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Contents

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EDITORIAL

Are all prostate cancer patients "fit" for salvage radiotherapy?

Carmen González-San Segundo, Alfonso Gómez-Iturriaga, Felipe Couñago

ORCID number: Carmen González-San Segundo (0000-0002-5489-5327); Alfonso Gómez-Iturriaga (0000-0002-1094-5839); Felipe Couñago (0000-0001-7233-0234).

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Carmen González-San Segundo, Department of Radiation Oncology, HGU Gregorio Marañon, Complutense University, Madrid 28007, Spain

Alfonso Gómez-Iturriaga, Biocruces Health Research Institute, Cruces University Hospital, Barakaldo 48903, Spain

Felipe Couñago, Department of Radiation Oncology, Hospital Universitario Quirónsalud Madrid, Madrid 28003, Spain

Corresponding author: Carmen González-San Segundo, MD, PhD, Professor, Department of Radiation Oncology, HGU Gregorio Marañon, Complutense University, C/Doctor Esquerdo 46, Madrid 28007, Spain. cglezss@gmail.com

Abstract

The indication for salvage radiotherapy (RT) (SRT) in patients with biochemically-recurrent prostate cancer after surgery is based on prostate-specific antigen (PSA) levels at the time of biochemical recurrence. Although there are clear criteria (pT3-pT4 disease and/or positive margins) for the use of adjuvant radiotherapy, no specific clinical or tumour-related criteria have yet been defined for SRT. In retrospective series, 5-year biochemical progression-free survival (PFS) ranges from 35%-85%, depending on the PSA level at the start of RT. Two phase 3 trials have compared SRT with and without androgen deprivation therapy (ADT), finding that combined treatment (SRT+ADT) improves both PFS and overall survival. Similar to adjuvant RT, the indication for ADT is based on tumour-related factors such as PSA levels, tumour stage, and surgical margins. The number of patients referred to radiation oncology departments for SRT continues to rise. In the present article, we define the clinical, therapeutic, and tumour-related factors that we believe should be evaluated before prescribing SRT. In addition, we propose a decision algorithm to determine whether the patient is fit for SRT. This algorithm will help to identify patients in whom radiotherapy is likely to improve survival without significantly worsening quality of life.

Key words: Prostate cancer; Salvage radiotherapy; Comorbidity; Fit; Androgen deprivation therapy

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Core tip: Salvage radiotherapy (SRT) is an effective treatment for biochemically-recurrent prostate cancer after prostatectomy. Proper patient selection is crucial. While tumour-related factors are important, the indication for SRT should also be based on clinical factors and dosimetric variables. Patients with non-aggressive tumours who have

a life expectancy of less than 10 years are unlikely to benefit from radiotherapy and should thus be considered "unfit" for SRT. The development of advanced imaging techniques such Ga-PSMA positron emission tomography/computed tomography, which are capable of localizing the recurrent lesion when prostate-specific antigen ≤ 0.5 ng/mL, has forced clinicians to reconsider whether patients should undergo radiotherapy without locate first the recurrence.

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INTRODUCTION

Salvage radiotherapy (RT) (SRT) is the standard treatment for patients with biochemically-recurrent prostate cancer (PCa) following radical prostatectomy[1,2]. Findings from several phase 3 clinical trials demonstrating the value of adjuvant RT in these patients[3-5], together with the growing interest among urologists in the surgical treatment of high-risk PCa, have led to an increase in the number of patients who receive RT postoperatively.

After the findings of those clinical trials confirmed the benefits and efficacy of SRT - especially for early recurrences [defined as prostate-specific antigen (PSA) < 0.5 ng/mL][6-8] - most subsequent studies have focused on the role of tumour-related variables (*e.g.*, PSA levels, PSA kinetics, Gleason score, and surgical margins) in establishing the treatment indication. However, those studies have largely ignored the clinical characteristics that could potentially contraindicate this treatment.

A significant proportion of patients who develop biochemical recurrence (BCR) undergo SRT. However, the use of high-dose, hypofractionated RT in tissues previously subjected to surgery, together with the poor anatomical condition of these tissues (often associated with urinary incontinence), are important factors to consider when deciding whether SRT is indicated given the increased risk of radiation-induced toxicity and the potential to worsen quality of life (QoL).

In the present article, we propose a decision algorithm for SRT. This algorithm was developed after a careful analysis of the literature involving an assessment of a wide range of factors - apart from the well-known tumour characteristics associated with progression-free survival (PFS) - including comorbidities, life expectancy, expected toxicity, and dosimetric variables.

CLINICAL ASPECTS

Life expectancy

Compared to other malignant tumours, PCa has a long clinical course, which explains why survival outcomes are usually reported at a median follow-up of 10 years. In the United States, data from population registries show that 5-year survival rates in patients with PCa are greater than 90%[9]. In most clinical guidelines, life expectancy ≥ 10 years is an important criterion for treatment selection, especially in patients with low-grade tumours[1,2]. However, in patients with biochemically-recurrent PCa, life expectancy is not usually considered in the treatment selection process, as evidenced in phase 3 trials of postoperative adjuvant RT in which age (< 75 years) is an inclusion criterion but life expectancy is not[3-5]. However, the two randomized clinical trials (RCT) that compared SRT with or without androgen deprivation therapy (ADT)[10,11] did include life expectancy (< 10 years) as an exclusion criterion. Patients who develop BCR after prostatectomy are, on average, 3-5 years older than when the surgery was performed. For this reason, it is important to statistically determine life expectancy, especially in patients with late onset, non-aggressive BCR (based on PSA kinetics and Gleason score). Importantly, patients whose life expectancy is < 10 years at detection of BCR are unlikely to benefit from SRT, except for those with symptomatic, locally-recurrent disease with elevated PSA levels[12], in which case SRT plus ADT can be considered on an individual basis.

Comorbidities

Many studies have found that the presence of significant comorbidity is associated with worse survival in PCa patients who undergo radiotherapy[13,14]. Most clinical guidelines recommend the use of validated scales to assess comorbidity in order to facilitate decision-making[1,2]. Specific scales are available to assess comorbidity in patients with PCa[15] and these scales can be used both to predict QoL in the six month period following diagnosis and to estimate the probability of survival in the next 3.5 years. Patients with greater comorbidity, as determined by the total illness burden index for PCa (TIBI-PCa), have a 13-fold greater risk of dying from causes other than PCa in the 3.5 years after diagnosis[15]. Crawford *et al*[13] showed that survival outcomes in patients with significant comorbidities who underwent RT were significantly worse than in patients who did not receive oncological treatment. At 10-years of follow-up, those patients had a higher risk of PCa-specific mortality (PCSM; 62 deaths in the treatment group *vs* 42 in the supportive care group, $P = 0.08$). Moreover, patients with significant comorbidities had a greater risk of mortality of non-PCSM than patients with no or minimal comorbidity (16.1% *vs* 8.2%)[13].

The RCTs published to date that have evaluated SRT plus ADT have only included patients with performance status ranging from 0-2[10,11]. The TROG 03.06 trial[16] excluded patients with a life expectancy < 5 years (due to the presence of comorbidities). Based on these data, we recommend the use of comorbidity scales at the time of BCR; in addition, patients with a TIBI-PCa > 11 or a Charlson index > 3 should not be offered active treatment because the presence of these risk factors implies a high probability (> 50%) of non-PCSM mortality in the following 3 years.

Baseline urinary status

The use of validated scales such as the International Prostate Symptom Score (IPSS) or the Expanded Prostate Cancer Index to obtain an accurate assessment of urinary symptoms is crucial before deciding whether SRT is indicated. Most studies of postoperative RT have found a direct association between baseline urinary status and the risk of radiation-induced toxicity[17-19]. Patients with poor postoperative urinary function, a previous history of transurethral radical prostatectomy (TURP), or who require repeated bladder catheterization present an increased risk of developing stenosis of the bladder neck and urethra, which can cause a significant deterioration in urinary function. Although the studies that have reported toxicity outcomes associated with postoperative RT have reported similar findings with regard to the impact on urinary function[17-19], this variable was not included in the selection criteria of the prospective trials conducted to date. Neither of the two phase 3 trials that evaluated SRT with or without ADT[10,11], and none of the three phase 3 trials that assessed adjuvant RT[3-5], have reported data on urinary function, nor have they described whether RT negatively impacted urinary function. The SWOG trial only excluded patients who developed total urinary incontinence after surgery[5].

The recently published study by Pollack *et al*[20] on hypofractionation in patients undergoing primary RT found that late urinary toxicity was significantly higher in patients with high IPSS scores and a history of TURP. The poor urinary status prior to RT in patients who had previously undergone prostatectomy (versus surgery-naive patients) may explain why hypofractionation is not considered standard in this group of patients. In the study by Cozzarini *et al*[21], the 5-year rate of urinary toxicity rate ≥ grade 3 was 18.1% in the hypofractionated group (2.3-2.9 Gy) versus only 6.9% in the conventional fractionation group.

Given the lack of validated data from prospective studies on the role of urinary function, we cannot recommend a definition of "unfit" based on urinary parameters, nor can we recommend the routine use of hypofractionated schemes. Patients who present poor urinary function prior to RT should be informed of the increased risk of urinary complications (stenosis, hematuria, stranguria, *etc*.). In addition, it is essential to analyse the risks and benefits of performing RT in patients with poor urinary function. In these patients, dosimetric parameters and clinical variables must be considered together. If the rectal and bladder constraints cannot be met (Table 1), then RT is contraindicated and the recommended treatment approach should be either observation or, in high-risk patients, hormonotherapy.

Concomitant medications

Although no specific drugs are contraindicated in patients scheduled to undergo SRT, the use of anticoagulant and antiplatelet medications increases the risk of rectal and/or urinary bleeding[17,19,22]. Takeda *et al*[23] found that anticoagulant use was significantly correlated ($P = 0.027$) with higher rates of chronic rectal toxicity ≥ grade 2. Even if the use of such medications does not contraindicate RT *per se*, patients should be informed about the increased risk of bleeding. By contrast, the available evidence indicates that hormonotherapy - sometimes administered concomitantly with SRT - does not increase urinary or radiation-induced rectal toxicity[17,24].

Table 1 Constraints recommended in salvage radiotherapy with conventional fractionation

Organ at risk	Constraints
Bladder	V70 < 30%
	V55 < 50%
Rectum	V70 < 20%
	V65 < 25%
	V60 < 35%
	V50 < 50%
Femoral heads	V50 ≤ 10%
	Dmax < 45 Gy
Small bowel	V55 < 5 mL
	V15 < 120 mL

Quantitative analysis of normal tissue effects in the clinic.

However, in patients with cardiovascular risk factors, the prolonged use of hormonotherapy with SRT should be limited to patients with a poor prognosis, defined as the presence of local and/or regional recurrence, a PSA doubling time (PSADT) < 6 mo, and/or Gleason score > 7.

TUMOUR-RELATED VARIABLES

Recently, our group proposed a risk classification system - similar to the risk stratification used in patients at the initial diagnosis of PCa - to classify patients with biochemically-recurrent PCa into three risk groups[25]. That framework was designed to facilitate decision-making for the use of ADT based on several key prognostic variables (Table 2) assessed at the time of BCR. Low-risk patients, in whom ADT is not indicated, fulfil all of the conditions for good prognosis: PSA ≤ 0.5 ng/mL; PSADT> 12 mo; interval from surgery to recurrence > 18 mo; Gleason score 6 or 7 (3 + 4); free margins; and stage pT2pN0. This subgroup of low-risk patients has the best survival outcomes (PFS) after SRT, which is expected given that they have the least aggressive disease. However, the benefits of RT in this subgroup must be carefully weighed against the risk of radiation-induced toxicity. Two other variables - age and (especially) comorbidities - play a key role in deciding whether to prescribe active treatment or not. We believe that low-risk patients, patients over age 75, and/or those with comorbidities that reduce their life expectancy to < 5-10 years (based on validated scales) should be considered "unfit" for SRT because the treatment is likely to worsen QoL without providing a clear survival benefit.

PSA at diagnosis of BCR

As early as 2002, Choo *et al*[26] described the lack of efficacy of SRT - with 5-year biochemical control rates < 35% - in patients with PSA levels > 2 ng/mL or with local macroscopic recurrence. In the meta-analysis by King and colleagues[27], the PSA level prior to SRT was directly related with the probability of disease response and control: for each 0.1 ng/mL increase in the PSA level at the time of BCR, the biochemical relapse-free survival (BRFS) rate decreased by 2.6%. Numerous authors consider PSA ≤ 0.5 ng/mL as the optimal level at which to initiate "early" SRT[6-9]. In their study, Fossati *et al*[7] found that biochemical control in patients who underwent SRT with PSA levels ≤ 0.5 ng/mL was comparable to that obtained in patients who received adjuvant RT; however, patients with persistently elevated postoperative PSA levels were excluded from the comparison.

The available evidence indicates that the lower the PSA level at the time of BCR, the better the outcomes of SRT. To date, however, no PSA cut-off levels have been established to contraindicate SRT. Choline positron emission tomography/computed tomography (PET/CT) should be performed in patients with PSA values > 1 ng/mL or a PSADT < 6 mo[28]. According to current European Association of Urology Guidelines, prostate-specific membrane antigen (PSMA) PET/CT should be performed prior to SRT in patients with PSA > 0.2 ng/mL at the time of BCR[29]. It is important to keep in mind that administering SRT in patients with PSA levels > 1 ng/mL without first localizing the lesion *via* imaging tests increases the risk that the affected area (particularly lymph node regions) will not be adequately irradiated.

Table 2 Risk groups for salvage radiotherapy

Risk group	Factors
Low-risk	PSA < 0.6 ng
	PSA-DT > 12 mo
	Gleason score ≤ 7 (ISUP 1,2)
	pT2 pN0
	IBR > 18 mo
	Negative margins
Intermediate risk	PSA = 0.6 to < 1 ng
	PSA-DT 6-12 mo
	Gleason score 7 (ISUP 3)
	pT2-T3a pN0 or pNx
	IBR > 18 mo
	Positive margins
High-risk	PSA ≥ 1 ng
	PSA-DT < 6 mo
	Gleason score 8-10 (ISUP 4,5)
	pT3b pN0 or pNx
	IBR < 18 mo
	Positive margins

ADT: Androgen deprivation therapy; PSA: Prostate-specific antigen; PSA-DT: Prostate-specific antigen doubling time; IBR: Interval to biochemical recurrence; ISUP: International Society of Urological Patheology.

We recommend performing SRT in patients with PSA values < 0.5 ng/mL provided that the patient has a life expectancy > 10 years and no medical contraindications. Choline or PSMA PET/CT (based on availability) should be performed when PSA values exceed 0.2 ng/mL and/or in cases with PSADT < 6 mo. If there is a visible locoregional recurrence without evidence of distant metastasis, then the radiation target volume can be adjusted to the findings of the imaging tests; in these cases, concomitant ADT is indicated, even in patients with PSA values > 2 ng/mL. Local SRT is not indicated in cases with extrapelvic involvement; instead, systemic therapy should be prescribed after a multidisciplinary tumour board has reviewed and approved the treatment. Finally, in patients with normal imaging tests and PSA values ranging from 0.5-2 ng/mL, the recommendations of the phase 3 GETUG and RTOG trials should be followed[10,11].

