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*REVIEW*

# Management of genitourinary syndrome of menopause in breast cancer survivors: An update

Daniel María Lubián López

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## Abstract

There is increasing attention about managing the adverse effects of adjuvant therapy (Chemotherapy and anti-estrogen treatment) for breast cancer survivors (BCSs). Vulvovaginal atrophy (VVA), caused by decreased levels of circulating estrogen to urogenital receptors, is commonly experienced by this patients. Women receiving antiestrogen therapy, specifically aromatase inhibitors, often suffer from vaginal dryness, itching, irritation, dyspareunia, and dysuria, collectively known as genitourinary syndrome of menopause (GSM), that it can in turn lead to pain, discomfort, impairment of sexual function and negatively impact on multiple domains of quality of life (QoL). The worsening of QoL in these patients due to GSM symptoms can lead to discontinuation of hormone adjuvant therapies and therefore must be addressed properly. The diagnosis of VVA is confirmed through patient-reported symptoms and gynecological examination of external structures, introitus, and vaginal mucosa. Systemic estrogen treatment is contraindicated in BCSs. In these patients, GSM may be prevented, reduced and managed in most cases but this requires early recognition and appropriate treatment, but it is normally undertreated by oncologists because of fear of cancer recurrence, specifically when considering treatment with vaginal estrogen therapy (VET) because of unknown levels of systemic absorption of estradiol. Lifestyle modifications and nonhormonal treatments (vaginal moisturizers, lubricants, and gels) are the first-line treatment for GSM both in healthy women as BCSs, but when these are not effective for symptom relief,

other options can be considered, such as VET, ospemifene, local androgens, intravaginal dehydroepiandrosterone (prasterone), or laser therapy (erbium or CO2 Laser). The present data suggest that these therapies are effective for VVA in BCSs; however, safety remains controversial and a there is a major concern with all of these treatments. We review current evidence for various nonpharmacologic and pharmacologic therapeutic modalities for GSM in BCSs and highlight the substantial gaps in the evidence for safe and effective therapies and the need for future research. We include recommendations for an approach to the management of GSM in women at high risk for breast cancer, women with estrogen-receptor positive breast cancers, women with triple-negative breast cancers, and women with metastatic disease.

**Key Words:** Genitourinary syndrome of menopause; Breast cancer survivors; Aromatase inhibitors; Vaginal moisturizers and lubricants; Vaginal estrogens; Laser



**Core Tip:** Genitourinary syndrome of menopause (GSM) is commonly experienced by breast cancer survivors (BCSs) receiving antiestrogen therapy, specifically aromatase inhibitors. Vaginal dryness, itching, irritation and dyspareunia produce impairment of sexual function and negatively impact on the quality of life. Healthy women, and even more so BCSs, are reluctant to discuss this problem with their general practitioner or oncologist. Safety of vaginal estrogen therapy for management of GSM refractory to other nonhormonal treatment in BCSs has not been definitively established, and recommendations for use remain controversial. This review aims to summarize the clinical approach and emerging therapeutic alternatives, considering the efficacy and potencial adverse effects in this population.

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## INTRODUCTION

### *Genitourinary syndrome of menopause*

Vulvovaginal atrophy (VVA) (also referred to as vaginal atrophy, urogenital atrophy, or atrophic vaginitis) results from estrogen loss and is often associated with vulvovaginal complaints (*e.g.*, dryness, burning, dyspareunia) and less often with urinary frequency and recurrent bladder infections in menopausal patients[1].

In 2014, the new term Genitourinary Syndrome of Menopause (GSM) was introduced by the International Society for the Study of Women´s Sexual Health and the North American Menopause Society[2]. This term encompasses all of the atrophic symptoms patients may have in the vulvovaginal and bladder-urethral areas from loss of estrogen that occurs with menopause. The spectrum of adverse consequences makes long-term treatment essential in many patients, not only for relief of symptoms, but also for the more troublesome problems that may occur, such as, postcoital bleeding and recurrent urinary tract infections. This in turn can complicate the process of sexual arousal and achievement of orgasm, thus, leading to sexual dysfunction[3].

The prevalence of VVA, as confirmed by physical examination or pH measurement, has been described as between 69% and 98% in postmenopausal women[4,5], but it is even more frequent in young patients receiving anti-estrogenic or antineoplastic drugs for breast cancer[6]. These symptoms are often underdiagnosed and undertreated due to underreporting by the patients and limited awareness by professionals[7].

### *Genitourinary syndrome of menopause in breast cancer survivors*

Improved treatment and screening for female breast cancer in developed countries has resulted in higher survival rates over the past two decades, with five-year survival rates currently as high as 90% (99% for women free of lymph node metastases in comparison to 84% if lymph nodes are positive)[8]. As a result, there are many millions of BCSs living in Western countries. In these countries, approximately 43% are ≥ 65 years old and 25% are ≤ 50 at diagnosis[9].

There are many definitions and phases of cancer survivorship. A cancer survivor is defined as any person with cancer, starting from the moment of diagnosis[10]. This is consistent with definitions from the National Coalition for Cancer Survivorship[11] and the National Cancer Institute[12]. The majority

of women with hormone receptor-positive early breast cancer are offered adjuvant endocrine therapy, including tamoxifen (TAM) or aromatase inhibitors (AIs), for at least 5 years to reduce the risk of recurrence and death. Practice guidelines now recommend up to 10 years of endocrine therapy and this has significant implications for compliance with treatment and ensuring that the adverse effects of treatment are adequately managed[13]. Many BCSs are still of premenopausal age and have the potential risk of receiving antineoplastic treatments that may affect ovarian function or anti-estrogenic treatments that mimic a postmenopausal state[14]. This hypoestrogenic state can lead to climacteric symptoms inducing significant alterations in their quality of life[15]. Many BCSs are already in a postmenopausal state at diagnosis, and the treatments used to treat BC worsens their basal hypoestrogenic state, which enhances associated problems. Due to dependence on estrogen, the vaginal epithelium can progress to VVA because of antiestrogenic treatments or natural menopause. Data suggest that long-term BCSs often report normalization of physical and emotional functioning but experience continued difficulty with sexual functioning and satisfaction for 5 or more years after treatment[16]. Women may be reluctant to bring up the topic of vaginal and sexual health and are often relieved when their clinicians begin a conversation. Many clinicians are uncertain about how to treat these symptoms in BCSs[17,18], and lack of treatment usually leads to a worsening of VVA over time [19].

