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Case Report and Review of Literature

The role of radiotherapy (RT) in the treatment of Adenoid Cystic Carcinoma of the Breast: case report of RT retreatment and literature review

Valeria Masiello[1], Fabio Marazzi[1], Daniela Smaniotto[1,2], Daniela Terribile[3], Francesca Moschella[3], Stefano Luzi[1,2], Luca Boldrini[1], Gianluca Franceschini[2,3], Riccardo Masetti[2,3], Vincenzo Valentini[1,2]

[1]Fondazione Policlinico Universitario "A. Gemelli" IRCCS, UOC di Radioterapia Oncologica, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Roma, Italia

[2]Università Cattolica del Sacro Cuore, Istituto di Radiologia, Roma, Italia

[3]Fondazione Policlinico Universitario "A. Gemelli" IRCCS, UOC di Senologia, Roma, Italia

ARTICLE INFO

Article history:
Received: 25 February, 2019
Accepted: 12 March, 2019
Published: 27 March, 2019

ABSTRACT

Aim: This study reviews the recent literature on the role of definitive radiotherapy (RT) in the management of adenoid cystic carcinoma of the breast (ACCB) and presents comprehensive data on clinical outcomes. A case report of radiotherapy retreatment in ACCB is reported for first time in literature.

Methods: The authors performed a literature review using PubMed (1981-2019) to identify all studies that match with keywords. Inclusion criteria were articles reporting patients underwent radiotherapy after ACCB diagnosis with follow up reporting. Data analyzed were number of pts, age, study design, multimodality treatment management with radiotherapy schedule, stage of disease, pathological risk factors, local relapse free survival (LFRS), metastases free survival (MFS) and overall survival (OS).

Results: Of the 60 identified studies, 15 met the inclusion criteria. All studies had a retrospective design. Overall, 967 patients (median, 64; range, 1-478) were included. A high heterogeneity was found across studies in terms of pathological features available, local approach in multimodality management, adjuvant RT administration, and reported outcomes. Mean LRFS reported by case reports was 24 months (range 20-48). Mean DFS reported by case series and retrospective series was 87.9% (range 69-100%). Mean OS reported in case reports was 30 months (range 12-84). Mean 5-years OS reported in retrospective series was 89.7%. Mean 10-years OS reported in retrospective series was 78.7%. In some retrospective series radiotherapy was found significantly related to local control (p=0.03) and with an absolute survival benefit of 9% at 5 year and of 21% at 10 years (p=0.005).

Conclusion and implications for practice: To our knowledge this is the first report on radiotherapy retreatment in ACCB local relapse.

This study also reviews the recent literature on the role of adjuvant RT in the management of ACCB and presents comprehensive data on long-term clinical outcome. Some significant results about RT are improvement in local control and survival benefit also since at 10 years in some series. Further studies are needed to confirm these results.

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Correspondence to: Valeria Masiello, Department of Radiology, Radiation Oncology and Hematology, Institute of Radiology, Fondazione Policlinico A. Gemelli IRCCS, Catholic University of the Sacred Heart, Rome, Italy; E-mail: lucvalgio@hotmail.it

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http://dx.doi.org/10.31487/j.COR.2019.01.107

Aim

Adenoid Cystic Carcinoma of the Breast (ACCB) is a rare subtype, representing <0.1% of all breast cancer diagnosed [1]. ACCB usually affects women, in whom it is more frequent in the sixth decade of life [2]. Histologically presentation shows a double component both luminal epithelial and basal myoepithelial cells, without oestrogen, progesterone and Her-2 receptor expression [3, 4]. Despite its belonging to triple-negative class breast tumor, clinical presentation of this disease is usually isolated to breast gland, in 2% of pts patients (pts) there is a nodal involvement and rarely it can metastasize in other parenchyma[1, 2, 5, 6]. This is due to downregulation of genes involved in migration, proliferation and the immune response [7]. In a study of Ro JY et al. a grading of ACCB was reported as sequent: Grade 1 (no solid element), Grade 2 (<30% solid elements) and Grade 3 (>30% solid elements). In their study tumours with more solid elements tended to be more aggressive and at higher risk of recurrence, so surgery should be conservative for Grade1 and radical also on axilla for Grade 3 [21]. Surgery is an established indication for treating this tumor, but there are still controversies about management with local excision rather than mastectomy [6]. In this landscape, also adjuvant radiotherapy still represents a controversial treatment in local control due to lack of extensive prospective series [8].

This study report first case in literature of re-quadrantectomy followed by reirradiation for a local relapse of ACCB. A systematic review of the recent literature on the role of adjuvant radiotherapy (RT) in the management of ACCB reports comprehensive data on clinical outcomes.

