0.969)	0.003

HR, hazard ratio; CI, confidence interval; AR, androgen receptor.

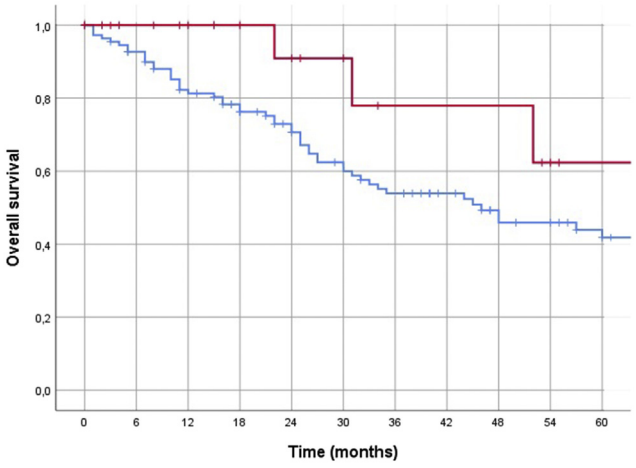

Fig. 3. Kaplan–Meier survival curves of the overall survival (OS) of adjuvant ADT-treated patients (red) and the control group (blue). OS was defined as the time from diagnosis until death or last follow-up; $P = 0.074$. ADT, androgen deprivation therapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

duration of treatment. However, in prostate cancer, a recent phase III trial found no difference in survival between patients treated with 18 months or 36 months of adjuvant ADT in high-risk patients, with the 18-month group experiencing a better quality of life [20]. Although we should be careful to translate trial results from a different tumour to SDC, these data provide at least some suggestion on the optimal duration of adjuvant ADT.

Next to ADT, the difference in DFS and OS could be caused by other factors. First of all, we did not perform a randomised trial but a retrospective cohort study with a historical control group of patients who received regular curative treatment in other Dutch hospitals. Differences between both groups were small, but some differences between the groups were found: all ADT-treated patients ($n = 22$) had stage 4a SDC at diagnosis, while in the control group, three patients had stage 4b SDC and 111 patients had stage 4a SDC. We removed the three patients with stage 4b SDC from our control group to have more similar groups at baseline. Next to this, the number of lymph node metastases, the only prognostic factor for OS and distant metastatic-free survival in a multivariable Cox regression analysis in 177 Dutch SDC patients [3], was different: nine ADT-treated patients (42.9%) had $\geq$15 positive lymph nodes in comparison to 27 patients (27.3%) in the control group. However, this would not lead to a better DFS in the ADT-treated patients. Furthermore, all ADT-treated patients had AR-positive tumours, compared to 102 patients (91.9%) in the control group, but AR positivity was not a prognostic factor in our prognostic factor analysis [3]. Next to AR, HER2 is an important therapeutic target in SDC. In the control group, more patients were HER2-positive compared with the ADT-treated patients (31.6% versus 13.6%). However, HER2 is not a prognostic factor in SDC [3], and DFS and OS were not significantly different in HER2-positive controls compared to HER2-negative controls.

Second, the use of historical controls may have introduced bias. Adjuvant ADT-treated patients received their primary treatment between 2007 and 2018. Patients in the historical control group received their primary treatment between 1990 and 2018. When we take only the historical control patients treated in the same time-frame ($n = 77$) as the adjuvant ADT-treated patients (2007–2018), the median DFS was 20 months, which is comparable to the 21 months in the entire historical control group.

Finally, four ADT-treated patients received adjuvant chemoradiotherapy instead of adjuvant radiotherapy. One patient received 300 mg/m^2 of cisplatin in three cycles every 21 days. The second patient received 250 mg/m^2 of cisplatin with the same regimen. The third patient received cisplatin every 7 days for 6 cycles, probably 40 mg/m^2 per cycle. The fourth patient received 2 cycles of carboplatin with an area under the curve (AUC) of 5 mg/m^2. Of these four patients, two patients had disease recurrence (patients 2 and 3). Next to this, Osborn *et al.* [15] reported no differences in 3- and 5-year overall survival between patients receiving either chemoradiotherapy or radiotherapy alone. In order to account for aforementioned possible confounders, a univariable and multivariable Cox regression analysis was performed for DFS and OS. With this model, we found a significant difference in DFS and OS for ADT-treated patients compared with the control group.

One may wonder whether ADT is as effective in women as in men. In the palliative setting, we have no reason to presume diminished efficacy in women, with two of five women having a partial response [9]. In the adjuvant setting, it is more difficult to establish efficacy. In this study, three of 22 patients were women. They have no evidence of disease after 1, 3 and 14 months of follow-up.

In case of disease recurrence despite adjuvant ADT, most patients received palliative systemic treatments. Although adjuvant ADT-treated patients have one line of antihormonal treatment less than control patients, they received more palliative systemic treatments. Therefore, the longer OS in adjuvant ADT-treated patients could be biased by the higher number of palliative treatments. The reason for this difference is probably that the adjuvant ADT-treated patients were treated in a salivary gland cancer referral centre, whereas most patients in the control group were not.

It is of utmost importance that future research will focus on resistance mechanism to ADT. The response rate of 18–64.7% to palliative ADT in advanced SDC shows that only a subgroup of patients respond to therapy. Understanding these mechanisms will prevent ineffective treatment in resistant tumours. Possible causes of resistance include the level of androgen

receptor expression [10], the expression of androgen receptor splice variants [21], the expression of steroidogenic enzymes, such as AKR1C3 [22], functional inactivity of the androgen receptor-pathway [23] and IL-23 produced by myeloid-derived suppressor cells [24].

Taking the aforementioned limitations into consideration, we believe that the results of this study are very promising. We would strongly support a prospective, randomised phase II trial to validate our results and to find the optimal treatment regimen before adjuvant ADT is adopted into routine practice. Given the rarity of SDC, such a trial is only feasible as multicentre study, preferably in an international partnership, such as EORTC or a worldwide network. Translational research focussing on prediction of treatment response and mechanisms that control the development of castration resistance should be a vital part of such a study. Unfortunately, to treat each patient with this rare cancer in a clinical study is not feasible. Therefore, another way to improve the prognosis for SDC patients is to centralise care and research and register the results ('real-time') of pathology, gene sequencing, and outcomes of treatment.

5. Conclusion

This is the first study describing the efficacy of adjuvant ADT in patients with poor-risk, AR-positive SDC. We showed a significantly longer DFS compared with the control group. Differences in OS were just below and above significance level, depending on whether there was or no correction for confounders. Our results require confirmation, preferably in a prospective trial, before adjuvant ADT is adopted into routine practice.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.12.035.

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