Therefore, the management of breast cancer, the most common cancer in women, can lead to a variety of symptoms that can impair the quality of life (QoL) of many survivors. Although GSM affects more than 50% of the general population of postmenopausal women, it is even more prevalent in survivors of breast cancer (over 70%)[20-27], most of whom are undiagnosed and untreated[28-32]. This wide range of symptoms is a consequence of the decreased levels of circulating estrogen caused by ovarian failure induced by chemotherapy, bilateral oophorectomy performed in some patients, or by the use of endocrine therapies with AIs and selective estrogen receptor modulators (SERMs), such as TAM, in estrogen-receptor-positive BCs (ER+BCs), resulting in a faster transition to menopause[14,15].

Postmenopausal women treated with AIs may experience a severe form of vulvovaginal atrophy (VVA) with significantly higher rates of vaginal dryness (16.3%) and dyspareunia (17.8%) than women taking TAM (8.4% and 7.5%, respectively), as reported by The Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial[33]. Data originating from a follow-up study of women with breast cancer no longer on therapy and 6 years on average after diagnosis showed that in the group of women aged 50 to 59, 72.8% reported vasomotor symptoms (VMS), and 80.8% reported sexual symptoms[20]. Another study with 97 BCSs reported moderate or severe symptoms of vaginal atrophy in 58% of patients on AIs and in 32% of those on TAM[34].

Several studies have suggested a deterioration of quality-of-life scores due to GSM in BCSs[35,36].

In a recent study, Lubián *et al*(2020)[37], observed a high prevalence of sexual inactivity among BCSs (47.6%) regardless of AI use. Patients with AI use presented a significantly higher prevalence of female sexual dysfunction (FSD), worse QoL, and greater anxiety.

We can conclude that AI users usually report more negative effects on sexual life than TAM users. These differences could be explained by some estrogenic effect of TAM over vaginal tissues in postmenopausal women, whereas AI can dramatically reduce plasma estradiol levels to less than 3 pmol/L[38].

Therefore, the aim of this review was to provide an update and overview of the most relevant and recent literature on therapeutic interventions with demonstrated efficacy in BCSs presenting GSM and the current evidence of their safety profiles. In addition, we provide recommendations for an approach to the management of GSM in women at high risk of breast cancer, women with estrogen receptor-positive breast cancers (ER+BCs), women with triple-negative breast cancers (TN BCs), and women with metastatic disease.

## BIOLOGICAL CHANGES ASSOCIATED WITH GENITOURINARY SYNDROME OF MENOPAUSE IN BREAST CANCER SURVIVORS

Systemic loss of estrogen results in physiological and structural modifications within the genital structures and vaginal mucosa. Postmenopausal estrogen depletion induces changes that include a reduction in cervical gland secretions, deterioration of tissue, decrease in blood flow, loss of elasticity, thinning of tissue and epithelium, and an increase in pH[39-41]. The vaginal mucosa has reduced glycogen content and lack lactobacilli which convert glycogen into lactic acid to maintain a healthy vaginal pH in the range of 3.5-4.5. A reduction in lactic acid increases vaginal pH to the range of 5.0-7.5 [39,42]. Such atrophic changes predispose women to symptoms and vaginal infections, as the more basic pH environment is conducive for infection from pathogenic bacteria such as staphylococci and Group B streptococci[39]. In summary, atrophic vaginitis is a result of multiple changes in the external genitalia and internal mucosa with inflammation, overgrowth of pathogens, and a resultant acidic environment [41].

## EFFECTS OF BREAST CANCER TREATMENT IN GENITOURINARY SYNDROME OF MENOPAUSE

The majority of women with BC receive systemic treatment (chemo-, hormonal- or biologic therapies) to reduce their risk of systemic disease. These therapies have significantly improved clinical outcomes but they can lead to biological changes that affect long-term vaginal health and impact quality of life in survivors. Pre- and postmenopausal women can experience symptoms of estrogen deprivation, including VVA[43], at higher rates than age-matched women without BC.

### *Chemotherapy*

In a cohort of premenopausal BCSs receiving chemotherapy (CTx), vaginal dryness was reported by 23.4% of women[44]. CTx can promote a chemotherapy-induced ovarian failure (CIOF). The use of chemotherapy during the first year after the diagnosis of breast cancer significantly increases the risk of CIOF[45-47]. CIOF occurs secondary to CTx agents, which cause follicular destruction[45,47]. Consequently, decreases in the levels of estrogen and progesterone are observed. Forty- and fifty-year-old women undergoing CTx were found to have an increased risk of developing CIOF (40% and 90%, respectively) *vs* an increased risk of CIOF in healthy age-matched forty- and fifty-year-old women (< 5% and 20%, respectively)[47]. Postmenopausal women can also experience increased or recurrent symptoms of estrogen deprivation, depending on the amount of endogenous estrogen circulating in their system, including estrogen produced by the adrenal glands and estrogen stores in body fat.

### *Endocrine therapy*

A total of 70%-80% of all BCSs are estrogen receptor-positive[48]. Endocrine therapy is extremely successful in suppressing circulating estrogen, an effect desired for efficacy. Endocrine therapies for the management of breast cancer include aromatase inhibitors (AIs), tamoxifen (TAM) (a selective estrogen receptor modulator-SERM-) and fulvestrant. These drugs can trigger the onset of VVA or exacerbate existing symptoms[49].