Case Report

A 64-year-old woman presented with a lump in her left breast. Examination showed a 1.5 cm mass in the superior-external quadrant. Mammography showed a nodular lesion localized between superior-external/SSQQs of left breast. Ultrasound reported an ipo-echogenous ovalar lesion of 2.4 cm with vascular spots both intra and peri-nodular. On January 2013, patient underwent conservative surgery with sentinel node biopsy. Definitive pathology exam reported a ACCB G1 of 1.7 cm, pT1c pN0, ER0%, PgR0%, Ki67 45% C-ERB-B2 0. For histological type, patient underwent adjuvant radiotherapy according to hypofractionated schedule (4005 cGy/267 cGy). Further follow up controls were negative since to May 2018, when a local relapse was diagnosed at instrumental exam. Mammography with tomosynthesis study reported a lesion with lobular margin of 2.2 cm at the superior-external quadrant of left breast. Echography described a polilobular lesion with regular margins disomogenous and ipo-echogenous of 2 cm with intralesional vascular behaviour. Total body CT was negative for distant relapse. On August 2018 patient underwent re-quadrantectomy of superior external left quadrant with sentinel node biopsy. Definitive pathology exam showed a relapse of tubule-glandular ACCB of 2.2 cm, pT2 pN0, ER0%, PgR0%, Ki67 7%, HER2 1+. The area around ACCB was surrounded by granulomatous lypophagic flogisis. Considering good performance status and local aesthetic result, the local relapse with absence of distant metastases, time from previous radiotherapy and total dose given with previous treatment, multidisciplinary discussion proposed a re-irradiation of tumor bed according to RTOG 1014 schedule (4500 cGy/150 cGy BID) [9]. Radiotherapy re-treatment was well tolerated and no acute toxicity more than G1 were recorded during treatment. Six months follow-up didn't show local or distant relapse neither sub-acute loco-regional toxicities.

Methods

In order to perform a clinical review on adjuvant RT role for ACCB in clinical practice a literature search on PUBMED was performed with keyword "adenoid cystic carcinoma radiotherapy", "adenoid cystic carcinoma adjuvant radiotherapy", "adenoid cystic carcinoma RT", "adenoid cystic carcinoma adjuvant RT". A further research was done into bibliography of paper selected. Inclusion criteria were case report, case series and retrospective analysis in which adjuvant radiotherapy was administered after surgery and follow up was reported. Data analysed in the studies were number of pts, age, study design, multimodality treatment management with radiotherapy schedule, stage of disease, pathological risk factors, local relapse free survival (LFRS), metastases free survival (MFS) and overall survival (OS).

Table 1: Literate review results

Author	Age	Study Design	Multimodality Treatment Management with Radiotherapy schedule	Disease Stage and pathological risk factors	LRFS	MFS	OS
Case Reports							
Mhamdi, 2017	65	Case Report	Mastectomy + Linfadenectomy (LA) followed by RT	T3N0 2009	2013 48 months Local relapse	2014 60 months Lung, kidney, brain	2016 84 months Death
Canyilmaz, 2013	58	Case Report	Breast conserving surgery (BCS) + Sentinel node biopsy (SNB) followed by RT 50 Gy + 10 Gy + Endocrine Therapy (ET) with Tamoxifene 10 mg	T1cN0 Peri-neural invasion(+)	LRFS 20 months 100%	MFS 20 months 100%	OS at 20 months 100%
Spiliopoulos,	52	Case Report	Modified radical	T4N0	LRFS	MFS	OS