PSA doubling time

Many authors consider the PSADT to be the most important prognostic factor at the time of BCR, even though this variable was not an inclusion criterion in any of the RCTs published to date, nor was it used for risk stratification[3-5,10,11]. However, most clinical guidelines recommend the application of systemic therapy in patients with a PSADT < 6-10 mo at BCR[1]. The PSADT plays no role in determining whether SRT is contraindicated or not, nor should it be used to determine radiation volumes. However, when the PSADT is < 6 mo, ADT should be prescribed, in addition to SRT.

Disease-free interval

The GETUG study evaluated the influence of the time interval between radical prostatectomy and BCR on treatment outcomes in patients undergoing SRT plus androgen suppression therapy (goserelin)[10]. Patients were grouped into early (< 30 mo) or late BCR. However, no significant differences in biochemical control were observed. By contrast, other authors have found that biochemical control rates are worse in patients with a disease-free interval (DFI) < 18 mo and in patients with persistently-elevated PSA levels after prostatectomy[30], which suggest the presence of high-risk tumours and/or involved surgical margins. Nevertheless, the DFI does not condition the use of SRT, although ADT should be started in patients with a DFI < 18 mo, especially in cases with a short PSADT (< 6 mo). In patients with late onset BCR (> 10 years), the indication for SRT should be evaluated in the context of the patient's age and comorbidities.

Risk group: Gleason score

In patients who develop BCR after primary external beam RT, eligibility for salvage should include the patient's risk group classification at the initial diagnosis of PCa. Local salvage treatment is not advised in high-risk patients and/or those with Gleason 8-10[31]. The phase 3 trials that evaluated adjuvant RT did not include the Gleason score as an inclusion criterion[3-5]. However, the RCTs that have evaluated SRT with and without ADT found no significant between-group differences in survival [PFS or overall survival (OS)] based on the Gleason score, although the course of disease was worse in patients in the placebo group with Gleason scores ≥ 7[10,11].

In recent years, a growing proportion of high-risk patients undergo radical prostatectomy, mainly as part of the multimodal treatment approach supported by urologists. However, the risk of BCR in these patients is high, ranging from 50%-70% in most series[32]. Gandaglia *et al*[33] found that, together with nodal involvement and stage pT3-T4 disease, the presence of GS 8-10 was the third least favourable factor in patients treated with adjuvant RT. Indeed, patients who presented all three of these unfavourable factors had the worst prognosis, with 10-year OS rates of 62% when no adjuvant RT was performed.

There is no evidence to suggest that the Gleason score or the initial risk group are contraindications for SRT in patients who develop BCR after surgery. However, from a radiation oncology perspective, the presence of these factors creates uncertainties regarding: (1) The optimal target volume (especially in patients who did not undergo initial lymphadenectomy); (2) The indication and duration of concomitant ADT; and especially (3) Whether SRT should be performed in the absence of data from imaging tests ruling out distant disease.

DOSIMETRIC FACTORS

Table 1 shows the recommended dose constraints for the organs at risk used in most studies of SRT. The difficulty of bladder filling in previously-operated patients increases the risk of both acute and chronic urinary toxicity. Numerous publications have recommended limiting the radiation dose and/or treatment volume to avoid an exponential increase in treatment-related complications and long-term sequelae[34-36]. Although the use of rectal spacers has been proven to reduce rectal toxicity in brachytherapy, their efficacy has not been validated in SRT. In patients with unfavourable dose-volume histograms (DVH), no other local measures are available to reduce the dose to the rectum and bladder. Consequently, image-guided RT is imperative in these cases to ensure accuracy and to optimize the dosimetric parameters. In addition, the treating radiation oncologist should discuss with the patient the risks of radiation-induced toxicity (based on the DVH values) and the expected benefits of the radiotherapy treatment. If the patient's comorbidities are likely to increase the risk of developing toxicity > grade 3 in patients with unfavourable DVH values, then it is reasonable to rule out SRT, just as surgery is often ruled out in high-risk (ASA III-IV) patients.

EXCLUSION CRITERIA IN PHASE 3 TRIALS OF SALVAGE RT

Given the lack of universally-accepted criteria regarding the contraindications of SRT, in Table 3 we provide a summary of the exclusion criteria used in the phase 3 RCTs that have evaluated SRT with and without ADT. That table also includes the exclusion criteria in currently ongoing studies comparing adjuvant RT to SRT. Based on those data, we have developed a decision algorithm to identify patients considered "unfit" for SRT (Figure 1). As with most therapeutic indications, it is important not only to define the patients who are likely to benefit from a given treatment, but also to identify those patients in whom treatment could reduce life expectancy and/or lead to complications without providing a clear clinical benefit. Patients considered "unfit" for SRT would therefore include those who meet several of the following criteria: (1) > 75 years of age; (2) Significant comorbidities; (3) Poor baseline urinary function; (4) Low risk of developing BCR; and (5) Unfavourable DVH values. These patients should be offered alternative approaches, which may include surveillance or hormonal therapy depending on the patient's individual characteristics, life expectancy, and the "aggressiveness" of the recurrent disease. Finally, in patients with PSA > 1 ng/mL and/or PSADT < 6 mo, SRT should not be performed until the recurrence has been localized on imaging tests or at least until distant metastasis has been ruled out.

Table 3 Exclusion criteria in postoperative radiotherapy phase 3 trials

Postoperative radiotherapy	Trial	Exclusion criteria
Adjuvant RT	EORTC 22911	> 75 yr old
		WHO PS > 1
		PSA > 0.3 ng/mL
	ARO 96-02/AUOAP 09/95	> 75 yr old
		WHO PS > 1
		Detectable PSA
	SWOG 8794	WHO PS > 2
		Total urinary incontinence
		Pelvic infection or urinary extravasation
		Intraoperative rectal injury
Salvage RT ± ADT	RTOG 9601	Life expectancy < 10 yr
		I. Karnofsky < 80%
		Evidence of hepatic disease
		PSA > 4 ng/mL
	GETUG-AFU-16	WHO PS > 1
		Life expectancy < 10 yr
		Inadequate cardiac function
		Another invasive cancer
		PSA > 2 ng/mL
Salvage *vs* adjuvant RT ± ADT	RAVES 08.03	WHO PS > 1
		Concurrent cytotoxic medication
		Hip prosthesis
		Co-morbidities that would interfere with treatment or 5-yr follow-up
		PSA > 0.10 ng/mL
	RADICALS	Other active malignancy
		PSA > 0.20 ng/mL
	PAC GETUG	WHO PS > 1
		Other active malignancy
		Life expectancy < 10 yr
		PSA > 0.10 ng/mL
		Severe and uncontrolled arterial hypertension

ADT: Androgen-deprivation therapy; PSA: Prostate-specific antigen; PS: Performance status; WHO: World Health Organization; RT: Radiotherapy.

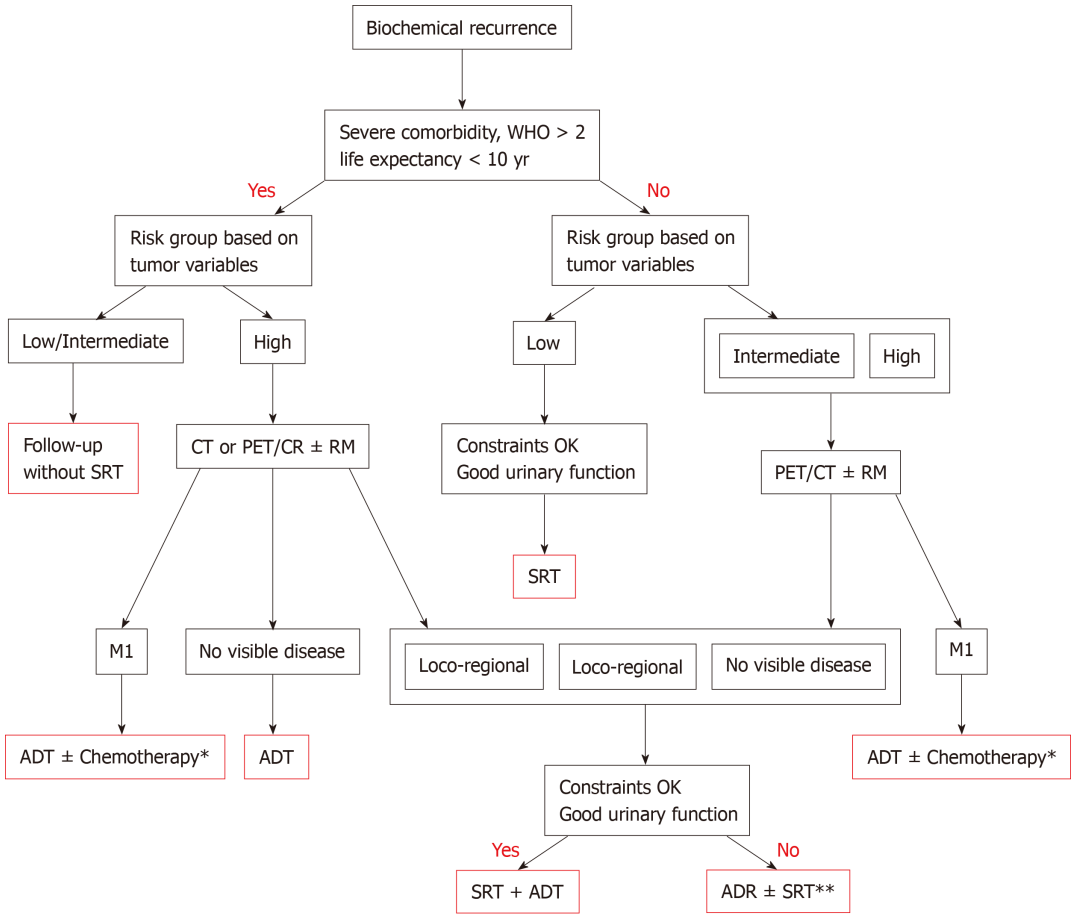

Figure 1 Algorithm to identify patients considered "unfit" for salvage radiotherapy. Risk group stratification based on reference 25. One asterisk: Chemotherapy addition according multidisciplinary board decision; two asterisks: Salvage radiotherapy if patients assume the risks. SRT: Salvage radiotherapy; ADT: Androgen deprivation therapy; CT: Computed tomography; PET: Positron emission tomography; RM: Resonance magnetic.

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ORIGINAL ARTICLE

Retrospective Study

Predictors of distant metastasis in acinic cell carcinoma of the parotid gland

Syed Ahmed Ali, Kevin J Kovatch, Jonah Yousif, Sonali Gupta, Andrew J Rosko, Matthew E Spector

ORCID number: Syed Ahmed Ali (0000-0001-7922-4426); Kevin J Kovatch (0000-0002-4750-2521); Jonah Yousif (0000-0002-3471-6731); Sonali Gupta (0000-0002-0905-5644); Andrew J Rosko (0000-0001-6432-5451); Matthew E Spector (0000-0001-7646-6075).

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Syed Ahmed Ali, Kevin J Kovatch, Jonah Yousif, Sonali Gupta, Andrew J Rosko, Matthew E Spector, Department of Otolaryngology - Head and Neck Surgery, Michigan Medicine, Ann Arbor, MI 48104, United States

Corresponding author: Matthew E Spector, MD, Associate Professor, Department of Otolaryngology - Head and Neck Surgery, Michigan Medicine, 1500 East Medical Center Drive, Ann Arbor, MI 48104, United States. ahmedali@med.umich.edu

Abstract

BACKGROUND

AiCC is a primarily indolent disease process. Our aim with this study is to determine characteristics consistent with rapidly progressive AiCC of the parotid gland.

AIM

To report on patients with metastatic lung disease from AiCC and potential correlative factors.

METHODS

Single-institution retrospective review of patients treated at the University of Michigan between 2000 and 2017. Univariate analyses were performed.

RESULTS

A total of 55 patients were identified. There were 6 patients (10.9%) with primary AiCC of the parotid gland who developed lung metastases. The mean age at diagnosis for patients with lung metastases was 57.8 years of age, in comparison to 40.2 years for those without metastases ($P = 0.064$). All 6 of the patients with lung metastases demonstrated gross perineural invasion intraoperatively, in comparison to none of those in the non-lung metastases cohort. Worse disease-free and overall survival were significantly associated with gross perineural invasion, high-grade differentiation, and T4 classification ($P < 0.001$).

CONCLUSION

AiCC of the parotid gland is viewed as a low-grade neoplasm with good curative outcomes and low likelihood of metastasis. With metastasis, however, it does exhibit a tendency to spread to the lungs. These patients thereby comprise a unique and understudied patient population. In this retrospective study, factors that have been shown to be statistically significant in association with worse disease-free survival and overall survival include presence of gross facial nerve invasion, higher T-classification, and high-grade disease.

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Core tip: This is a retrospective study to evaluate clinical outcomes in patients with primary acinic cell carcinoma of the parotid gland treated at a tertiary care medical center. Among 55 primary cases, 6 patients developed lung metastases. These patients uniformly demonstrated gross facial nerve invasion intraoperatively. Additional factors that were associated with worse disease-free survival and overall survival included higher T-classification and high-grade disease on pathology.

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INTRODUCTION

Salivary gland tumors comprise a rare disease process in which malignant cells form in the tissues of the minor and major salivary glands. These can be subdivided into epithelial and non-epithelial neoplasms, approximately 95% of which are epithelial. Approximately 90% of primary epithelial salivary gland tumors occur in the parotid gland; the remainder occur in submandibular, sublingual and other minor salivary glands. The rate of malignancy in each salivary gland is inversely correlated with the size of the salivary gland; approximately 20%-25% parotid gland tumors are malignant in comparison to 60%-80% of minor salivary gland tumors[1]. Amongst primary parotid gland malignancies, acinic cell carcinoma (AiCC) accounts for 1% to 6% of all epithelial salivary gland tumors and 10%-15% of all primary parotid malignant tumors[2]. It is typically diagnosed by pathology, as it can easily be mistaken clinically or radiologically for a different disease process[3].

AiCC is considered a low-grade, indolent salivary gland carcinoma with cure rate of 89% at 5 years[4]. High-grade transformation, formerly known as de-differentiation, is a rarely recognized event in AiCC that has been increasingly reported in the past 10-15 years[5]. A large National Cancer Database (NCDB) study performed by Xiao *et al*[6] found that amongst eight identified histopathologies, AiCC demonstrated positive clinical nodal disease in 10% of cases and occult positive nodal disease in 4.4% of cases. Further, high-grade differentiation was significantly predictive for nodal metastasis and worse overall survival in AiCC. Cases of AiCC with distant metastases are largely reported in case reports and smaller case series in the literature, with such studies identifying higher stage, presence of lymph node involvement, lymphovascular invasion and perineural invasion (PNI) as possible predictive characteristics[1]. While surgical excision is well-established for low-grade tumors with favorable pathologic characteristics, the treatment paradigm for high-grade malignancies is less well-defined. The majority of studies describe treatment with surgery and adjuvant radiation therapy, with occasional implementation of chemotherapy[7]. Treatment planning is of particular importance as a small subset of patients with high-grade tumors have shown propensity to develop lung metastases (LM). Thus, identification of primary tumor characteristics that predispose patients to developing distant metastases is crucial for appropriate surveillance and adjuvant considerations for this unique patient population.