**Aromatase inhibitors:** AIs are frequently prescribed for postmenopausal breast cancer patients[50,51]. Multiple clinical trials have shown that AIs have better clinical outcomes in these patients than SERM; thus, they have become the standard of care[50,51]. These drugs inhibit the activity of the enzyme aromatase, which is utilized to convert androgens to estrogens[52], and significantly reduce plasma concentrations of estrogen from 20 pmol/L to 3 pmol/L or less[35]. These changes explain the commonly reported side effects as vaginal dryness and decreased libido[35]. The increasing use of AIs over SERMs (including for premenopausal women in conjunction with a gonadotropin-releasing hormone agonist- GnRH-a-) suggests that more women may experience new or increased atrophic vaginitis[35,50] than when TAM alone was used. Additionally, the recommended duration of these therapies has been extended from 5 to 10 years[53]. The severity of menopausal side effects, including VVA, may compromise compliance with AIs over time[54].

**Tamoxifen:** Tamoxifen (TAM) has been the most widely used traditional SERM and continues to be prescribed for premenopausal women with ER+BC[55]. TAM acts as an antagonist to estrogen positive breast cancer cells, although it often acts as an agonist to alfa estrogen receptors in the vagina. Hence TAM provides a quasi-estrogenic effect on the vulva and vagina and increases vaginal secretions without the presence of estrogen[35]. Due to its estrogenic effect, the incidence rate of vaginal dryness with TAM is only 8%, compared to 18% with AIs[35]. Therefore, this effect may inhibit the onset of atrophic vaginitis and actually improve existing vaginal dryness induced by CTx or menopause.

**Fulvestrant:** Fulvestrant is a competitive estrogen receptor antagonist that acts as an estrogen receptor downregulator, and is used in patients with metastatic BC[56]. Overall, six studies reported gynaecological toxicity (urinary tract infection, vulvovaginal dryness, vaginal haemorrhage, vaginitis, and pelvic pain) and no difference was observed between fulvestrant and control arms (RR 1.22, 95%CI 0.94 to 1.57; 2848 women; $I^2$ = 66%; $P$ = 0.01; high□quality evidence)[57]. Because of its mechanism of action, rates of GSM may be less when compared with aromatase inhibitors[58] but higher than with tamoxifen therapy.

## SYMPTOMS OF GENITOURINARY SYNDROME OF MENOPAUSE IN BREAST CANCER SURVIVORS

Vulvar and vaginal atrophy (VVA) are major components of the genitourinary syndrome of menopause (GSM). Symptoms of atrophic vaginitis include vaginal dryness, dyspareunia, irritation of genital skin, pruritus, burning, vaginal discharge, and soreness[19,41,59,60].

The related vaginal dryness and dyspareunia are chronic and progressively worsening conditions that affect quality of life (QoL) and intimate relationships in both healthy women and BCSs[36,61]. Atrophic vaginitis can disrupt sexual activity, and lead to problems such as pain with vaginal penetration (dyspareunia), decreased lubrication, and fear of pain with sexual activity[41]. Typical symptoms of atrophic vaginitis usually occur within 4-5 years after a woman's last menstrual cycle[62], but women who undergo menopause at an accelerated rate (CTx, surgical removal or radiation therapy of the ovaries or anti-estrogen therapy) can experience earlier onset of GSM[31,32].

Atrophic vaginitis as a survivorship issue impacts women of all ages. Premature menopause with associated symptoms in young breast cancer survivors may have a profound negative impact on quality of life secondary to sexuality and intimacy changes[58]. Regardless, women of all ages seek to preserve their sexual function and improve their sexual quality of life[63,64]. Many young women are at increased risk for premature menopause following adjuvant treatment for BC. These women must deal with consequences of menopause, including loss of fertility and physiologic symptoms such as night sweats, hot flashes, vaginal dryness, and weight gain. These symptoms can be particularly distressing for young women and can adversely affect both health-related and psychosocial quality of life (QoL). BSC patients in Eastern countries are younger and more likely to have related problems. While there are a wide range of pharmacologic and non-pharmacologic interventions available to help with these symptoms and in turn, improve QoL, there is little data available about the use and efficacy of these interventions in younger women who become menopausal as a result of their breast cancer treatment. Consequently, it is suggested that future studies should focus on this vulnerable population, with the goal of identifying effective strategies to relieve symptoms and improve QoL in young BCSs.

Atrophic vaginitis is prevalent in women with and without breast cancer. Complaints of vaginal dryness were 67% *vs* 49%, fear of pain with vaginal penetration 31% *vs* 19% and irritation from toilet tissue 21% *vs* 9%, respectively[42].

## DIAGNOSIS AND ASSESSMENT OF GENITOURINARY SYNDROME OF MENOPAUSE IN BREAST CANCER SURVIVORS

Validating the effect of GSM on BCSs and the importance of seeking treatment for relieving symptoms and improving quality of life (QoL) is critical. Clinicians should explain the pathophysiology of GSM and review the potential genitourinary effects of breast cancer treatment[65,66]. Despite these bothersome symptoms, few women discuss them with their health-care professional or seek gynecological care[65], in part due to embarrassment, lack of knowledge, and an awareness of menopausal changes. The underdiagnosis and undertreatment of the condition lead to chronicity, disease progression and a considerable impact on women's daily living, despite the currently available therapeutic options. Therefore, it is imperative that clinicians ask both partnered and unpartnered patients about potential physical changes and alterations that can be associated with atrophic vaginitis [5,66,67].

The simplest approach for clinicians to detect sexual problems related to GSM is to start a conversation with the woman when it feels relevant during the encounter. Clinicians can also ask a direct screening question such as, 'Do you have any problems or concerns related to sex or pain with sexual activity?

There are readily available, simple, and effective tools for the identification of symptoms and assessment of the effect on QoL, including the Day-to-Day Impact of Vaginal Aging questionnaire[68] and the Sexual Symptom Checklist for Women After Cancer[69]. The structured approach to incorporating sexuality into clinical practice, devised specifically for patients with cancer, is The BETTER model (B - bringing up the topic, E - explaining the importance of sexuality, T - telling the patient about resources, T - addressing timing, E - educating about sexual side effects of treatment, and R - recording the discussion)[70].