2015			mastectomy +LA followed by chemotherapy and RT	Peri-neural invasion(+)	12 months 100%	12 months 100%	12 months 100%
Franceschini, 2010	67	Case Report	BCS + SNB followed by adjuvant RT	T2mN0M0	LRFS 12 months 100%	MFS 12 months 100%	OS 12 months 100%
Kumar, 2015	40	Case Report	BCS + LA followed by adjuvant RT to entire breast 50 Gy/2 Gy with a 10 Gy boost	T1cN0M0 Peri-neural invasion (-)	LRFS 12 months 100%	MFS 12 months 100%	OS 12 months 100%
Acar T, 2014	59	Case Report	BCS followed by adjuvant CT + RT	T1N0M0 Margin 1 cm	LRFS 40 months 100%	MFS 40 months 100%	OS 40 months 100%
Case Series/Retrospective Series							
Bhutani, 2017	60.7 (range 37-81)	Case Series 11 pts	CT (CMF or CAP) or nothing No RT	T1N0M0	Mean DFS 39.6 months (Range 35-48)		Mean OS 51.6 months (Range 40-75)
			RT post breast conserving or radical surgery +/- CT (CMF or CAP)	T2N0M1/0	Mean DFS 37.4 months (Range 21-75)		Mean OS 46.8 months (Range 27-100)
Franzese C, 2013	51 (range 39-71)	Case Series 13 pts	Conservative surgery +/- SNB followed by adjuvant RT (range 50-60 Gy)	pT(is-2)pN(0-2c) G1-2	LRFS 74 months 76,9%	MFS 74 months 76,9%	OS 74 months Pts all alive
Kasagawa, 2006	57	Case Series 2 pts	Mastectomy + LA followed by chemotherapy (CMF) and RT	T2N1M0	LRFS 12 months 100%	MFS 12 months 100%	OS 12 months 100%
	71		Conservative surgery + LA, followed by RT	T2N0M0	LRFS 12 months 100%	MFS 12 months 100%	OS 12 months 100%
Romeira, 2016	Case 1: 59	Case Series 2 pts	Lumpectomy followed by adjuvant RT 60 Gy/2Gy	T1bN0M0 2009	LRFS 2015 72 months Free	MFS 2015 72 months Free	OS 72 months pts alive
	Case 2: 43		Modified Radical Mastectomy followed by adjuvant chemotherapy (FECx6) followed by adjuvant RT 50 Gy/2 Gy	T3N1M0 2010	LRFS 2015 60 months Free	MFS 2015 60 months Free	OS 60 months pts alive
Arpino G 2002	66 (range 40-96)	Case series 28 pts	Primary surgery (19 MRM; 3 SM; 6 CS) 17 pts	T1c(1b-3)N0(X-1)	5-year DFS rate: 100% 10-year DFS rate: 93.8% (95% CI, 81.9-100)		5-y OS rate: 85% (95% CI, 71.7-98.6)
			Primary surgery (19 MRM; 3 SM; 6 CS) + RT 6 pts		No recurrences in RT group		
RCN study Khanfir K, 2012	59 (range 28-94)	Retrospective multicentre Analysis 61 pts	Surgery followed by adjuvant RT in 66% of pts Median total RT dose was 50 Gy (range 45-70.4 Gy) in 25 fr	T1 30 pts (49%) T2 24 pts (40%) T3 3 pts (5%)	5- and 10- y LRC rates were 95% (95% CI, 89-100%) and 87% (95% CI, 76-98%) 5- and 10-year DFS rates were 82% (95%CI, 71-93%) and 74% (95% CI, 61-87%)		

				T4 4 pts (6%) pN0 51 pts (84%) cN0 10 pts (16%)	5- and 10-year OS were 94% (95% CI, 88-100%) and 86% (95% CI, 75-97%) RT was the only factor significantly correlated with LC in the breast-conserving surgery group (p=0.03)		
SEER database Coates 2010	63	Retrospective multicentre analysis 376 pts (129 underwent RT)	No adjuvant RT	T1 143 pts (58%) T2 76 pts (31%) T3 14 pts (6%) T4 4 pts (2%) NA 10 pts (4%) N0 148 pts (60%) N1 11 pts (4%) NA 88 pts (36%)	OS 5-years benefit of adjuvant RT of 9% OS 10-years benefit of adjuvant RT of 21% (p=0.005) Multivariate analysis confirmed RT as significant prognostic factor for OS (HR 0.44, 95% CI 0.22-0.88)		
	61		Adjuvant RT	T1 83 pts (64%) T2 38 pts (30%) T3 2 pts (2%) T4 1 pt (1%) NA 5 pts (4%) N0 100 pts (78%) N1 5 pts (4%) NA 24 pts (19%)			
Sun JY, 2016	< 50y 105 pts >50y 373 pts	Retrospective multicenter analysis 478 pts	RM alone 154 pts (32.2%) RM+ adjuvant RT 20 pts (4.2%) BCS alone 107 pts (22.4%) BCS + adjuvant RT 197 (41.2%)	T1 288 pts T2 170 pts T3 20 pts N0 457 pts N1 20 pts N2 0 pts N3 1 pt	5-y CSS was 93.2% 10-y CSS was 87.5% 5-year CSS were 96.1%, 91.8%, 90.2%, and 94.1% in patients that received a lumpectomy + adjuvant RT, lumpectomy alone, mastectomy alone, and a mastectomy + adjuvant RT, respectively (p=0.026) 5-y OS was 88.7% 10-y OS was 75.3% Effect of local treatment strategies for OS were not deemed to have significant differences (p = 0.130). When stratified by group, lumpectomy + adjuvant RT patients had a better OS than mastectomy only patients (p = 0.019)		
Millar BAM, 2004	58 (range 35-76)	Retrospective series 18 pts	Surgery +/- adjuvant RT (only 9 pts) 40 Gy in 16 fr + boost of 12.5 Gy in 5 fr	T(1c-3) N(0-1)	LRFS 10-y 69%	/	OS 10-y 75% CSS 10-y 100%