Our primary goal was to examine the incidence of lung metastasis in our cohort of patients with AiCC. We aimed to assess demographic, histopathologic and clinical factors that may indicate increased risk of developing LM in this cohort.

MATERIALS AND METHODS

Study population

We performed an IRB-approved single-institution retrospective case series of patients

with AiCC of the parotid gland. Patients who underwent parotidectomy (superficial or total) for treatment of AiCC between 2000-2017 were included. Specifically, those who underwent primary surgical treatment at our institution were included. Patients who did not undergo parotidectomy as initial therapy were excluded from the study, as were patients who underwent initial surgery at a separate institution. Patients who presented with distant metastases at initial presentation were excluded. Demographics, clinical and pathologic T-, N-, and M-classifications, overall stage, primary treatment modality, histopathologic characteristics, mortality and recurrent-specific data were tabulated. Data were collected using clinical notes, pathology reports, and imaging available in our electronic medical records system. Patients were staged in accordance with the 7th edition American Joint Committee on Cancer Staging System[8].

Statistical analysis

Bivariate associations between clinical variables were tested with nonparametric tests (*i.e.*, Fisher's exact test, chi-square test with Monte Carlo estimates for error terms). SPSS version 22 software (IBM; Armonk, NY, United States) was used to perform statistical analyses. All statistical tests of significance were two-sided with α of 0.05. The Kaplan-Meier method was used to generate curves for disease-free survival and overall survival.

RESULTS

Patient demographics

Fifty-five total patients with AiCC were evaluated. Patient demographic information is available in Table 1 and delineates patient cohorts with and without LM. There were 6 out of 55 (10.9%) total patients who developed LM in our cohort. Median follow-up time was 47 mo (range 1-172 mo).

Pathologic characteristics

Patients with LM presented with larger overall tumors as demonstrated on surgical pathology, with a greatest size of 4.32 cm in comparison to 2.57 cm in the non-LM cohort. There were no patients in the study who presented preoperatively with clinically detectable facial nerve weakness. Overall staging was on average greater for patients in the LM cohort with all six patients with stage IV disease. In comparison, 82% (n = 40) of the non-LM cohort had overall stages of I or II. All of the LM patients had at least T4a classification given presence of gross facial nerve invasion. The average T-classification comparison between the groups was significant (P < 0.0001), with 2 patients in the non-LM cohort with stage IV disease. Both patients had T4a classification due to skin invasion that was resected at the initial operation. They both required free tissue transfer for reconstruction and received post-operative adjuvant radiotherapy Few patients had nodal disease. Only one patient in the LM cohort had positive nodal disease on final pathology from their initial operation, in comparison to 2 (4.1%) of the non-LM cohort. All 6 of the patients in the LM cohort had gross facial nerve invasion, in comparison to none of the patients in the non-LM group (P < 0.0001).

Metastasis characteristics

Patient characteristics for LM patients is available in Table 2. Those with LM were on average older in age (57.8 years) compared to those without LM (40.2 years). Five out of six (83.3%) of patients with LM were male. Three of the patients in the LM cohort experienced isolated distant spread to the lungs. While six of the patients in the non-LM cohort experienced local recurrence, none of them experienced regional recurrence. Eighty-three percent of the patients (n = 5) in the LM cohort underwent adjuvant radiation therapy, in comparison to 29% (n = 14) of patients in the non-LM cohort. The remaining patient refused radiation treatment. Three of the patients in the LM group underwent chemotherapy as primary modality of treatment for their recurrent cancer.

Survival characteristics

Kaplan-Meier survival curves were generated for disease-free survival and overall survival. In a univariate analysis, there were significant differences in the survival of patients who had T4 disease, high-grade differentiation, and the presence of gross facial nerve invasion (Figure 1). Positive margins and N-stage were not associated with disease-free survival. Additionally, there were significant differences in the overall survival of patients who had high-grade differentiation tumors and gross facial nerve invasion (P < 0.001). Overall survival was also worse in patients with at

Table 1 Demographics and clinical information, *n* (%)

Characteristic	Patients with lung metastases (*n* = 6)	Patients without lung metastases (*n* = 49)	*P* value
Age at diagnosis (yr)	57.8	40.2	0.064
Gender			
Male	5 (83.3)	21 (42.9)	
Female	1 (16.7)	28 (57.1)	
Parotidectomy type			0.00013
Superficial	1 (16.7)	39 (79.5)	
Total	5 (83.3)	10 (20.4)	
Neck dissection	3 (50.0)	7 (14.3)	0.08
Positive margins	1 (16.7)	6 (12.2)	0.77
Gross nerve invasion	6 (100)	0	< 0.0001
Greatest dimension	5.20 cm	2.58 cm	< 0.0001
Initial overall stage			
I	0	21 (42.8)	
II	0	19 (38.7)	
III	0	06 (12.2)	
IV	6 (100)	2 (4.1)	
Unknown			
Initial T-stage			
T1	0	24 (48.9)	
T2	0	18 (36.7)	
T3	0	6 (12.2)	
T4	6 (100)	1 (2.0)	
Tx	0	0	
Initial nodal status			
N0	5 (83.3)	47 (95.9)	
N1	0	1 (2.0)	
N2	1 (16.7)	1 (2.0)	
N3	0	0	
Nx	0	0	
High-grade	3 (50)	1 (2.0)	0.019
Adjuvant XRT	5 (83.3)	14 (28.6)	< 0.001

XRT: X radiotherapy.

least T4 classification in comparison to those with lower T-classification.

DISCUSSION

AiCC has historically been considered an indolent tumor, with the literature commonly referring to it as a good actor in overall salivary gland carcinoma. Within the last 15 to 20 years, there have been increasing reports of high-grade transformation in these tumors, the sequelae of which include greater risk of recurrence and metastasis, as well as reduced overall survival. While clinical and pathologic factors that portend poor disease-free survival and overall survival are well-characterized, there is a paucity of information regarding factors correlative with distant metastases in this patient population. In this retrospective review, clinical and pathologic data from 55 patients with primary AiCC of the parotid gland were analyzed. Six patients (10.9%) developed distant metastases, all of which involved the lungs. Advanced T-classification (particularly T4), high-grade differentiation, and gross facial nerve invasion were all implicated in shorter disease-free survival; high-grade differentiation on pathology is demonstrated in Figure 2. These data suggest that patients with these high-risk characteristics, and no evidence of distant disease on presentation, may warrant consideration for additional imaging for screening purposes.

For a relatively rare pathologic classification of head and neck cancer, salivary

Table 2 Characteristics of patients with lung metastases

Patient characteristics	Grade	T-classification	Facial nerve invasion	Recurrence sites
63 yr Male	High	T4a	Yes	Local, distant (lungs)
77 yr Female	Low	T4a	Yes	Distant (lungs)
44 yr Male	High	T4a	Yes	Distant (lungs)
52 yr Male	High	T4a	Yes	Distant (lungs)
71 yr Male	Low	T4a	Yes	Regional, distant (lungs)
40 yr Male	Low	T4a	Yes	Local, regional, distant (lungs)

gland malignancies demonstrate remarkable variability in their pattern and propensity for distant spread. Overall, approximately 20% of salivary gland malignancies will develop distant metastasis (DM), with high-grade pathologies demonstrating significantly greater propensity for DM[9]. Among salivary gland malignancies, salivary ductal carcinoma has demonstrates the highest rate of distant spread, with DM reported in as high as 57%-82% of patients[9]. Adenoid cystic carcinoma, particularly the solid histopathologic type, demonstrates reported rates of DM ranging from 25% to 38%[10]. Mucoepidermoid carcinoma, while considered a better actor in terms of DM, demonstrated rates of 16.3% in one large retrospective review[11]. Indeed, propensity toward distant spread is greater in lesions of intermediate and high-grade, in comparison to low-grade pathologic types. Myoepithelial carcinoma demonstrated the lowest rates of DM in a large single-institution study at 6% (one out of sixteen patients)[12]. Typical time to detection of DM also varies significantly amongst salivary gland malignancies. In adenoid cystic carcinoma, time to development of DM is approximately 3 years, although metastatic disease developing as late as nearly 10 years after initial diagnosis have been reported[13]. Salivary ductal carcinoma, on the other hand, tends to present more often with DM and rarely do patients develop late distant spread[14]. The most common sites for DM in salivary gland tumors include the lungs, bone, and liver; approximately one-half of all cases with distant spread will include LM[9].

Our AiCC cohort had a rate of DM of 10.9% at a mean latency of 17.8 mo (median follow-up 47 mo). A large retrospective study of AiCC from the Mayo Clinic demonstrated that 20.6% of their cohort developed DM[15]. Median time to development of DM was 3 years, with one outlier demonstrating distant spread nearly 30 years following initial diagnosis. The lungs are among the most commonly described sites of DM, although spread to the liver and to various bony anatomic sites have also been reported in various case reports and series[1].

There are a few larger retrospective reviews in the literature that discuss factors predictive of poor prognosis in patients with AiCC. In regards to demographic and clinical features, pain, older age, male gender, mass fixation, African-American race, facial palsy and short duration of symptoms are associated with poor prognosis[15,16]. Additional pathologic features that relate to poor prognosis microscopic features of desmoplasia, atypia or increased mitotic activity, and invasion of the lateral skull base[15,16]. In a large NCDB report, Hoffman *et al*[17] identified higher grade, regional or DM at presentation, and age greater than 30 years to be significantly associated with worse disease-specific survival. A Surveillance, Epidemiology, and End Results registry based study of 1129 cases demonstrated that patients with poorly differentiated tumors and those with DM had very poor 20-year survival rates[18]. A retrospective review from Beijing demonstrated that pathologic characteristics of high-grade differentiation, nodal stage, presence of PNI and ALI were associated with worse overall survival and disease-free survival[19]. In a smaller clinical analysis on AiCC, 3 out of 20 analyzed patients who developed DM were described to have more aggressive clinical features, although these were not specified in the study[20]. In a clinicopathologic review of 25 patients, Thompson *et al*[21] demonstrated that high-grade transformation in AiCC was associated with a high rate of DM. A large retrospective review from Brazil on major salivary gland carcinomas demonstrated that clinical stage, positive lymph nodes, facial paralysis and invasion of adjacent structures were predictors of DM[12]. The study is limited in application to our discussion, as there were only 17 patients with AiCC, 2 of whom developed DM.

In our cohort, we identified 55 patients who underwent superficial or total parotidectomy for AiCC from 2000 to 2016. Amongst those, we identified 6 patients who developed LM. Factors that correlated with DM in our patient cohort included T4 classification, high-grade differentiation and presence of gross facial nerve invasion. Factors of older age, positive nodal status, positive margins were not found

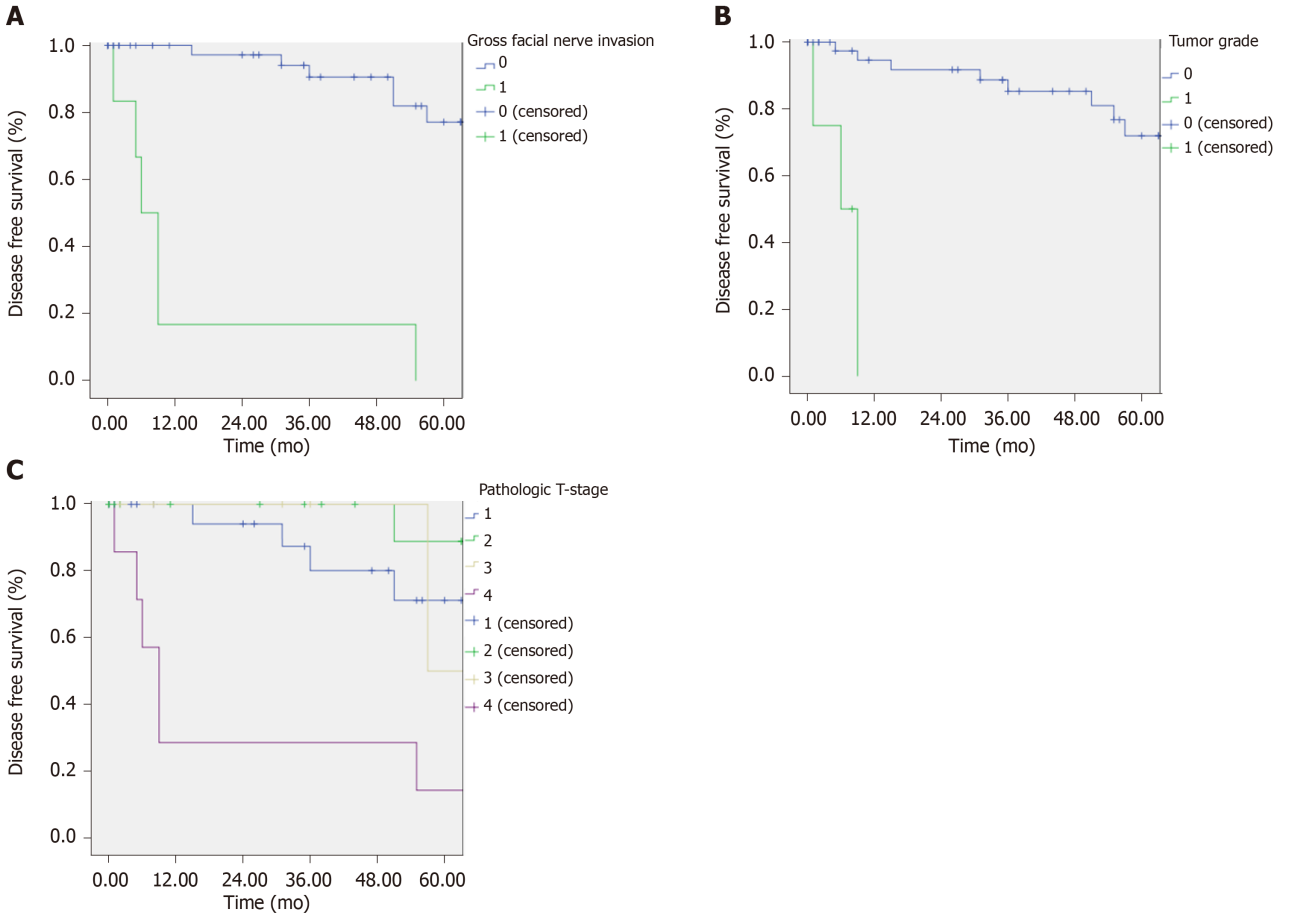

Figure 1 Disease-free survival (time in months) by gross facial nerve invasion, grade, and T-stage. A: Gross facial nerve invasion; B: Grade; C: T-stage.

to be associated with DM in our population. This may be secondary to the smaller natures of our study. Given its overall indolent nature, the vast majority of patients with AiCC will have low-grade differentiation (93% of patients in our cohort, Figure 3). Six (100%) of LM patients demonstrated evidence of gross facial nerve invasion intra-operatively, necessitating sacrifice of various branches of the facial nerve. Interestingly, none of these patients demonstrated pre-operative facial nerve weakness, perhaps indicating that preoperative testing may not be helpful in assessing for possible gross nerve invasion intraoperatively. None of the non-LM cohort exhibited facial nerve invasion on pathology. Indeed, nerve invasion is considered a poor prognostic marker in many other the subtypes of cancers of the head and neck and may be predictive of distant metastases in patients with AiCC specifically.