It is important to gain a clear understanding of a woman's genitourinary symptoms and how they affect her QoL and intimate relationship. In addition to a complete history, which includes review of potential medications that might cause vaginal dryness, women with genitourinary complaints should undergo a physical examination before starting treatment. The examination should include visual external inspection, speculum, and bimanual pelvic examination as clinically relevant and to exclude other conditions that might mimic GSM, such as vaginitis, lichen sclerosus, or other dermatopathology.

During an examination, the woman and clinician can review areas of concern, and women can be educated regarding anatomy and instructed in the application of local therapies, using a hand mirror as needed[65].

When assessing women with GSM with a history of breast cancer, it is important for the clinician to identify factors that may affect decision-making[71]. These factors include balancing the risk of recurrence, which is influenced by the stage and grade of the cancer; presence of lymphovascular invasion; hormone-receptor status; use of endocrine therapy; and the time since diagnosis, with the severity of genitourinary symptoms, QoL, and efficacy of conservative therapies. Although data are lacking, based on the consensus recommendations from The North American Menopause Society and

The International Society for the Study of Women's Sexual Health, women with an overall lower risk of recurrence *vs* higher risk; with receptor-negative *vs* receptor-positive disease; using TAM *vs* AIs; and with severe symptoms and greater concerns about quality of life *vs* fewer symptoms and concerns may be better candidates for local hormone therapy[65].

Counseling patients with or at high risk of breast cancer about treatment options for GSM should include a shared decision-making approach employing the principles of informed consent[67]. The discussion about treatment options should include the mechanism of action, if known; potential adverse effects; current data regarding efficacy and safety; as well as the benefits and risks of each treatment option[72]. Clinicians should evaluate the woman's perceived need for treatment *vs* fears regarding breast cancer risk or recurrence risk. Additionally, consultation with a woman's oncology team is suggested[65,73,74]. A recent study found that 41% of breast oncologists refer BCSs to gynecologists for treatment of vulvovaginal atrophy, and 35% manage it independently. Seventy-one percent of oncologists mentioned that the main reason not to prescribe vaginal estrogen therapy is the probability of increased cancer recurrence[31].

Finally, when therapy is initiated, follow-up care should be arranged to ensure improvement in or resolution of symptoms and to assess compliance and barriers to treatment.

## CURRENT TREATMENT OPTIONS FOR GENITOURINARY SYNDROME OF MENOPAUSE IN BREAST CANCER SURVIVORS

The growing awareness of quality-of-life issues in BCSs has done that management of GSM has been increasingly emphasized as a major problem that oncologist should know. The key is to determine the severity of the signs and symptoms of VVA and the degree of discomfort, tailoring the treatment to the individual needs of the patient.

The primary goal for the treatment of genitourinary symptoms is to improve or alleviate symptoms and to reverse the atrophic changes arising from estrogen deprivation[64,75]. Currently available treatments for GSM include both over-the-counter treatments (OTCs), such as nonhormonal vaginal moisturizers and lubricants, and prescription drugs, including local estrogen therapy (LET), intravaginal dehydroepiandrosterone (DHEA), or systemic therapies. These prescription drugs aim to treat the underlying condition of GSM, while OTC drugs only treat the symptoms, such as vaginal dryness, itching, burning and dyspareunia. Ideally, the optimal therapy for estrogendeficiency symptoms is systemic or topical estrogen administration[76]. However, estrogen may be contraindicated in women with a history of hormone receptor-positive breast cancer[77]. As a result, patients and their clinicians are sometimes reluctant to use topical estrogens[78], and effective alternative approaches with nonhormonal lubricants and moisturizers are needed.

Clinician reluctance to treat may reflect the paucity of evidence regarding the safety of currently available therapies for GSM in women with or at high risk of breast cancer[79]. The unintended consequence is that women are driven to untested and non-FDA-approved therapies. In women with a history of breast cancer, the decision of how to treat GSM depends on many factors, including receptor status, genetic characteristics, extent of disease time interval since diagnosis, and response to prior therapies. Care for women with or at high risk of breast cancer would be enhanced by an evidence-based compilation of available GSM treatment options, along with a discussion of the limitations in the science concerning risks specific to this population[16,29,80].

According to international guidelines, nonhormonal therapies are the first-line treatment for mild-moderate VVA. Therefore, survivorship guidelines from the American Society of Clinical Oncology (ASCO)/American Cancer Society (ACS)[81] and the North American Menopause Society[82] recommend the use of nonhormonal therapies, specifically water-or silicone-based lubricants and vaginal moisturizers, as first-line therapy for dyspareunia and vaginal dryness in BCSs. Severe signs or symptoms usually require pharmacological management (local hormonal therapy)[83].

Treatment of GSM in BCSs remains an area of unmet need. Vaginal estrogen is not generally advised, particularly for those on AIs, because it is absorbed in small amounts and raises blood levels within the normal postmenopausal period and could potentially stimulate occult breast cancer cells. The safety of intravaginal dehydroepiandrosterone and oral ospemiphene after breast cancer has not been established. Vaginal laser therapy is being used for VVA in BCSs, but efficacy and safety data from clinical trials are lacking. Therapies such as lasofoxifene, neurokinin B inhibitors and stellate ganglion blockade are undergoing development[84]. To date, there is no consensus on how to treat moderate-severe GSM in BCSs.

### *Lifestyle modifications*

As a first-line therapy for mild symptoms, lifestyle modifications (healthy diet, smoking cessation, losing weight, maintaining adequate vitamin D and calcium levels, limiting alcohol and regular physical activity) may be sufficient[85,86]. Smoking cessation may decrease the atrophic effects due to increased capillary refill[87], while weight loss of 5-10% of total body weight has been shown to improve urinary incontinence (UI)[88].