Results

From 2002 to 2019, 60 studies were selected from PubMed. Revision of them and of their bibliography lead to selection of 15 studies that met inclusion criteria for our analysis. Based on study design, 6 were case reports, while 9 were case series or retrospective studies. Overall number of pts analysed was 967. Mean number of pts reported by case series/retrospective studies was 106 (range 2-478). Our clinical review results are reported in (Table 1). Mean LRFS reported by case reports was 24 months (range 20-48) [3, 4, 8, 10-12]. Mean DFS reported by case series and retrospective series was 87.9% (range 69-100%) [2, 5, 13-16]. Mean OS reported in case reports was 30 months (range 12-84) [3, 4, 8, 10-12]. Mean 5-years OS reported in retrospective series was 89.7% [2, 16, 17]. Mean 10-years OS reported in retrospective series was 78.7% [5, 16, 17].

Discussion

Most significant evidences about radiotherapy role were found in retrospective series. In Arpino et al. 6 pts who underwent radiotherapy did not present local relapse at 10-y follow up [2]. In a study of Khanfir K et al. based on data from 16 institutions participating to Rare Cancer Network, RT resulted significantly related to local control in the breast-conserving surgery group (p=0.03) [16]. In addition, in a Surveillance, Epidemiology and End Results (SEER) registry analysis of patients from 1988 and 2005, univariate analysis showed a significant difference in overall survival based on receipt of RT with an absolute survival benefit of 9% at 5 years and 21 % at 10 years (p=0.005) [18]. This evidence was confirmed also at the multivariate analysis in which RT continued to be a significant factor with a HR of 0.44 (95% CI=0.22-0.88), even after accounting for demographic data, stage and type of surgery. In another SEER analysis conducted on patient from 1998 to 2011 by Sun JY et al., on 478 pts 5-y cancer specific survival results 96.1%, 91.8%, 90.2% and 94.1% respectively for pts who underwent BCS + RT, BCS, mastectomy and mastectomy + RT (p=0.026) [17]. Effect on OS was significant only for subgroup of patients who underwent BCS + RT (p=0.019).

In another review of literature, 5-year survival rate for ACCB is reported to be 85-90%, with a 100% disease-free survival rate [22]. Local recurrence for ACCB after conservative surgery are not so rare and can occur in a range from 6 to 37%, more frequently between patients not underwent adjuvant treatment [5, 7, 17]. Global reported recurrence interval in the literature was as short as 6 months and as long as 22 years after excision[2]. For this reason, an active 10 year follow up should be considered with also parenchymal evaluation.

In a clinical review of Boujelbene N et al., published in 2012, some case series were reported to define adjuvant RT role [7]. Most significant conclusion were of this review were: adjuvant RT improves relapse-free-survival; adjuvant RT improves by 12% the 5-year locoregional control rates in breast-conserving group (95% vs. 83%) without impact on survival; adjuvant RT is a strong prognostic factor for overall- and cause-specific survival [13, 17, 22]. Finally, because metastases can occur without axillary involvement, adjuvant radiotherapy to the breast may decrease the burden of any residual microscopic disease, and therefore, reduce the likelihood of haematogenous spread [13]. Principal limitations of available literature are missing of uniformed data about pathological characterization in order to find useful prognostic factor to be related with an adjuvant RT.

Conclusion and Implication for Practice

Adjuvant radiotherapy is a controversial option for consolidating local control in ACCBs, especially after breast conserving surgery or if other risk factors for local relapse are present. Some series reported a significant role of radiotherapy in local control and also for 10-years survival for ACCB. Active follow up is mandatory for these patients because distant relapse can occur since after 9 years from diagnosis. In addition, to our knowledge, this is the first report in literature of ACCB radiotherapy retreatment. Retreatment is a safe and well tolerated option, as for common epithelial breast cancer. Possible criteria for conservative retreatment in ACCB are G1, absence of distant metastases, good aesthetic result. Multicentre pooled analysis or otherwise multicentre prospective studies would provide further consideration about radiotherapy indication in ACCB.

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