On average, the non-LM cohort was younger (40.2 *vs* 57.8). This is consistent with previous finding by Neskey *et al*[22] that earlier age of presentation, specifically age < 45, is significantly associated with improved survival. This group also found that larger primary lesions, specifically tumors larger than 3 cm were significantly associated with decreased overall survival, consistent with the findings in our study, where all patient presenting with LM had primary tumors of 4 cm or greater.

While this study is limited by the low overall incidence of AiCC and commensurate low overall rates of distant metastases, when examined in context with larger database-driven reports there is evidence of potential important predictors of distant metastases. In particular, patients with higher T-classification, high-grade differentiation and presence of gross facial nerve invasion may warrant consideration for heightened surveillance with screening for metastasis. Considerations for heightened surveillance could include greater attention paid to pulmonary signs and symptoms, as well as more frequent utilization of chest imaging. Further study is needed to determine the clinical utility of routine screening by chest x-ray or chest CT for high risk patients. Future studies could follow high-risk patients in a longitudinal fashion to determine propensity for development of LM. Analyzing tumor specimens from patients who developed LM for molecular biomarkers could potentially lead to the discovery of actionable or predictive targets.

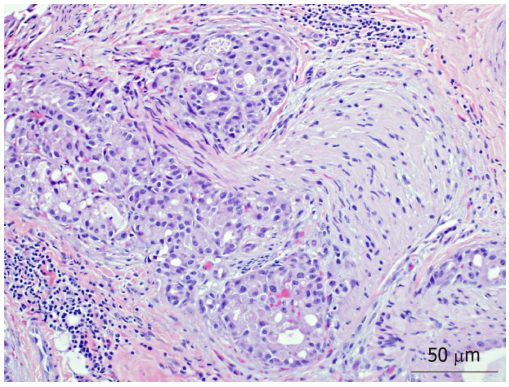

Figure 2 Hematoxylin-eosin staining of high-grade acinic cell carcinoma with perineural invasion. Images are magnified at 400× (40× objective lens × 10× ocular lens). Scale bar represents 50 μm.

In conclusion, AiCC of the parotid gland is widely viewed as a low-grade neoplasm with good curative outcomes and low likelihood of metastasis. With metastasis, however, this pathology does exhibit a tendency to spread to the lungs. These patients thereby comprise a unique and understudied patient population. This study suggests that patients with the identified high-risk characteristics, specifically advanced T-stage and gross facial nerve invasion, may warrant higher suspicion and heightened surveillance for metastatic lung disease.

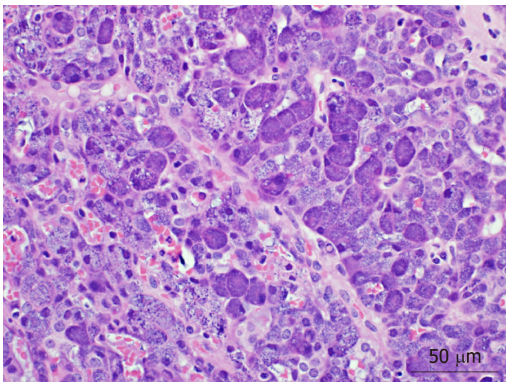

Figure 3 Hematoxylin-eosin staining of low-grade acinic cell carcinoma. Images are magnified at 400× (40× objective lens × 10× ocular lens). Scale bar represents 50 μm.

ARTICLE HIGHLIGHTS

Research background

AiCC is regarded as a low-grade, indolent primary cancer of the salivary gland. There are few reports in the literature of high-grade AiCC or instances of distant metastases.

Research motivation

This study aims to further identify potential predictors of distant metastases in this predominantly low-grade carcinoma. This will allow us to identify patients at risk for distant metastases and those who should be closely followed after treatment.

Research objectives

The main objective was to identify predictors of distant metastases in patients with AiCC of the parotid gland. We were able to identify gross facial nerve invasion as a unique predictor. Realizing this objective will allow us to sequence tissue from these poorly behaving carcinoma specimens and potentially identify actionable targets.

Research methods

The research methods for this study involved utilizing a thorough search *via* high-yield keywords and International Classification of Diseases (ICD) codes to identify all patients with AiCC treated at the study institution. Further narrowing and identification of the final dataset was undertaken through manual means.

Research results

This study identified gross facial nerve invasion as an intra-operative predictor of distant metastases in patients with AiCC of the parotid gland. Additional factors that were associated with worse disease-free survival and overall survival included higher T-classification and high-grade disease on pathology. Further studies could sequence specimens from these patients and determine possible contributing mutations or biomarkers.

Research conclusions

This study determines that gross facial nerve invasion is an intraoperative predictor of distant metastases in patients with AiCC of the parotid gland. Patients with gross facial nerve invasion should be carefully followed and potentially screened for distant metastases as part of their post-treatment surveillance. High-grade pathology and greater T-stage are associated with worse disease-free and overall survival in this patient population. Intraoperative findings a supplement pathologic findings in determining post-operative treatment plans and need for additional screening or follow-up. The new hypothesis proposed is the potential for additional predictors of poor outcomes in a largely low-grade and indolent carcinoma. This study utilized extensive keyword and ICD code-based review of a single-insitution's database. Gross facial nerve invasion is found to be predictive of distant metastases in AiCC of the parotid gland. This study confirmed our hypothesis that there are additional predictive clinical factors in patients with AiCC who develop distant metastases. This study can help identify patients who may benefit from closer dedicated follow-up or additional screening.

Research perspectives

Despite previous literature and similarly sized retrospective reviews, there can be additional useful information available in performing similar retrospective studies. Future research must take place on the basic science or translational level. This could entail sequencing tumor specimens of patients with distant metastatic development and identifying potential targetable biomarkers or mutations.

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ORIGINAL ARTICLE

Retrospective Study

Ipsilateral breast tumor recurrence in early stage breast cancer patients treated with breast conserving surgery and adjuvant radiation therapy: Concordance of biomarkers and tumor location from primary tumor to in-breast tumor recurrence

Juhi M Purswani, Fauzia Shaikh, S Peter Wu, Jennifer Chun Kim, Freya Schnabel, Nelly Huppert, Carmen A Perez, Naamit K Gerber

ORCID number: Juhi M Purswani (0000-0003-1068-9449); Fauzia Shaikh (0000-0002-9274-9734); S Peter Wu (0000-0003-1692-6935); Jennifer Chun Kim (0000-0003-3752-6826); Freya Schnabel (0000-0002-6393-7453); Nelly Huppert (0000-0002-0658-4161); Carmen A Perez (0000-0002-6759-5358); Naamit K Gerber (0000-0002-6061-0498).

Author contributions: Purswani JM and Gerber NK designed the research; Purswani JM, Gerber NK and Wu SP performed the research; Purswani JM and Wu SP analyzed the data; Purswani JM, Gerber NK, Kim JC, Schnabel F, Huppert N and Perez CA wrote the paper.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of New York University School of Medicine on December 13, 2017. This is an exempt study, annual renewal is not required.

Informed consent statement: Patients were not required to give informed consent to the research study. The analysis used anonymized clinical data obtained after each subject agreed to treatment with written consent.

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Juhi M Purswani, Fauzia Shaikh, S Peter Wu, Nelly Huppert, Carmen A Perez, Naamit K Gerber, Department of Radiation Oncology, New York University School of Medicine, New York, NY 10016, United States

Jennifer Chun Kim, Freya Schnabel, Department of Surgery, New York University School of Medicine, New York, NY 10016, United States

Corresponding author: Naamit K Gerber, MD, Assistant Professor, Department of Radiation Oncology, New York University School of Medicine, 160 E. 34th Street, New York, NY 10016, United States. naamit.gerber@nyumc.org

Abstract

BACKGROUND

Patients with an in-breast tumor recurrence (IBTR) after breast-conserving therapy have a high risk of distant metastasis and disease-related mortality. Classifying clinical parameters that increase risk for recurrence after IBTR remains a challenge.

AIM

To describe primary and recurrent tumor characteristics in patients who experience an IBTR and understand the relationship between these characteristics and disease outcomes.

METHODS

Patients with stage 0-II breast cancer treated with lumpectomy and adjuvant radiation were identified from institutional databases of patients treated from 2003-2017 at our institution. Overall survival (OS), disease-free survival, and local recurrence-free survival (LRFS) were estimated using the Kaplan Meier method. We identified patients who experienced an isolated IBTR. Concordance of hormone receptor status and location of tumor from primary to recurrence was evaluated. The effect of clinical and treatment parameters on disease outcomes was also evaluated.

RESULTS

We identified 2164 patients who met the eligibility criteria. The median follow-up

conflicts of interest, and/or acknowledgments for all the authors.

Data sharing statement: No additional data are available.

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for all patients was 3.73 [interquartile range (IQR) 2.27-6.07] years. Five-year OS was 97.7% (95%CI: 96.8%-98.6%) with 28 deaths; 5-year LRFS was 98.0% (97.2-98.8) with 31 IBTRs. We identified 37 patients with isolated IBTR, 19 (51.4%) as ductal carcinoma *in situ* and 18 (48.6%) as invasive disease, of whom 83.3% had an *in situ* component. Median time from initial diagnosis to IBTR was 1.97 (IQR: 1.03-3.5) years. Radiotherapy information was available for 30 of 37 patients. Median whole-breast dose was 40.5 Gy and 23 patients received a boost to the tumor bed. Twenty-five of thirty-two (78.1%) patients had concordant hormone receptor status, HER-2 receptor status, and estrogen receptor (ER) (P = 0.006) and progesterone receptor (PR) (P = 0.001) status from primary to IBTR were significantly associated. There were no observed changes in HER-2 status from primary to IBTR. The concordance between quadrant of primary to IBTR was 10/19 [(62.2%), P = 0.008]. Tumor size greater than 1.5 cm (HR = 0.44, 95%CI: 0.22-0.90, P = 0.02) and use of endocrine therapy upfront (HR = 0.36, 95%CI: 0.18-0.73, P = 0.004) decreased the risk of IBTR.

CONCLUSION
Among patients with early stage breast cancer who had breast conserving surgery treated with adjuvant RT, ER/PR status and quadrant were highly concordant from primary to IBTR. Tumor size greater than 1.5 cm and use of adjuvant endocrine therapy were significantly associated with decreased risk of IBTR.

Key words: : Ipsilateral breast tumor recurrence; Breast conservation; Adjuvant radiation

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Core tip: Distinguishing a new primary breast tumor from a true ipsilateral breast tumor recurrence (IBTR) based on clinical features alone is challenging among patients with early stage breast cancer treated with breast conserving surgery and adjuvant radiotherapy. Our aim was to describe primary and recurrent tumor characteristics in patients who experienced an IBTR. We retrospectively analyzed patients with isolated IBTR. Estrogen/progesterone receptor status from primary tumor to IBTR was highly associated, as was the concordance between the quadrant of primary to IBTR. Tumor size greater than 1.5 cm and use of adjuvant endocrine therapy decreased the risk of IBTR.

Citation: Purswani JM, Shaikh F, Wu SP, Kim JC, Schnabel F, Huppert N, Perez CA, Gerber NK. Ipsilateral breast tumor recurrence in early stage breast cancer patients treated with breast conserving surgery and adjuvant radiation therapy: Concordance of biomarkers and tumor location from primary tumor to in-breast tumor recurrence. *World J Clin Oncol* 2020; 11(1): 20-30
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INTRODUCTION

Breast conserving surgery (BCS) followed by whole breast irradiation (WBI) is an established treatment paradigm for early stage breast cancer with numerous studies showing equivalent outcomes with mastectomy with regard to disease-specific and overall survival (OS)[1-3]. However, despite excellent outcomes with breast conservation, there is still a risk of in-breast tumor recurrence (IBTR). In the EBCTG meta-analysis, the rate of IBTR was 35% with BCS alone and was reduced to 19.3% with radiation[2]. In more modern series, the rates of IBTR at 5-years range from 1.1%-3.3%[4,5]. Studies demonstrate that the time to IBTR is not confined to the first few years after surgery and radiation, but that late recurrences do occur, particular for estrogen receptor (ER) positive disease[6,7].

Multiple risk factors have been found to increase the risk of IBTR. These include young age[8], the size of the primary tumor, stage, high grade disease[9], positive margin status[9,10], presence of lymphovascular invasion (LVI) and the biology of the

tumor [approximated by subtype defined by ER, progesterone receptor (PR), and HER-2 receptor status].

Patients with an IBTR after BCS have an increased risk of distant metastasis and disease-related mortality, with older women and those with larger tumors having the highest mortality[11]. The management of patients with IBTR represents a complex clinical challenge. In the modern era, local therapy after an IBTR in the setting of prior radiation has evolved from standard salvage mastectomy with axillary dissection. The recently published RTOG 0104 supports a paradigm of salvage lumpectomy and partial breast radiation for patients with small recurrences and favorable tumor biology. In order to spare patients who are clinically node-negative after IBTR from undergoing extensive axillary clearance, repeating sentinel lymph node biopsy may represent a feasible option[12]. The role of chemotherapy is often guided by the biomarkers of the tumor[13].

One controversy that complicates the decision on how to manage recurrences, particularly late IBTRs, is whether the disease event represents a true recurrence or a new primary. Distinguishing between these two entities based on clinical features and/or outcomes remains a challenge; and the paucity of data with regard to outcomes after IBTR makes distinguishing between the two based on outcomes alone difficult.

The purpose of our study was to identify patients treated with breast conserving surgery and WBI who experienced an IBTR. The study aimed to characterize features of the primary tumor and recurrent disease and determine which parameters increase the risk for IBTR. It also aimed to better define the relationship between the primary tumor and IBTR in the context of location in the breast and biologic subtype. Finally, this study examined disease outcomes in these patients and determined which if any primary disease characteristics or IBTR characteristics influenced outcome after IBTR.

MATERIALS AND METHODS

Patients

All women in the cohort were aged > 18 years and diagnosed with pathologically staged 0-II *in situ* and invasive breast cancer treated with BCS and adjuvant whole-breast radiation at a single institution.

Patients were from four institutional review board-approved prospective clinical trials investigating the use of hypo-fractionated radiation in this patient population (n = 1317) and from an institutional database of breast cancer patients treated at our institution during the period of 2003-2015 (n = 1248). Disease status was updated for all patients from these 4 studies and from the institutional database using study visits, breast imaging, or visits with other breast-cancer physicians. Follow-up, local recurrence, and distant recurrence data were collected by review of electronic medical records or physical charts. Three hundred and thirty-nine patients were enrolled in both the prospective clinical trials and the institutional database and were counted only once in the analysis. Sixty-two women had no physical or electronic charts available and were thus excluded from the list of patients. The final number of patients included in the overall analysis was 2164. This study was approved by the Institutional Review Board (IRB 17-00993).