Sexual activity maintenance should also be encouraged. Regular coitus and masturbation can increase blood flow to the genital area, helping to keep this tissue healthy and maintaining normal vaginal pH [18,39,89]. Vaginal penetration with lubricated fingers or vaginal dilators may prevent fibrotic changes. Scented hygiene products should be avoided as they may reduce normal vaginal flora[18].

### *Control of underlying medical conditions*

Women with pre-existing comorbidities (diabetes, obesity or hypertension) are more likely to develop VVA, UI and sexual dysfunction[90]. Thus, optimal management of these comorbidities may help to improve genitourinary and sexual health[90,91]. Furthermore, underlying depression treatment has been shown to improve both sexual functioning and quality of life (QoL) in breast cancer patients[92]. If an antidepressant is prescribed, an option that may be appropriate for TAM users is the SNRI venlafaxine, which increased libido in women with early breast cancer without interfering with the metabolism of TAM[93], or the SNRI desvenlafaxine[94]. Other options, given their minimal effect on sexual function and no appreciable inhibitory effect on CYP2D6, are mirtazapine and agomelatine[95, 96].

### *Complementary and alternative therapies*

Between 48%-83% of BCSs use at least one type of complementary or alternative therapy following diagnosis[97,98] despite limited evidence of the effectiveness/toxicity of these therapies in managing GSM in these patients[98-101]. This is important because at least half of breast cancer patients do not discuss their use of an alternative therapy with their clinicians[98,101]. Patients who use an alternative or complementary treatment should check with the manufacturer regarding whether the product contains estrogen or other hormones.

**'Natural products':** BCSs are very attracted to 'natural' products and generally have the impression that they are less toxic than conventional medicine[102]. In a clinical trial, dietary supplements with soy, black cohosh, and some other herbs did not show superiority over placebo in relieving a range of genitourinary symptoms[103].

Also, the safety of many of these products is unknown and there may be possible interactions with TAM and unknown effects on breast cancer cells[102]. Indeed, there is increasing concern about the lack of rigorous quality-control measures with regard to purity and levels of 'active compound' by some manufactures of herbal medicines as pointed out by the North American Menopause Society (NAMS) [103]. Clearly, there is the need in the long-term to investigate adequately designed RCTs to determine whether these products are of any help to breast cancer patients experiencing GSM-related symptoms. Most importantly, a risk assessment should be performed to help define their safety. Until such evidence- based data are available, their use merits caution[101].

**Acupuncture and cognitive behavioral therapies:** Stress management may be helpful in decreasing the anxiety associated with fear of painful intercourse[104,105]. There is very limited clinical data on the efficacy of acupuncture and behavioral interventions in the management of GSM in healthy women and none in BCSs. Acupuncture can decrease the urogenital subscale scores on the Menopause Rating Scale [106] and improve bladder capacity, urgency and frequency[107], but there are no evidence-based data [108]. In an RCT, cognitive behavioral therapy, physical exercise and a combination of both significantly decreased urinary symptoms and increased sexual activity in BCSs with treatment-induced menopausal symptoms compared to controls[109]. However, further studies are needed to recommend these treatments in BCSs.

**Nonhormonal vaginal treatments:** Lifestyle modification measures alone are usually insufficient to significantly improve atrophic vaginitis in BCSs. Nonhomonal vaginal therapies may provide additional treatment options to alleviate or improve vaginal dryness, irritation and itching by increasing vaginal moisture[104,105,110]. Local nonhormonal therapies include vaginal moisturizers, vaginal lubricants, vaginal pH-Balance Gel, vaginal autologous platelet-rich plasma (A-PRP) and avoidance of perfumed soaps and toilet tissue, rubber products, synthetic garments including panties, and certain fabric softeners[59]. Clinicians treating BCSs need to inquire about type and severity of their symptoms and the individual women's expectations of treatment. So, if the most important concern for a woman is pain during intercourse, lubricants during sexual intimacy[110] may be recommended[78]. Additionally, adding vaginal moisturizers on a regular basis may promote hydration of the epithelium, providing more long-term (a few d) relief of symptoms such as itching, irritation and dyspareunia[111]. However, these therapies are not able to reverse atrophy once it occurs, and they may not completely solve the problem, especially in women with severe symptoms. Nevertheless, the evidence to support the efficacy of these formulations is limited (level II)[111]. Carter *et al*[112] (2011) developed a patient handout that summarizes how to best use vaginal lubricants, moisturizers and pelvic floor exercises.

According to international guidelines, nonhormonal therapies are the first-line treatment for mild-moderate VVA in both healthy women and BCSs[113]. According to a systematic review carried out this year (2021) by Mension *et al*[114] about current treatment options for genitourinary syndrome of menopause in BCSs, there are 10 studies related to nonhormonal options (excluding laser therapy) (4 prospective studies and 6 randomized controlled trials (RCTs)) (Table 1).

**Table 1 Non-hormonal treatments (Classic moisturizers and lubricants and innovative preparations) in breast cancer survivors: Summary of studies and their outcomes**