Tumor characteristics

Histopathological and tumor information was obtained through review of pathology reports. The following biological markers were evaluated at initial presentation and at IBTR: grade, LVI, tumor size, nodal status, ER, PR, and HER-2 status, and Ki-67 (< 10% *vs* > or = 10%). We classified each IBTR as receptor discordant if the IBTR hormone status was ER/PR negative while the original primary was ER/PR positive; or when the IBTR hormone status was ER/PR positive while the original primary was ER/PR negative.

The tumor quadrant in the breast was determined based on mammography and/or magnetic resonance imaging prior to BCS at initial presentation and at recurrence. IBTRs that occurred in the same quadrant of the breast were considered concordant; skin recurrences and recurrences outside the original quadrant were considered discordant.

Statistical analysis

Disease and patient characteristics were summarized using descriptive statistics. Local recurrence-free survival (LRFS), disease-free survival (DFS), DFS after IBTR [second recurrence (DFS-SR)], and OS were estimated using the Kaplan-Meier method and follow-up was estimated using the method of Schemper *et al*[14]. All initial event

and follow-up times were measured from the date of surgery for the primary tumor. Event and follow-up times after IBTR were measured from the date of histologically proven disease at the time of recurrence. The Chi-square test was used to assess the association between receptor subtype concordance and location concordance from primary to IBTR. The univariate Cox proportional-hazards model was used to assess the association between patient age, ER, PR, size, grade, tumor margins, LVI, Ki-67 and completion of hormone or chemotherapy at the time of primary disease, with the time interval to the first IBTR. All statistical tests were two-sided with alpha = 0.05. Statistical significance is expressed as $P < 0.05$. The statistical review of this study was performed by a biomedical statistician.

RESULTS

Patient characteristics

The median follow-up for all 2164 patients was 3.73 years [Interquartile range (IQR) 2.27-6.07]. Five-year OS was 97.7% (95%CI: 96.8%-98.6%) with 28 deaths. 5-year LRFS was 98.0% (97.2-98.8) with 31 IBTRs.

IBTR

Forty patients experienced an isolated IBTR (1.85%), defined as local recurrence without either regional or distant recurrence. Three patients with IBTRs were excluded due to insufficient pathology information.

The clinicopathologic characteristics of the primary tumor for the patients who experienced an IBTR are summarized in Table 1. The median age at diagnosis was 64 (range 32-91), with 48.6% of patients with invasive disease and 51.4% with ductal carcinoma *in situ* (DCIS). Median whole-breast dose was 40.5 Gy. The median dose with a boost was 48 Gy. Of the patients with invasive disease (n = 18), 83.3% had invasive ductal carcinoma (IDC) and 83.3% had an *in situ* component. 55.6% had high-grade disease and 27.8% had LVI. The majority of patients with invasive cancers had disease in the upper outer quadrant (55.6%), were hormone receptor positive (ER 66.7% and PR 66.7%) and HER-2/neu amplification negative (77.8%). The majority of invasive tumors were less than 2 cm (56.3%), node negative (85.0%), and evaluated by sentinel lymph node biopsy (87.3%). 88.9% had negative surgical margins. 61.1% of patients with invasive disease were treated with adjuvant chemotherapy and 61.1% were treated with hormone therapy. 16.7% of patients with invasive disease received anti-HER-2/neu therapy. Of the patients with DCIS (19), 47.3% had high grade DCIS, the majority were ER positive (73.7%) and PR positive (63.2%), with two patients who were ER positive, but PR negative. The majority of patients had negative surgical margins (68.4%), and disease in the upper outer quadrant (63.2%). 36.8% of patients with *in situ* disease were treated with endocrine therapy.

Clinical and treatment characteristics at the time of IBTR

Characteristics of the IBTRs are summarized in Table 2. The median time to IBTR was 1.97 (IQR: 1.03-3.5) years. 45.9% of IBTRs were invasive, and 51.4% were DCIS. Of the patients with invasive disease at initial diagnosis, 72.2% had invasive disease at recurrence and 27.8% had pure DCIS at recurrence. Of the patients with DCIS at initial diagnosis, 73.7% had DCIS at recurrence and 26.3% had invasive disease at recurrence. 55.6% of invasive IBTRs had an *in situ* component. At the time of IBTR, 86.5% of patients underwent salvage surgery (43.2% bilateral mastectomy, 24.3% unilateral mastectomy, and 16.2% local excision), 21.6% received chemotherapy, 43.2% received endocrine therapy, and 16.2% (those who had a local excision) underwent re-irradiation of the ipsilateral breast. Median follow-up for all patients was 2.13 years (IQR: 0.97-4.7) following IBTR.

Twenty-five of thirty-two (78.1%) patients had concordant hormone receptor status, and ER and PR receptor status from primary to IBTR were highly associated (ER: $\chi^2 P = 0.006$; PR: $\chi^2 P < 0.05$). Thirteen patients initially had ER or PR positive disease and became ER and PR negative. Four patients were ER and PR negative at diagnosis and were hormone receptor positive at recurrence. Of the patients who were triple negative at diagnosis (n = 4), 100% remained triple negative. There were no changes in HER-2 status from primary to IBTR. The concordance between the quadrant of primary to IBTR was 23/37 (62.2%), $\chi^2 P < 0.05$). There was no association between concordance of tumor location or biomarker status with time to IBTR.

Tumor size greater than 1.5 cm (HR: 0.44; 95%CI: 0.22-0.90, $P < 0.05$), and endocrine therapy decreased the risk of IBTR (HR: 0.36; 95%CI: 0.18-0.73, $P < 0.05$) with a median interval to IBTR of 54 wk in patients with tumors < 1.5 cm (*vs* 119 wk in patients with tumor greater than or equal to 1.5 cm) and a median time to IBTR of 54.5

Table 1 Clinicopathologic characteristics of primary tumors in patients who experienced an ipsilateral breast tumor recurrence

	Overall	DCIS	Invasive
n	37	19	18
Age [years, mean (SD)]	63.08 (14.52)	65.74 (11.49)	60.28 (17.05)
Race (%)			
White	27 (73.0)	13 (68.4)	14 (77.8)
African American	7 (18.9)	3 (15.8)	4 (22.2)
Asian	1 (2.7)	1 (5.3)	0 (0.0)
Declined	2 (5.4)	2 (10.5)	0 (0.0)
ER Positive (%)	26 (70.3)	14 (73.7)	12 (66.7)
PR Positive (%)	24 (64.9)	12 (63.2)	12 (66.7)
ILC	2 (5.4)		2 (11.1)
IDC	15 (40.5)		15 (83.3)
Mixed invasive	1 (2.7)		1 (5.6)
Invasive only: DCIS present (%)			
No			3 (16.7)
Yes			15 (83.3)
Invasive only: HER-2 Status (%)			
Negative			14 (77.8)
Positive			3 (16.7)
Not performed			1 (5.6)
Invasive only: Pathologic grade (%)			
1			4 (22.2)
2			4 (22.2)
3			10 (55.6)
Invasive only: Ki 67 Status (%)			
Low (< 10)			8 (44.4)
High (≥ 10)			8 (44.4)
Not performed			2 (11.1)
Invasive only: LVI (%)			
Not present			12 (66.7)
Present			5 (27.8)
Close			1 (5.6)
DCIS only: Nuclear grade (%)			
Grade 1		0 (0)	
Grade 2		10 (52.6)	
Grade 3		9 (47.3)	
T - stage (%)			
0	19 (51.4)	19 (100.0)	0 (0.0)
1	11 (29.7)	0 (0.0)	11 (61.1)
2	7 (18.9)	0 (0.0)	7 (38.9)
Positive margins (%)	8 (21.6)	6 (31.6)	2 (11.1)
Chemotherapy (%)	11 (29.7)	0 (0.0)	11 (61.1)
Hormone therapy (%)	18 (48.6)	7 (36.8)	11 (61.1)
Tumor axis/quadrant (%)			
3:00	1 (2.7)	1 (5.3)	0 (0.0)
6:00	1 (2.7)	0 (0.0)	1 (5.6)
9:00	1 (2.7)	1 (5.3)	0 (0.0)
Central	2 (5.4)	1 (5.3)	1 (5.6)
LIQ	1 (2.7)	0 (0.0)	1 (5.6)
LOQ	3 (8.1)	2 (10.5)	1 (5.6)
UIQ	6 (16.2)	2 (10.5)	4 (22.2)
UOQ	22 (59.5)	12 (63.2)	10 (55.6)

DCIS: Ductal carcinoma *in situ*; ER: Estrogen receptor; PR: Progesterone receptor; ILC: Invasive lobular carcinoma; IDC: Invasive ductal carcinoma; LVI: Lymphovascular invasion; LIQ: Lower inner quadrant; LOQ: Lower outer quadrant; UIQ: Upper inner quadrant; UOQ: Upper outer quadrant.

wk in patients who did not receive endocrine therapy (*vs* 138.1 wk in patients treated with endocrine therapy). The primary tumor grade, chemotherapy up-front, margins, ER, PR, and patient age were not associated with the time interval to IBTR (Table 3). Among patients with invasive primary tumors, HER-2 receptor status, LVI, and Ki-67 were not associated with a shorter time interval to IBTR. The presence of an *in situ* component at the time of invasive recurrence was not associated with the time interval to IBTR.

Seven patients (18.9%) with an isolated IBTR experienced a second disease event during the follow-up period. The 5-year DFS after IBTR [second recurrence (DFS-SR)] was 81.1%. There were four patients who experienced an isolated LR after the first IBTR, two who developed a distant recurrence and 1 who developed a regional recurrence. Of the 4 who had an isolated LR after the first IBTR, 2 had undergone lumpectomy at the time of first recurrence, 1 had undergone mastectomy and 1 did not undergo further surgery. Among all four patients, the second recurrence had concordant biomarkers with the primary tumor and the first recurrence. Among three patients, the second recurrence also had concordant tumor location with the primary and first recurrence. There was no effect of concordance of biomarkers, concordance of tumor location, presence of an *in situ* component at recurrence, invasive *vs in situ* disease, hormone positive *vs* hormone negative disease on DFS-SR although the numbers were small.

DISCUSSION

This study identified and characterized IBTR in a large cohort of patients treated with BCS and adjuvant radiation. From a cohort of 2164 patients, we identified 40 patients who experienced an IBTR and had sufficient information to study 37 of these patients. We identified high concordance rates between ER/PR status of the primary and recurrent tumor and of the location of the primary and recurrent tumor. We also showed that tumor size greater than 1.5 cm and use of endocrine therapy up-front were associated with decreased risk of IBTR.

In our entire cohort, the OS of 97.7% at 5 years compares favorably with the outcomes of modern trials with early-stage breast cancer patients such as the START B trial and UK IMPORT LOW trial which had 5-year OS rates of 92.1%-95%[4,5]. The LRFS in our study of 98.0% was consistent with modern trials with a LR rate of approximately 2% at 5 years in the START B trial and 1.1% at 5 years in the UK IMPORT LOW trial. The overall low rate of recurrence in this single-institution series demonstrates that excellent local control can be obtained in this population of early stage breast cancer treated with BCS. All patients received radiotherapy and systemic treatment tailored to individual tumor biology.

In our study, there was a decreased risk of IBTR in patients with larger tumor size. Published trials have identified larger tumor size to be a predictor of local recurrence. In the MD Anderson experience, factors associated with improved local control on multivariate analysis among patients with an isolated local regional recurrence (LRR) after mastectomy included initial smaller tumor size (P = 0.03), time to initial LRR (P = 0.03), absence of gross tumor at the time of radiation (P = 0.001) and HER-2 status (P = 0.03)[15]. In Anderson *et al*[11], larger pathologic tumor size was a significant predictor of IBTR (HR = 1.44, 95%CI: 1.22-1.71, P < 0.0001) and mortality. A series from Harvard found that larger tumor size was associated with reduced DFS following LRR (HR = 1.3, 95%CI: 1.03-1.6, P = 0.02)[16]. Our finding that larger tumor size was associated with decreased risk of IBTR may be due to the fact that a majority of patients with larger tumor size received chemotherapy in our series (85% of T2 patients), which may have explained the longer interval to recurrence among patients with larger tumor sizes.

In our study, there was a high rate of biomarker and quadrant concordance between the primary tumor and IBTR with a 21.9% discordance in hormone receptor status and a 37.8% discordance in location. Similar rates have also been demonstrated in other series, with discordance of tumor phenotype ranging from 15%-40% in retrospective analyses[17-19]. In our study, concordance of receptor phenotype from primary to recurrence did not have a prognostic effect in the context of time to recurrence; however, our numbers were small and thus this cannot be stated definitively. Other studies have reported significantly improved post-recurrence

Table 2 Clinicopathologic characteristics of recurrences

Median time to IBTR (years IQR)	1.97 (1.03-3.5)
Invasive (%)	18 (45.9)
DCIS (%)	19 (51.4)
DCIS to invasive conversion (%)	5 (26.3)
Invasive to DCIS conversion (%)	5 (27.8)
In-situ component in invasive histology (%)	10 (55.6)
Concordant with original receptor subtype (%)	
Yes	25/32 (78.1)
No	7/32 (21.9)
Unknown	5/37 (13.5)
ER concordance (%)	
Same	25 (75.8)
Change from + to -	5 (15.2)
Change from - to +	2 (6.1)
PR concordance (%)	
Same	22 (66.7)
Change from + to -	8 (24.2)
Change from - to +	2 (6.0)
HER-2 concordance (%)	
Same	16 (100)
Change from + to -	0 (0)
Change from - to +	0 (0)
Concordant with original location (%)	
Yes	23 (62.2)
No	14 (37.8)
Salvage surgery (%)	32 (86.5)
Bilateral mastectomy	16 (43.2%)
Unilateral mastectomy	9 (24.3)
Local excision	6 (16.2%)
Salvage systemic therapy (%)	
Chemotherapy only	3 (8.1)
Hormone therapy only	11 (29.7)
Both	5 (13.5)
Re-irradiation of ipsilateral breast	6 (16.2%)

IBTR: Ipsilateral breast tumor recurrence; IQR: Interquartile range; DCIS: Ductal carcinoma *in situ*; ER: Estrogen receptor; PR: Progesterone receptor.

survival and OS among patients who maintain their tumor phenotype. In a retrospective analysis of 139 patients, the loss of hormone receptor positivity resulted in a worse post-recurrence survival (P = 0.01) and OS (P = 0.06), compared with the corresponding concordant-positive cases[17]. A small prospective study of 29 patients demonstrated that changes in hormone status from primary to recurrent disease led to a 20% change in disease management[20].

In order to further classify IBTRs, studies have tried to distinguish between new primaries (NP) and true recurrences (TR) incorporating multiple factors including receptor subtype with the theory that NPs will have improved outcomes compared to TRs and that NPs are less likely to have concordant biomarkers and/or tumor locations. Patients with NPs tend to have a longer median time to relapse than TR patients (7.3 *vs* 3.7 years, $P < 0.0001$)[21]. Haffty *et al*[22] classified an NP based on the fulfilment of at least one of the following three criteria: New location, histological subtype, or conversion from aneuploidy primary to a diploid relapse using DNA flow cytometry. In their series, 62% of patients had an isolated IBTR with a concordant location, and 74% with a concordant histology at a median follow-up of 10.2 years[22]. Post-breast recurrence survival rate for TRs was 3.16% compared to 5.42% for NPs ($P < 0.05$). In a series by Braunstein *et al*[16], there was a 68% concordance of biologic subtype from primary tumor to IBTR approximated by ER, PR, HER-2 and tumor

Table 3 Results of univariate Cox model assessing the association of clinical variables with risk of the first ipsilateral breast tumor recurrence

Clinical variable	Hazard ratio (95%CI)	*P* value
Patient age (continuous)	1.004 (0.98-1.02)	0.73
ER negative	1	-
ER positive	0.53 (0.26-1.11)	0.093
PR negative	1	-
PR positive	0.75 (0.38-1.50)	0.423
Tumor grade: Low	1	-
Tumor grade: Intermediate	0.791 (0.25-2.5)	0.689
Tumor grade: High	1.624 (0.54-4.8)	0.385
Margins negative	1	-
Margins positive	0.793 (0.36-1.75)	0.565
No chemotherapy	1	-
Chemotherapy up-front	1.282 (0.63-2.6)	0.499
No endocrine therapy up-front	1	-
Endocrine therapy up-front	0.362 (0.18-0.73)	0.004
Biomarker not concordant	1	-
Biomarker concordant	1.04 (0.95-1.10)	0.92
Location not concordant	1	-
Location concordant	1.265 (0.63-2.53)	0.506
Size < 1.5 cm	1	-
Size ≥ 1.5 cm	0.442 (0.22-0.90)	0.023
Invasive primary tumors		
LVI none	1	-
LVI present	0.617 (0.20-1.92)	0.404
HER2 negative/equivocal	1	-
HER2 positive	0.837 (0.28-2.55)	0.754
Ki-67 (continuous)	1.002 (0.99-1.02)	0.745

IBTR: Ipsilateral breast tumor recurrence; HR: Hormone receptor; ER: Estrogen receptor; PR: Progesterone receptor; LVI: Lymphovascular invasion.

grade at a median follow-up of 105 mo. Patients with triple negative breast cancer who developed LRR were at high risk of subsequent recurrence with significant worse DFS after IBTR compared with women with luminal A disease (ER and PR positive, HER-2 negative and grade 1 or 2 disease) (37.5% *vs* 88.3% at 5 years, $P < 0.005$). In a series by Komoike *et al*[23], classification of TR/NP was based on location of the primary and secondary tumor, initial surgical margin, and histological features. The 5-year survival rates were 71.0% in TRs *vs* 94.7% in NPs ($P = 0.022$). NP was a prognostic risk factor for a second local relapse ($P = 0.003$)[23]. In light of these findings, further research is warranted to identify prognostic factors for post-recurrence DFS and OS given that different studies are using variable definitions for TRs and NPs. In our study, there were too few events after IBTR to effectively determine an association between outcomes after IBTR and quadrant concordance, biomarker concordance, or the presence of an *in situ* component.

There are multiple limitations in this study. This was a retrospective study of patients enrolled in prospective clinical trials as well as in a large institutional database. The overall low rate of local recurrence in our cohort could be due in part to a lack of follow-up and missing information. There is also possible selection bias in that it is possible that patients with inferior outcomes (*e.g.*, recurrence) were more likely to seek care at outside institutions and therefore be more likely to have missing follow-up information than those patients who did not experience a recurrence. Another limitation of this study is the lack of statistical power to determine associations between tumor or patient characteristics and outcomes given our small number of patients who experienced IBTR. Finally, this is a single institutional series which may also limit its applicability and generalizability.

Our study found an overall low rate of IBTR in a large series of patients treated with BCS and adjuvant radiation. We found that tumor size and endocrine therapy at

initial diagnosis correlated with decreased risk of IBTR, and biomarker and tumor location were highly concordant from primary tumor to IBTR. We did not find an association between disease outcomes after IBTR and quadrant concordance, biomarker concordance or the presence of an *in situ* component though our numbers were small. Early *vs* late IBTR, biomarker and quadrant concordance may serve as useful classifiers; however, more evidence is necessary to accurately classify IBTRs in a way that is prognostic of outcomes. In an era where options for the management of IBTRs often represents a complex clinical challenge, a better understanding of what is a recurrence and what may represent a new primary will refine our treatment paradigms.

ARTICLE HIGHLIGHTS

Research background

Patients with an in-breast tumor recurrence (IBTR) after breast conserving therapy have a high risk of distant metastasis and disease-related mortality. The management of patients with IBTR represents a complicated clinical challenge. Local therapy after an IBTR in the setting of prior radiation has evolved in the modern era from standard salvage mastectomy with axillary dissection. Recent literature supports salvage lumpectomy and partial breast irradiation for patients with small tumor recurrences that have favorable tumor biology. The role of chemotherapy is guided by the biomarkers of the tumor.

Research motivation

One controversy that complicates the decision on how to manage recurrences is whether the disease event represents a true recurrence or a new primary. Distinguishing these processes based on clinical features alone remains a challenge given the dearth of data with regard to outcomes after the first recurrence.

Research objectives

The purpose of our study was to identify patients treated with BCS and whole breast irradiation who experienced an IBTR. We aimed to characterize the features of the primary tumor and the recurrence and determine the factors that increase the risk for IBTR. The study also aimed to better define the relationship between the primary tumor and the ipsilateral breast recurrence with respect to location of recurrence in the breast and the biologic subtype based on histopathology markers. Lastly, the study investigated the disease outcomes in these patients and elucidated whether any primary disease characteristics or IBTR characteristics influence outcomes after the first recurrence.

Research methods

Patients were identified from institutional databases of patients treated from 2003-2017 at our institution. All women in the cohort were > 18 years diagnosed with pathological stage 0-II *in situ* and invasive breast cancer treated with lumpectomy and adjuvant radiation. Histopathological and tumor information for the primary tumor and the ipsilateral breast recurrence were obtained through review of pathology reports. We classififed each IBTR as receptor discordant if the IBTR hormone status was estrogen receptor/progesterone receptor (ER/PR) negative, while the original primary tumor was ER/PR positive; or when the IBTR hormone status was ER/PR positive, while the original primary tumor was ER/PR negative. The tumor quadrant in the breast was determined based on mammography and/or magnetic resonance imaging prior to BCS at initial presentation and at recurrence. IBTRs that recurred in the same quadrant of the breast were considered concordant; skin recurrences and recurrences outside the original quadrant were considered discordant. Overall survival (OS), disease-free survival, and local recurrence-free survival (LRFS) were estimated using the Kaplan Meier method. We identified patients who experienced an isolated IBTR. Concordance of hormone receptor status and location of tumor from primary to recurrence were evaluated using the Chi-square test. The effect of clinical and treatment parameters on disease outcomes was evaluated using a univariate Cox proportional-hazards model. All statistical tests were two-sided with alpha = 0.05.

Research results

We identified 2164 patients who met the eligibility criteria. The median follow-up for all patients was 3.73 [Interquartile range (IQR) 2.27-6.07] years. Five-year OS was 97.7% (95%CI: 96.8%-98.6%) with 28 deaths; 5-year LRFS was 98.0% (97.2-98.8) with 31 IBTRs. We identified 37 patients with isolated IBTR, 19 (51.4%) as ductal carcinoma *in situ* and 18 (48.6%) as invasive disease, of whom 83.3% had an *in situ* component. Median time from initial diagnosis to IBTR was 1.97 (IQR: 1.03-3.5) years. Radiotherapy information was available for 30 of 37 patients. Median whole-breast dose was 40.5 Gy and 23 patients received a boost to the tumor bed. Twenty-five of thirty-two (78.1%) patients had concordant hormone receptor status, HER-2 receptor status, and ER ($P = 0.006$) and PR ($P = 0.001$) receptor status from primary to IBTR were significantly associated. There were no observed changes in HER-2 status from primary to IBTR. The concordance between quadrant of primary to IBTR was 10/19 [(62.2%), $P = 0.008$]. Tumor size greater than 1.5 cm [HR = 0.44, 95%CI: 0.22-0.90, $P < 0.05$), and endocrine therapy decreased the risk of IBTR (HR = 0.36, 95%CI: 0.18-0.73, $P < 0.05$) with a median interval to IBTR of 54 wk in

patients with tumors < 1.5 cm (*vs* 119 wk in patients with tumor greater than or equal to 1.5 cm) and a median time to IBTR of 54.5 wk in patients who did not receive endocrine therapy (*vs* 138.1 wk in patients treated with endocrine therapy). The primary tumor grade, chemotherapy up-front, margins, ER, PR, and patient age were not associated with time interval to IBTR. Among patients with invasive primary tumors, HER-2 receptor status, lymphovascular invasion, and Ki-67 were not associated with a shorter time interval to IBTR. The presence of an *in situ* component at the time of invasive recurrence was not associated with time interval to IBTR.

Research conclusions

The OS rate in our entire cohort compares favorably with the outcomes of modern trials with early stage breast cancer patients. Among patients with early stage breast cancer who had BCS treated with adjuvant RT, ER/PR status and quadrant were highly concordant from primary to IBTR. Tumor size greater than 1.5 cm and use of adjuvant endocrine therapy were significantly associated with decreased risk of IBTR. We did not find an association between disease outcomes after IBTR and quadrant concordance, biomarker concordance or the presence of *in situ* component, although our numbers were small.

Research perspectives

In order to further classify IBTRs, studies have attempted to distinguish between new primaries and true recurrence with the idea that new primaries will have improved outcomes compared to true recurrences. Early *vs* late IBTR, biomarker and quadrant concordance may serve as useful classifiers; however, more evidence is necessary to accurately classify IBTRs in a way that is prognostic of outcomes. In an era where options for the management of IBTRs often represent a complex clinical challenge, a better understanding of what is a recurrence and what may represent a new primary will refine our treatment paradigms. These questions should be further investigated in larger multi-institutional prospective clinical studies with the statistical power to determine associations between the characteristics of primary tumor and IBTRs, treatment and disease outcomes.

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SYSTEMATIC REVIEW

Current concepts in ameloblastoma-targeted therapies in B-raf proto-oncogene serine/threonine kinase V600E mutation: Systematic review

Rogelio González-González, Sandra López-Verdín, Jesús Lavalle-Carrasco, Nelly Molina-Frechero, Mario Isiordia-Espinoza, Ramón G Carreón-Burciaga, Ronell Bologna-Molina

ORCID number: Rogelio González-González (0000-0003-4457-704X); Sandra López-Verdín (0000-0002-8397-1720); Jesús Lavalle-Carrasco (0000-0002-5771-8684); Nelly Molina-Frechero (0000-0002-0435-053X); Mario Isiordia-Espinoza (0000-0001-8389-6866); Ramón G Carreón-Burciaga (0000-0002-4637-0782); Ronell Bologna-Molina (0000-0001-9755-4779).

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Rogelio González-González, Jesús Lavalle-Carrasco, Ramón G Carreón-Burciaga, Department of Research, School of Dentistry, Universidad Juárez del Estado de Durango, Durango 34000, Mexico

Sandra López-Verdín, Research Institute of Dentistry, Health Science Center, Universidad de Guadalajara, Guadalajara 4430, Mexico

Nelly Molina-Frechero, Department of Health Care, Xochimilco Unit, Universidad Autónoma Metropolitana Xochimilco, México 04960, Mexico

Mario Isiordia-Espinoza, Department of Clinics, Biomedical Sciences Division, Centro Universitario de los Altos, Universidad de Guadalajara, Tepetitlán de Morelos 47620, Mexico

Ronell Bologna-Molina, Molecular Pathology Area, School of Dentistry, Universidad de la República, Montevideo 11600, Uruguay

Corresponding author: Ronell Bologna-Molina, DDS, MSc, PhD, Molecular Pathology Area, School of Dentistry, Universidad de la República, Las Heras 1925, Montevideo 11600, Uruguay. ronellbologna@odon.edu.uy

Abstract

BACKGROUND

Ameloblastomas are common benign epithelial odontogenic neoplasms that present an aggressive and unpredictable behavior that may modify treatment strategies. Different signaling pathways that participate in the progression of these tumors have been identified. B-raf proto-oncogene serine/threonine kinase (BRAF) is a protein involved in the behavior of ameloblastomas, and it is related to many cell mechanisms. BRAF gene mutations have been identified in ameloblastomas, of which the BRAF V600E (valine substituted by glutamic acid at amino acid 600) mutation has been the most common and can be present concomitantly with other mutations that may be involved in its behavior. Targeted therapies have been used as an alternative in the case of resistance or contraindications to conventional treatments.

AIM

To document the presence of BRAF V600E and additional mutations, their behavior, and targeted therapies in these tumors.

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METHODS
An electronic literature search was conducted according to PRISMA guidelines in PubMed/MEDLINE, Cochrane, EMBASE, and SpringerLink using the terms "ameloblastomas", "BRAF V600E", "additional mutations", and "targeted therapies". Ameloblastomas were classified according to WHO guidelines. Inclusion criteria were articles in English, published not more than 10 years ago, and studies with laboratory works related to BRAF V600E. Articles were evaluated by two independent reviewers and retrieved for full-text evaluation. The EBLIP Critical Appraisal Checklist was used to evaluate the quality of the eligible studies. Descriptive statistical analysis was performed.

RESULTS
Two independent reviewers, with a substantial concordance indicated by a kappa coefficient of $k = 0.76$, evaluated a total of 19 articles that were included in this study. The analysis registered 521 conventional ameloblastomas (AM), 81 unicystic ameloblastomas (UA), 13 ameloblastic carcinomas (AC), three metastatic ameloblastomas (MA), and six peripheral ameloblastomas (PA), of which the histopathological type, anatomic location, laboratory tests, expression of BRAF mutation, and additional mutations were registered. The BRAF V600E mutation was found in 297 AM (57%), 63 UA (77.7%), 3 AC (23%), 1 MA (50%), and 5 PA (83.3%). Follicular type predominated with a total of 116 cases (40%), followed by plexiform type with 63 cases (22.1%). Furthermore, both types presented additional mutations, in which alterations in JAK3 P132T, SMARCB1, PIK3CA, CTNNB1, SMO, and BRAF G606E genes were found. Four case reports were found with targeted therapy to BRAF V600E.

CONCLUSION
The identification of BRAF V600E and additional mutations as an aid in targeted therapies has been a breakthrough in alternative treatments of ameloblastomas where surgical treatments are contraindicated.

Key words: Ameloblastoma; B-raf proto-oncogene serine/threonine kinase; B-raf proto-oncogene serine/threonine kinase V600E; Additional mutations; Targeted therapies

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Core tip: Ameloblastoma is a common neoplasia that is developed from odontogenic epithelium. It is an aggressive and recurrent tumor that can present metastases or malignant transformation. This neoplasia is characterized by presenting different clinical and histological varieties as well as several mutations related to its behavior. Nowadays, there are several studies focused on targeted therapies against the mutations of this tumor, one of the most frequent ones being B-raf proto-oncogene serine/threonine kinase (BRAF) V600E, the treatment of which has been associated with good response. These targeted therapies are suitable for resistant tumors. This study focused on BRAF V600E mutations and its additional mutations and targeted therapies.