| Ref. | Yr | n[1] | Design | Treatment | Conclusion |
|---|---|---|---|---|---|
| Loprinzi *et al* [119] | 1997 | 45 | A double-blind, crossover, randomized clinical trial | Vaginal lubricating preparation, (Replens®) | Both Replens and the placebo appear to substantially ameliorate vaginal dryness and dyspareunia in breast cancer survivors |
| Lee *et al*[129] | 2011 | 44 *vs* 42 | Randomised controlled trial, double blinded | pH balanced gel *vs* placebo for 12 wk | Vaginal pH balanced gel could relieve vaginal symptoms |
| Juraskova *et al* [137] | 2013 | 25 | Prospective, observational study | polycarbophil-based vaginal moisturizer + olive oil as a lubricant during intercourse | Significant improvements in dyspareunia, sexual function, and quality of life over time |
| Goetsch *et al* [130,131] | 2014 2015 | 46 | Double-blind rct | 4% aqueous lidocaine *vs* saline | Significative and safe reduction in dyspareunia |
| Hickey *et al* [128] | 2016 | | In a single-center, randomized, double-blind, ab/ba crossover design | Water- *vs* silicone-based lubricants | Total sexual discomfort was lower after use of silicone-based lubricant than water-based |
| Juliato *et al* [126] | 2017 | 25 *vs* 25 | Randomised trial | Polyacrylic acid *vs* lubricant | Polyacrylic acid was superior to lubricant |
| Marschalek *et al*[136] | 2017 | 11 *vs* 11 | Randomised controlled trial, double blinded pilot study | Vaginal lactobacillus capsules *vs* placebo | Lactobacillus improves microbiota in BCSs |
| Hersant *et al* [139] | 2018 | 20 | Prospective, comparative (before/after) pilot study | A-PRP and evaluated at 0,1,3 and 6 mo | A-PRP improves vaginal mucosa in 6 mo treatment according VHI criteria |
| Chatsiproios *et al*[125] | 2019 | 128 | Open, prospective, multicentre, observational study. | oil-in-water emulsion during 28 d | This treatment seems to improve VVA symptoms with a short treatment |
| Carter *et al*[122] | 2021 | 101 | Single-arm, prospective longitudinal trial | Hyaluronic acid (HLA) vaginal gel for 12 wk | HLA moisturization improved vulvovaginal health/sexual function of cancer survivors |

[1]Cases *vs* control/placebo/other treatment. BC: Breast Cancer, BCSs: Breast cancer survivors; A-PRP: Autologous platelet-rich plasma; VHI: Vaginal Health Index.

**Vaginal moisturizers:** Vaginal moisturizers intend to replace normal vaginal secretions and maintain tissue integrity, elasticity, and pliability and should be used on a regular basis independent of sexual activity[105].

Although there is limited data to support the efficacy of over-the-counter products[113,114], vaginal moisturizers and lubricants are considered the initial and mainstay treatment options for GSM in women with breast cancer[40], and they are widely used[18], particularly for women with mild symptoms and those who want to avoid local estrogens[18,40]. However, these products are poorly differentiated and characterized[112].

In GSM induced by oncology treatment and with menopausal hormone treatment (MHT) contraindications, everyday use of a paraben-free with acidic pH and low osmolality vaginal moisturizer is indicated[115].

A 12-wk multicenter RCT compared vaginal estradiol tablets *vs* vaginal moisturizers *vs* placebo. All three groups demonstrated similar reductions in the most bothersome symptoms, with no evidence for the superiority of vaginal moisturizers or 10-mcg vaginal estradiol tablets over placebo gel[116].

In some studies, polycarbophil-based nonhormonal moisturizers (Replens©) were demonstrated to be more effective than lubricants and even as effective as vaginal estrogen creams in improving vaginal moisture, fluid volume, pH, and elasticity, as well as reducing dryness, itching, and dyspareunia[117,118]. This effect is not sustained over time unless the moisturizer is used on a regular basis[117,118]. However, in a double-blind, crossover randomized controlled trial (RCT) assessing 45 BCSs with a history of vaginal dryness or itching, a polycarbophil-based vaginal moisturizer was no more effective than placebo in relieving vaginal dryness and dyspareunia[119].

**Vaginal hyaluronic acid:** Another non-hormonal option is hyaluronic acid vaginal gel. Hyaluronic acid (HLA) releases water molecules into the tissue, thus alleviating the dry state of the vagina and also plays a role in tissue repair. RCTs comparing hyaluronic acid with estrogen cream in postmenopausal women found that both significantly improved clinical symptoms of vaginal dryness in women without breast cancer[120]. Moreover, Jokar *et al*[121], in an RCT, found that improvement in urinary

incontinence, dryness, the maturation index, and composite score of vaginal symptoms was better in the HLA group than in the estrogen cream group.

In a very recent prospective study (2021) including 101 postmenopausal patients with hormone receptor-positive breast and endometrial cancer, treatment with a hyaluronic acid vaginal gel for 12 wk. improved the vulvovaginal health/sexual function of cancer survivors. While HLA administration at 1-2×/week is recommended for women in natural menopause, a 3-5×/week schedule appeared to be more effective for symptom relief in cancer survivors[122]. One year earlier, these authors demonstrated that the HLA-based gel improved vulvovaginal health and sexual function in 43 endometrial cancer survivors in their perceived symptoms and clinical exam outcomes[123].

**Vaginal lubricants:** Lubricants (water-, glycerin- or silicone-based products) are designed to be applied during sexual activity, with direct application to the external genitalia, vaginal introitus, and vaginal mucosa to reduce friction and discomfort. Lubricants are shorter acting than moisturizers and have no effect on vaginal pH or underlying moisture content due to the ingredients and manufacturing of the product. The World Health Organization (WHO) suggests the use of lubricants with an osmolality of < 380 mOsm/kg, but most available lubricants do not list osmolality on the product label and have higher osmolality associated with mucosal irritation[117]. Lubricants with pH levels ≤ 3.0 are considered unacceptable for human use, given their association with vaginal irritation in animal models[124]. Additives (parabens, glycerin, flavors, and spermicides) should be avoided because they may irritate vaginal and vulvar tissues.

In dyspareunia induced by an oncology treatment and with MHT contraindicate, use of a paraben-free vaginal with acid pH and low osmolality lubricant during sexual intercourse is indicated[117].

In a prospective multicenter observational study by Chatsiproios *et al*[125], who evaluated the effect of an oil-in-water emulsion for 28 d in 128 patients diagnosed with BC and managed with chemotherapy or hormonal therapy, the authors concluded that there were improvements in symptom frequency after treatment and that the cream was an effective and safe nonhormonal topical option in the treatment of vulvovaginal dryness symptoms in patients undergoing breast cancer treatment. However, the study duration and follow-up time during 4 wk. as well as the non-randomized trial design are limitations of the study. The quality assessment (Qa) was fair.

Polyacrylic acid appeared to be superior to lubricants according to a randomized trial conducted by Juliato *et al*[126]. Fifty-two women (25 polyacrylic acid *vs* 25 Lubricant) with breast cancer who were being treated with TAM and who complained of vaginal dryness were evaluated. There was improvement in the female sexual function index (FSFI) after both treatments.

The polyacrylic acid group showed a decrease in sexual dysfunction from 96% to 24% ($P < 0.0001$) and the lubricant group showed a decrease from 88.9% to 55.6% ($P = 0.0027$). Polyacrylic acid was superior to the lubricant in treating sexual dysfunction [Qa = Good]. Products that contain glycerin may provide improved comfort during sexual activity as compared to water-based products. Silicone-based products may last longer than either water- or glycerin-based products. The ideal combination is to insert polycarbophil gels intravaginally 4-7 times per week, and utilize generous amounts of a glycerin-based vaginal lubricant before and during sexual activity[43]. This combination not reverse vaginal atrophy, but may provide additional short-term comfort during sexual activity.

Although the use of water-based lubricants are advised in cancer survivors[127], recent findings suggested that silicone-based lubricants may be more effective in treating discomfort during sexual activity in postmenopausal women with breast cancer, although both therapies were unlikely to reduce sexually-related distress[128].

**Vaginal pH-balanced gel:** A double-blinded RCT using vaginal pH-balanced gel in postmenopausal BCSs suffering from atrophic vaginitis was conducted in 2011. A total of 88 BCSs were randomly assigned to receive either pH-balanced gel (with lactic acid, pH 4 to 7.2) or placebo. The treatment was used three times per week for 12 wk. The pH-balanced gel provided significant ($P = 0.001$) improvements in vaginal dryness and dyspareunia compared to placebo and was effective in reducing the vaginal pH ($P < 0.001$). In addition, the pH-balanced gel enhanced vaginal maturation index ($P < 0.001$) and vaginal health index ($P = 0.002$). No significant difference in adverse events between the two gels was noted with minimal side effects (mild irritation during the first four wk. of therapy administration). These findings suggest that vaginal pH-balanced gel is an alternative option to alleviate vulvovaginal symptoms in symptomatic patients and can ultimately protect against vaginal colonization by nonvaginal microflora, which predisposes women to vaginal infections and UTIs[129].

**Vulvar lidocaine:** For women with pain isolated at the vulvar vestibule with penetration, topical lidocaine may provide relief[130]. A double-blinded RCT evaluating 4% aqueous lidocaine *vs* saline applied with a cotton ball to the vestibule for 3 minutes before vaginal penetration for insertional dyspareunia in 46 postmenopausal survivors of breast cancer with severe GSM for 4 wk. showed a significant reduction in dyspareunia of 88% *vs* 33% with saline ($P = 0.007$) and may be considered a safe option for painful intercourse in BCSs[131].

**Vitamins E and D:** Vaginal application of vitamin E capsules before intercourse increases vaginal

lubrication and provides some atrophic-related symptom relief[100,132]. Oral vitamin D supplementation may help squamous maturation of the vaginal epithelium [133], but there were no significant improvements in vulvovaginal symptoms or pH[134]. The available evidence does not support the use of vitamins for relief of genitourinary symptoms[3].

**Vaginal/oral probiotics:** Oral and vaginal probiotics to change the vaginal microbiota could possibly be beneficial for the treatment of symptoms of GSM, but comprehensive trials are needed for validation [135]. A prospective, randomized, double-blinded trial (2017) evaluating new options, such as capsules including Lactobacillus, for the maintenance of the vaginal microbiota in women with breast cancer during chemotherapy was shown to be useful. The quality assessment (Qa) was good[136].

**Olive oil, vaginal exercise, and moisturizer:** The OVERcome study (Olive Oil, Vaginal Exercise, and Moisturizer) resulted in significant improvements in quality of life, sexual function, and dyspareunia *(P* < 0.001). Maximal benefits were noted after 12 wk. of intervention. However, the quality of this study was very poor, with only 25 breast cancer patients recruited[137]. There is concern regarding the use of natural oils (*e.g.*, olive and coconut) for lubrication because these products are associated with vaginal infections[138].

**Vaginal autologous platelet-rich plasma:** Other recent options (2018) include autologous platelet-rich plasma (A-PRP), which was demonstrated in 20 patients with diagnosed BC, with a median age of 60.8 years, to improve vaginal mucosa following 6 mo. of treatment according to the Vaginal Health Index (10.7 to 20.75; $P < 0.0001$) in a prospective, comparative (before/after) pilot study [Qa = Fair][139].

**Vaginal dilators:** In addition to the use of vaginal moisturizers and lubricants, regular use of vaginal dilators has been recommended for symptomatic vaginal atrophy[40] and has been found to reduce pain with vaginal penetration by improving vaginal elasticity[140].

Patients should be counseled regarding the use of vaginal dilators of graduated sizes (either by themselves or with their partners) to promote stretching of vaginal tissues. Vibratory stimulation, applied either to the vagina or directly to the clitoris, has also been studied as a modality to reduce pain with vaginal penetration[141]. Finally, pelvic floor therapy under the care of a physical therapist trained in the management of pelvic floor disorders is recommended to reduce pain with vaginal penetration; physical therapists may also be helpful in the education of vaginal dilator therapy[142,143].

In summary, among nonhormonal therapies there are multiple options to treat symptoms of dyspareunia and daily wellbeing. However, these compounds do not reverse atrophy, and neither do they improve vaginal epithelium characteristics, and hence, the improvement observed is temporary and short term. These therapies are usually lubricants and moisturizer agents composed by non-hormonal substances, mainly based on water, silicone or vegetable oil. Water-based agents have fewer side effects compared to oil-based products[29].

The main limitation of non-hormonal therapies is the short-term efficacy. Among the trials included in this systematic review, 85% described efficacy with a 30-day follow-up or less. Further studies evaluating longer follow-up periods would be of interest.

The lack of data on hormonal receptor status and adjuvant treatments in the studies reviewed, as well as the absence of hormone levels and information about BC recurrence after treatment did not allow these trials to make conclusions in relation to safety. Nonetheless, from general population trials, it can be extrapolated that there is a low risk of potential side effects from nonhormonal therapies used for climacteric symptoms[144].