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INTRODUCTION

Ameloblastoma is defined by WHO as a benign epithelial odontogenic intraosseous neoplasia, which is characterized by expansion and a tendency for local recurrence[1]. It is an aggressive neoplasia formed by odontogenic epithelium with mature fibrous stroma and odontogenic ectomesenchyme[2]. Histologically, it is characterized by cyst like formations and tumor nests that remind the epithelial component of the enamel

organ, as well as by the anastomosis of strands of odontogenic epithelium limited by columnar cells that lack of morphological pattern of reticulum stellate-like cells[1-3]. Its underlaying origins are epithelial rests of Malassez, remnants of Hertwig's epithelial sheath, and dental lamina[3]. It is the most common odontogenic epithelial neoplasia, with severe clinical implications, capacity of malignant transformation, and metastases[2]. Ameloblastoma global incidence is 0.5 cases per million population, being more frequent in China and Africa, where it comprises 14% of all tumor and cystic lesions that appear in the maxilla and mandible[2]. The first therapeutic choice is total surgical resection, by which most of the cases achieve the total elimination of neoplasia[4]. In the appearance of recurrent ameloblastoma, either metastatic ameloblastoma (MA) or ameloblastic carcinoma (AC), adjuvant therapies are implemented, and they consist of radiotherapy (RT) and chemotherapy (CT), which are controversial in their use due to a high recurrence rate and unpredictable results when they are used as a first-line and sole therapy without surgical treatment[4,5]. Due to these facts, new strategies of targeted therapies have been implemented in order to knock down the signaling pathways that participate in the development of this neoplasia, highlighting the MAPK signaling pathway with its predominant B-raf proto-oncogene serine/threonine kinase (BRAF) V600E mutation and the presence of additional mutations[3]. Thus, the aim of this study was to produce a systematic review in which current concepts and advances in targeted therapies regarding the BRAF V600E mutation in ameloblastomas were evaluated.

MATERIALS AND METHODS

Search strategy

This study was developed according to the criteria established in the guidelines recommended by Preferred Reporting Items for Systematic Reviews and Meta-analyses. The electronic search was conducted in PubMed/MEDLINE, Cochrane, EMBASE and SpringerLink. The employed keywords were the following, including abbreviations: Ameloblastoma mutations, BRAF, BRAF V600E, PIK3CA, JAK P132T, SMARCB1, SMO and associated mutations to BRAF and BRAF V600E, and treatments in ameloblastoma. Ameloblastomas were defined according to their variants: Ameloblastoma (AM) (follicular and plexiform), unicystic ameloblastoma (UA) (luminal/intraluminal and mural), MA, AC and peripheral ameloblastoma (PA). The Booleans and/or were employed in order to search for the following terms: "Ameloblastoma" and/or "targeted therapies" and/or "BRAF" and/or "associated mutations", and/or "BRAF V600E". The same strategy was employed for AM, UA, MA, AC and PA. After the screening of titles and abstracts, the studies with useful information were retrieved for full text evaluation. Open access and restricted access articles were reviewed and were retrieved by institutional support. All AM, UA, MA, AC and PA were classified according to WHO[1]. Different classifications were adapted.

Inclusion criteria

Two independent evaluators reviewed the selected articles, which were considered eligible when they fulfilled all of the following criteria: (1) Studies whose content was clearly associated with targeted therapies against BRAF V600E mutation in AM, UA, MA, AC, or PA; (2) Articles that were published not more than 10 years before this study was conducted (January 1st 2009–2019); (3) Articles in the English language; (4) Articles with positive cases corroborated by molecular and immunohistochemical (IHC) techniques for the study of BRAF mutations and additional mutations; and (5) Articles included in PubMed/MEDLINE, Cochrane, EMBASE, and SpringerLink. Different types of studies were considered, such as systematic reviews, meta-analyses, and molecular studies whose objective was to evaluate targeted therapies in ameloblastomas.

Exclusion criteria

Exclusion criteria were the following: (1) Review articles, book chapters, systematic reviews, meta-analyses, and molecular studies in a language other than English; (2) Articles which were published more than 10 years before the established date; (3) Studies of targeted therapies not directly related to the established signaling pathways; and (4) Articles that study isolated mutations which are not BRAF V00E-related.

Quality assessment and data extraction

The quality of the eligible studies was evaluated by two independent reviewers using the EBLIP Critical Appraisal Checklist[6]. Disagreements between reviewers were

resolved by discussion. Both independent reviewers extracted the data required for this study from each article and finally evaluated and discussed the data to achieve concordance. All extracted data were registered in a table to eliminate possible mistakes.

RESULTS

The literature search recorded a total of 156 articles. After the evaluation by two independent reviewers, with a substantial concordance indicated by a kappa coefficient of $k = 0.76$, 19 articles, which fulfilled the inclusion criteria, were included in this study. The other 137 articles were excluded as they did not accomplish the inclusion criteria. Figure 1 summarizes the selection of the articles that were considered in the elaboration of this systematic review. The reviewed articles registered 521 AM, 81 UA, 13 AC, 3 MA, and 6 PA, of which the histopathological type, anatomic location, laboratory tests, expression of BRAF mutation, and additional mutations were registered. A total of 39 AM, 10 UA, and 7 AC presented the expression of BRAF. For AM, follicular type was the most predominant type of this expression, with 15 out of 39 found cases. Follicular and plexiform types registered the highest quantity of additional mutations to BRAF expression, among which mutations of NRAS Q161R, HRAS Q161R, FGFR2, KRAS, and other variants of BRAF (G606E, L548P, V590G) were found to have mutated. Bartels *et al*[7] reported the unique case of additional mutations with BRAF expression in which FGFR2 presented concomitant mutation of PTEN and TP53. BRAF V600E mutation was found in 297 AM (57%), 63 UA (77.7%), 3 AC (23%), 1 MA (50%), and 5 PA (83.3%) cases. Follicular type predominated with a total of 116 cases (40%), followed by plexiform type with 63 (22.1%). Additionally, both types presented additional mutations, in which alterations in JAK3 P132T, SMARCB1, PIK3CA, CTNNB1, SMO, and BRAF G606E genes were found. Figure 2 describes the anatomic location of the additional mutations, and Figure 3 describes the relation between BRAF and BRAF V600E expression with additional mutation. The complete collected data and results can be found in Table 1. Four cases of targeted therapy of ameloblastomas with the presence of BRAF V600E were found. Reported cases with targeted therapies are described in Table 2.

DISCUSSION

BRAF V600E

BRAF is a protein that leads to different cell mechanisms, such as metabolism and proliferation. There are different signaling pathways that are activated in these mechanisms in an extracellular and intracellular manner.

More than 40 mutations of BRAF were identified in different neoplasms. The most frequent ones are missense mutations of the 600 residues of the BRAF gene, in which valine is replaced by glutamine (V600E) and results in the constitutive activation of MEK/ERK signaling in tumors[8,9]. The BRAF V600E mutation has been employed as a predictive, diagnostic, and prognostic biomarker in different tumors. In ameloblastomas, the presence of this mutation was first described by Brown *et al*[10] and Kurppa *et al*[11], who indicated its influence on the resistance to the targeted therapy of EGF receptors. Furthermore, Jhamb *et al*[8] described the relation between BRAF and the RAS/MAPK pathway in the pathogenesis of AM. Since these findings, several studies focusing on targeted therapies against BRAF mutations have been developed. Sweeney *et al*[12] found the BRAF V600E mutation in 46% of the analyzed AM. Moreover, they reported other variants of the BRAF mutation (L597R), which results in the substitution of leucine residue by arginine in the 597 BRAF position by an increment of kinase activity[13] and associations with SMO and FGFR2, found in the maxilla. SMO is of interest as its mutations are frequent in ameloblastomas of the maxilla and is, unlike BRAF, frequently not associated with other mutations. It is important to highlight that in this review different mutational variants associated with BRAF V600E (G606E and L597R) were found in follicular and plexiform AM, respectively. Although the functional implication of these variants regarding treatment has not been studied[14], and there are few reports of these mutations in ameloblastomas. Further studies may possibly establish the relation between these variants and their histological pathways, tumor behaviors, and treatment resistance. Based on these findings, it is possible that additional mutations of BRAF V600E are mainly associated with the histological pathway of AM. In the present study, more than 500 cases of AM were analyzed, including those of the Sweeney *et al*[12] study, in which more than 50% of the total cases presented the BRAF V600E mutation.

Table 1 Presence of B-raf proto-oncogene serine/threonine kinase and B-raf proto-oncogene serine/threonine kinase V600E and the relation with additional mutations

BRAF type	Ameloblastoma			Histological pattern	Mutations	Additional mutation	Anatomic location
	Type	Cases with expression	Total cases	Histological pattern (cases)	Gene (cases/total)	Gene (cases)	Site (cases)
BRAF WT	Ameloblastoma	39	521	Follicular (15)	NRAS Q161R (2/15)		Mandible (9)
							Maxilla (1)
					G606E (1/15)		NS (5)
					L584P, V590G (1/15)		
				Plexiform (14)	HRASQ161R (2/14)		Mandible (10)
					FGFR2 p.C382R (2/14)		Maxilla (1)
							NS (3)
				Mixed (4)			Mandible (4)
				NS (6)	FGFR2 (4/12)	PTEN, TP53 (1)	NS (6)
					KRAS (1/12)		
	Unicystic ameloblastoma	10	81	Luminal/intraluminal (6)			Mandible (4)
							Maxilla (2)
				NS (4)			Mandible (1)
							NS (3)
	Ameloblastic carcinoma	7	13	Without cell variant (5)			Mandible (3)
							Maxilla (2)
				NS (2)			NS (2)
	Metastasizing ameloblastoma	0	2				
BRAF V600E	Ameloblastoma	297	521	Follicular (121)			Mandible (91)
					JAK3 P132T (3/121)		
					SMARCB1 (1/121		
					PIK3CA (1/121)		
					CTNNB1 (1/121)		
					SMO (1/121)		
					SMO (1/121)	FGFR2 (1)	Maxilla (4)
							Left frontal bone (1)
					G606E (2/121)		NS (25)
				Plexiform (65)	JAK3 P132T (1/65)		Mandible (38)
					SMARCB1 (1/65)		
					PIK3CA (1/65)		
					PIK3CA (1/65)		Maxilla (2)
					BRAF 597R (1/65)	SMO (1)	
							NS (25)
				No follicular (20)			Mandíbula (20)
				No plexiform (15)			NS (15)
				Granular-cell (4)			Mandible (4)
				Mixted (10)			Mandible (4)
							NS (6)
				Without cell variant (1)			Mandible (1)
				Desmoplastic (2)			Mandible (1)
							Maxilla (1)

				NS (59)	FGF2[1] (23)	Mandible (4)
					FGFR1[1] (24)	Maxilla (1)
						NS (45)
						Cavernus sinus (1)
						Coronoid process (1)
	Unicistyc ameloblastoma	63	81	Luminal/Intraluminal (21)		Mandible (19)
						Maxilla (2)
				Mural (20)		Mandible (20)
				NS (22)		Mandible (12)
						Maxilla (1)
						NS (9)
	Peripheral ameloblastoma	5	6	NS (5)		NS (5)
	Ameloblastic carcinoma	3	13	Without cell variant (3)		Mandible (3)
	Metastasizing	1	2	Follicular (1)		Mandible (1)
	NS			Acanthomatous (7)		Mandible (7)
				Granular cells (2)		Mandible (2)
				NS (2)	PIK3CA, CDKN2A (1)	Mandible (1)
					PIK3CA, PTEN (1)	Mandible (1)
				NS (2)	CDKN2A (1)	Mandible (1)
					CTNNB1 (1)	Mandible (1)
No mutations	Metastasizing Ameloblastoma	1	2	Plexiform (1)		Infratemporal fosa (1)
	Ameloblastic Carcinoma	3	13	NS (3)		NS (3)
	Unicistyc Ameloblastoma	1	81			NS (1)

[1]Expressed without mutation. NS: No specified; BRAF: B-raf proto-oncogene serine/threonine kinase; BRAF WT: B-raf proto-oncogene serine/threonine kinase Wild-type.

Additionally, studies on the detection of BRAF with IHC have been done using BRAF antibody clone VE-1, which shows a high specificity and sensitivity in cells that express this mutation[15]. This expression was associated with recurrence, osseous disruptions, and multilocular radiographic pathways[16], and although these variables are not evaluated in this review, it is important to indicate that the presence of the BRAF mutation is related to clinical behavior[10,12,16]. The presence of BRAF V600E in AM is commonly associated with other mutations and can frequently be present in younger patients[2,10,17,18].

In the analysis of UA, no additional mutations to BRAF V600E were reported. This difference in UA may be related to: (1) BRAF expression being presented earlier in tumorigenesis of ameloblastomas, and through tumor evolution this acquires mutations additional to BRAF V600E, or (2) UA may be a prior neoplasia of AM, in which mutated BRAF is present from the beginning of the pathology. Another important fact is that BRAF V600E expression is found in the same proportion in luminal/intraluminal and mural types, which may indicate that this mutation is not entirely associated with tumor behavior. This assumption may be supported by the data found in AM, as most ameloblastomas with aggressive behavior present an association between BRAF V600E and other mutations, and it is possible that these additional mutations are related to behavior.

AC is classified as aggressive ameloblastic tumor with a tendency to metastasis, mainly to the lung, with a median survival rate that varies between 5 and 17.6 years according to global surveillance and those from the maxilla being more aggressive. BRAF mutations have been described the same as for AM[1].

In this analysis, a total of 13 AC cases were registered, of which 23% (7) presented the BRAF V600E mutation, which was the opposite to UA, where a great number of

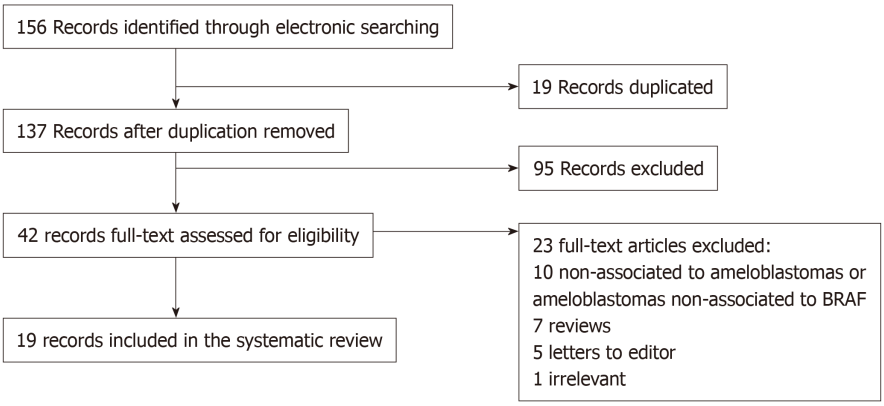

Figure 1 Flow diagram of articles identification and selection. BRAF: B-raf proto-oncogene serine/threonine kinase.

cases were registered with this mutation. Additionally, none of the cases presented any additional mutations, unlike AM, which presented a higher number of secondary mutations in the cases with BRAF V600E. These results may be associated mainly with the lack of cases reporting AC with BRAF analysis, which suggest that in further studies the presence of BRAF should be evaluated in order to establish a treatment strategy for more aggressive ameloblastomas, which may possibly lead to the discovery of new additional mutations.

Six cases of PA were registered, of which 83.3% (5) presented the BRAF V600E mutation, and one being an unspecified case. These ameloblastomas have a similar histological pathway as their opposite, the intraosseous type, which may support the expression of BRAF. However, the percentual difference is large (83.3% *vs* 57%) due to the low number of reported cases. However, because of their location, these ameloblastomas are not aggressive in comparison with their opposite, the intraosseous type.

MA is an ameloblastoma that develops metastases despite its benign appearance. Like most ameloblastomas, MA presents a higher predilection of metastasis to the mandible, and its metastatic nests are commonly found in the lung, followed by the lymph nodes. This neoplasia is usually of long latency before developing metastases and can be associated with repeated recurrences after surgical treatment. This is an uncommon entity and its outcome depends on the metastatic nests and surgical viability[1]. In this analysis, MA corresponds to less than 1% of the total cases registered, which indicates that it is an uncommon tumor and consequently poorly studied. Two of the three registered cases presented BRAF V600E (66.6%) without additional mutations. This allows us to conclude that secondary mutations of BRAF V600E are possibly exclusive to AM.

Location and additional mutations of BRAF V600E

Overall, ameloblastomas have a predilection for the mandible, mainly located in the body, ramus, and symphysis[1,2,17]. Registered data showed that BRAF V600E mutations were more frequent in the mandible with an approximate ratio of 21:1, although this data is not precise as 79 (24.6%) cases with the mutation were registered without the specific anatomic location.

In this analysis, BRAF V600E cases without additional mutations corresponded to 93.7%, compared with those that presented multiple mutations at 6.23%. This explains why treatment based on the knockdown of BRAF V600E may be successful. Overall, in mandible 4.3% (10/231) of the registered cases presented multiple mutations, whereas in maxilla the percentage was higher (27.7%). This could be an interesting finding, as it is possible that targeted therapies to BRAF are more successful in mandibular tumors, whereas in the maxilla, combined therapies should be considered as the more frequently registered secondary mutation was SMO[19]. Additionally, SMO mutations can be isolated, which may modify the treatment strategy. This result is interesting as the recurrence risk is related to the mutational status and tumors with multiples mutations are associated with high recurrences[19]. Although there are few additional mutations of BRAF V600E in ameloblastomas, these were more frequently present in the mandible, and it is possible that these mutations are exclusive to AM. Additional mutations that were frequently registered in this review were JAK P132T, SMO, SMARCB1, PIK3CA, and CTNNB1 in the mandible and BRAF L597R, FGFR2, PIK3CA, and SMO in the maxilla. Other secondary mutations with unspecified

Table 2 Targeted therapies to B-raf proto-oncogene serine/threonine kinase V600E in ameloblastomas

Ref.	Age	Evolution tumor (yr)	Gender	Tumor	Localization	Primary tumor/ recurrent	Previous treatments	Size	Course of the diseases	Mutation detected	Treatment	Evolution	Follow-up
Kaye *et al*[27]	40	30	M	MA	Left jaw, bilateral neck mass, pulmonary metastases	Recurrent	Surgical resection and radiotherapy	NS	Three recurrences (13, 9, 7 yr), surgical resection (two recurrences), RT (last recurrence), neck bilateral and lung metastasis. (imaging diagnosis CT)	BRAF V600E (gene profile and IHC)	BRAF/MEK inhibition (Dabrafenib 150 mg twice daily + Trametinib 2 mg once daily)	Decrease of the tumor size and metastases in the first four days	20 wk (tumor response to treatment, without toxicity)
Faden *et al*[26]	83	16	F	AM	Right jaw	Recurrent	Conservative surgery	3.79 cm × 5.87 cm × 5.62 cm	Two recurrences, difficult to nutrition, not suitable for surgery	BRAF V600E	Dabrafenib 75 mg twice daily	Decrease of the tumor size	12 wk (tumor response to treatment)
Fernandes *et al*[29]	29	12	F	AM	Ramus and left jaw	Recurrent	Surgical resection and radiotherapy	1.3 cm × 0.9 cm (residual tumor)	Tumor recurrence by conservative surgery for 16 yr, metastases in cavernous sinus and tumorl extention to orbit	BRAF V600E (PCR allele-specific)	Vemurafenib 960 PO twice daily and analgesic treatment	Decrease of the tumor size with symptomatology (anorexy, nausea and fatigue)	11 wk, asymptomatic with treatment tolerance
Tan *et al*[28]	85	NS	M	AM	Left jaw	Primary	Surgical resection	4 cm (CT Scan)	Tumor recurrence with pathological fracture	BRAF V600E (PCR allele-specific)	Dabrafenib 150 mg PO twice daily	Decreased of tumor size with development of actinic keratosis on face, back and scalp and thickening voice	16 wk, notable decrease of tumor size

NS: No specified; PO: Oral administration; BRAF: B-raf proto-oncogene serine/threonine kinase; IHC: Immunohistochemical; CT: Chemotherapy; MA: Metastatic ameloblastomas; AM: Ameloblastomas.

anatomic location were BRAF G606E, CTNNB1, CDKN2A, and PTEN.

To date, there are no references to the association between JAK3 P132T presence and ameloblastomas. However, this gene has been studied in some neoplasia, such as head and neck squamous cell carcinoma (HNSCC), with a reported relation to racial

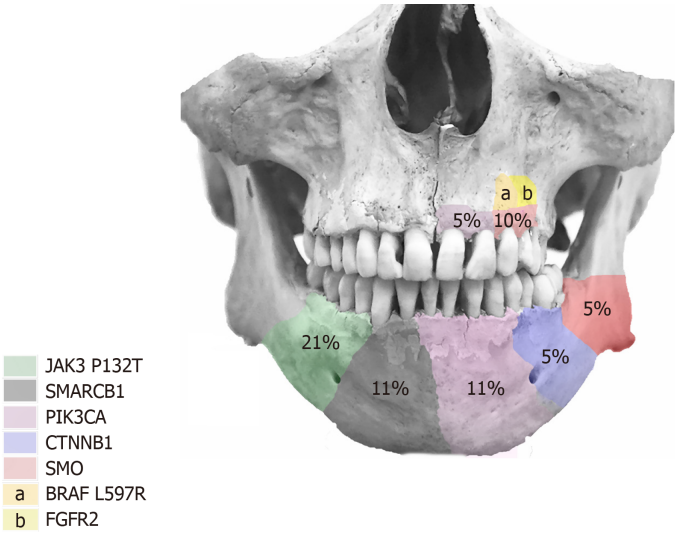

Figure 2 Anatomic location of B-raf proto-oncogene serine/threonine kinase V600E additional mutations. a, b: Additional mutations of the same ameloblastomas. Figure does not represent the specific site of each additional mutation, only whether it is present in the maxilla or the mandible.

predisposition and megakaryocytic leukemias related to leukemogenesis[20,21].

SMO is a protein whose upregulation is related to signaling of the Sonic Hedgehog (SHH) pathway participating in the pathogenesis of several malignant neoplasia[22]. However, the regulation of SMO in ameloblastomas is not well characterized, but it has been suggested that overexpression can lead to a constitutive activation of the SHH signaling pathway and finally contribute to cell survival and proliferation. The results observed in our analysis detected concomitant mutations of BRAF V600E with SMO and a higher predilection to the maxilla; thus, it is considered that this neoplasia may have a more aggressive behavior due the participation of SMO in the SHH signaling pathway and its relation to BRAF V600E. It is interesting that the presence of the isolated SMO mutation in maxillary ameloblastomas has been pointed out. This finding may be important, as it is possible that treatment of maxillary ameloblastomas should mainly focus on targeted therapies against SMO, and as this is present in the SHH signaling pathway, maxillary tumors may be more aggressive.

SMARCB1 is a gene that codifies for the SWI/SNF complex, which plays an important role in the regulation of transcriptional mechanisms. Its main function is the regulation of the cell cycle trough pRb and HDAC1. Furthermore, this gene is involved in the SWI/SNF complex that suppresses E2F activity knocking down the phase S. It is normally expressed in all the tissues. SMARCB1 alterations have been associated with rhabdoid malignant neoplasia as well as benign lesions such as schwannomatosis[23]. Of all the cases, 11% of additional mutations of BRAF V600E were associated with SMARCB1. Although the relation of this gene to ameloblastomas behavior has not been established.

PIK3CA is an important regulator of the signaling of the tyrosine kinase receptors that are crucial in the proliferation, growth, and differentiation mechanisms. It is one of the most frequently mutated oncogenes and is observed in different neoplasia[24]. The alterations in this gene have been observed in 10%–33% of HNSCC, whose amplification is related to a low expression of PTEN[24]. The findings in this study indicate the presence of the PIK3CA mutation in 11% of ameloblastomas with BRAF V600E, which may indicate that ameloblastomas with these mutations are more susceptible to recurrence.

Although a direct association between PIK3CA with recurrence was not found in this analysis, recurrence was involved in multiple mutations associated with BRAF V600E[19]. Thus, ameloblastomas related to BRAF V600E associated with multiple mutations are tumors that can acquire several characteristics from the additional mutated genes.

Targeted therapies against BRAF V600E

In vitro studies have been developed in order to evaluate the therapeutic use of treatments against the BRAF V600E mutation. Brown *et al*[10] evaluated the *in vitro* effects of vemurafenib in the activation of the MAPK signaling pathway and the proliferation in the AM-1 cell line. Their results demonstrated the knock-down of cell proliferation and indicated that vemurafenib treatment is a potential alternative in

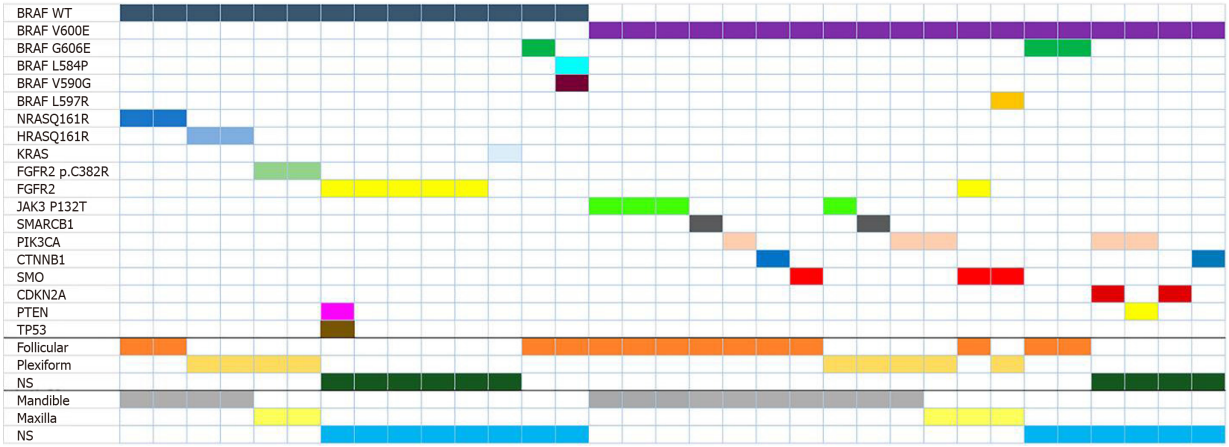

Figure 3 Mutation distribution and relationship with pathological features. Information on histology and anatomical site is included below for each case. NS: No specified. BRAF WT: B-raf proto-oncogene serine/threonine kinase wild-type.

ameloblastomas whose surgical treatment is related with significant facial deformities and frequent recurrences. Furthermore, vemurafenib is recommended in MA, local aggressive tumors, and non-candidate patients as an alternative to surgical treatment[10]. Thus, patients who present BRAF V600E mutation are eligible for targeted therapies, using combined treatments related to knocking down BRAF-related signaling pathways. A great example is combined therapy with vemurafenib (BRAF inhibitor) and trametinib (MEK inhibitor) of which some reported cases have shown excellent results, especially in MA[10,24].

Although there are no reports of serial cases that indicate the success of targeted therapies in ameloblastomas, they have been used as adjuvant or neoadjuvant therapies in order to improve the outcome of treatments, to increase functional mobility, and to improve cosmetic results[25-27]. Thus, the use of targeted therapies has been limited as previously described.

This analysis demonstrates most of the molecular alterations of ameloblastomas and their relation to anatomic location and possible association with behavior. The identification of BRAF V600E and the additional mutations as an aid in targeted therapies has been a breakthrough in alternative treatments of ameloblastomas where surgical treatment is contraindicated. The analyzed studies evaluate several mutations and their possible association with the biology of these tumors. The findings are an important advancement in the study of ameloblastomas and alternative treatments, although the latter is limited to few case reports. Further studies are necessary in order to adequately determine the success of targeted therapies and resistance to treatment by the BRAF V600E mutation.

ARTICLE HIGHLIGHTS

Research background

Ameloblastomas are benign tumors that arise from the odontogenic epithelium whose behavior is defined as aggressive, infiltrative, recurrent, with aesthetic implications and rarely propense to local and distant metastases. Recently B-raf proto-oncogene serine/threonine kinase (BRAF) V600E gene mutation has been reported in ameloblastomas. Thus, targeted therapies against this mutation have been evaluated as an alternative treatment. In this study, a systematic review was performed in order to evaluate the frequent mutation of BRAF and another associated mutations, as well as targeted therapies against them.

Research motivation

Performing a systematic review allows to know the reports of frequent mutations in ameloblastomas and alternative treatments against them, as well as evaluate therapeutic response.

Research objectives

The aim of this study was to evaluate the presence of BRAF V600E mutation and another related mutations in ameloblastomas and provide information about the role of the mutations in the behavior of ameloblastomas, as well as targeted therapies reported.

Research methods

A literature research was carried out between January 1st 2009-2019 in order to perform a

systematic review, of which 19 articles with relevant content regarding BRAF and its mutations in ameloblastomas were included, as well as targeted therapies against them.

Research results
A total of 624 ameloblastomas were evaluated, in which BRAF V600E was the most frequent mutation. Of the total of the included articles, four case reports registered targeted therapies against BRAF V600E.

Research conclusion
In the current study, the most frequent mutation was BRAF V600E, which interestingly was frequently associated to other mutations that conferred more aggressiveness with recurrence and metastases. Regarding anatomic location, it is suggested that associated mutations to BRAF V600E are more common in the mandible. Targeted therapies against this mutation represented a significant outcome in patients that presented these types of tumors. Since this is the first systematic review developed about this subject, it could be suggested that the use of targeted therapies as adjuvant to surgical treatment may offer important outcome in the clinical evolution and the follow up, specially in recurrent, metastatic and malignant ameloblastic tumors.

Research prospective
The information obtained in this review demonstrates the current implementation of targeted therapies against BRAF V600E mutation in ameloblastic tumors.

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