### *Hormonal treatment*

When nonhormonal methods fail in symptomatic survivors, local short-term hormonal therapy may be considered, following appropriate counseling and assessment of riskbenefits balance[145].

Whether the antiestrogen effect is induced by SERMs (tamoxifen or raloxifene) or by lowering endogenous estrogen production (e.g., bilateral oophorectomy, ovarian suppression with GnRH agonists, use of AIs), the goal of reducing the estrogen environment to lower breast cancer risk has remained the same. Therefore, both systemic and local estrogen-based treatments are controversial or discouraged for women with a history of or at high risk of breast cancer[81].

**Systemic estrogen or estrogen/progestogen treatment:** Healthy women can expect up to a 75% reduction in frequency and 87% reduction in severity of symptoms of GSM when prescribed systemic estrogen[146].

To date, there is a consensus in the literature that estrogen administration in BCSs or in women at high risk of BC should only be prescribed topically, since systemic administration has been shown to increase the risk of BC occurrence or recurrence[147] and is formally contraindicated by international guidelines (International Menopause Society-IMS)[148]. This consensus is supported by the results of two Swedish RCTs of systemic hormone therapy (HT) in survivors of early breast cancer. In 2001, the pivotal HABITS study (Hormonal Replacement Therapy After Breast Cancer—Is It Safe?) was conducted by Holmberg *et al*[149]. The authors studied the effects of systemic hormone replacement

therapy on breast cancer recurrence among Scandinavian BCSs. A total of 434 women who had completed treatment of stage 0 to II breast cancer with symptoms of menopause were randomly assigned to receiving cyclic or continuous combination hormonal therapy (HT) with estradiol hemihydrates and norethisterone acetate. In 2003, it was prematurely stopped after a median follow-up of 2.1 years because of a statistically significant increased breast cancer recurrence in the HT group *vs* non- HT group (HR of 3.5 (95%CI, 1.5 to 8.1). The HABITS study showed that BCSs who received HT not only had a higher risk of breast cancer recurrence but also a higher risk of adverse events than BCS patients receiving the best symptomatic treatment without hormones. A four-year follow-up of the study sample found that women in the hormone replacement therapy group had twice the rate of a breast cancer event as compared to the control group (HR = 2.4).

Another RCT (The Stockholm trial)[150] also studied BCSs ($n$ = 378) randomized to hormonal therapy or nonhormonal therapy for symptoms related to lack of estrogen. Hormonal therapy included cyclic estradiol and medroxyprogesterone acetate or estradiol valerate alone or non-HT. The trial, similar to HABITS, prematurely ceased due to safety concerns of breast cancer recurrence. In contrast to the HABITS trial, the Stockholm trial did not actually find an increase in breast cancer recurrence after a median follow-up period of 4.1 years in the hormone replacement study arm (HR = 0.82; 95%CI, 0.35 to 1.9). However, there was statistically significant ($P$ = 0.02) heterogeneity in the rate of recurrence between the two studies, and the Stockholm trial investigators concluded that HT may be associated with the recurrence of breast cancer. On the basis of these studies, HT is currently contraindicated in BCSs because of an increased risk of breast cancer recurrence or new primary development.

**Tibolone:** Tibolone is a synthetic steroid that, after absorption, is rapidly converted to three active metabolites (with weak estrogenic, progesterogenic, and androgenic properties) that bind to estrogen receptors in the vagina. In a nonrandomized, open-label study of healthy postmenopausal women ($n$ = 113), the use of tibolone over six years reversed vaginal atrophy and improved symptoms[151]. Later, tibolone was shown to improve vaginal dryness and may have a favorable effect on sexual function [152].

The Livial Intervention Following Breast Cancer; Efficacy, Recurrence and Tolerability Endpoints (LIBERATE) trial has been the most important study of the relationship between tibolone and BCSs[153, 154]. This prospective randomized placebo controlled study was conducted to evaluate the safety of tibolone in BCSs ($n$ = 3098) (1556 in the tibolone group and 1542 in the placebo group). The study showed that tibolone (2.5 mg) was effective in improving menopausal symptoms, including vaginal dryness and enhanced QoL in BCSs, but the trial was terminated early due to an increase in breast cancer-related events in the tibolone arm. After a median follow-up of 3.1 years, 237 of 1556 (15.2%) women on tibolone had a significantly increased risk of breast cancer recurrence compared with 165 of 1542 (10.7%) on placebo (HR 1.40 [95%CI 1.14-1.70]; $P$ = 0.001). Therefore, the use of tibolone was contraindicated after breast cancer, with the authors warning that any off-label use incurred a now proven risk[154]. The IMS has supported this recommendation[155].

**Bazedoxifene:** Two RCTs provided data for consideration of bazedoxifene, a Selective Estrogen Receptor Modulators (SERM), combined with conjugated equine estrogens (BZA/CE) to treat symptoms of postmenopausal vulvovaginal atrophy. In the first study, healthy, postmenopausal, nonhysterectomized women ($n$ = 652) with symptoms of moderate to severe vulvar/vaginal atrophy were randomized to different doses with BZA/CE or placebo. Treatment with BZA/CE for 12 wk. was shown to significantly improve sexual function and quality-of-life measures in symptomatic healthy postmenopausal women. As a single agent, bazedoxifene alone was not effective in relieving vulvovaginal symptoms. It remains unknown whether this combination will be safe and well tolerated in women with breast cancer[156].

Kagan *et al*[157] showed similar results in another RCT in which they concluded that BZA/CE was effective in treating moderate to severe VVA and vaginal symptoms. Because no studies have investigated drug safety in BCSs, it should not be recommended in these women.

**Ospemifene:** Ospemifene is a systemically administered SERM with therapeutic options for women with moderate-severe VVA and estrogen contraindications[82]. Comprehensive studies of ospemifene demonstrated an improvement in the vaginal maturation index and relief of most VVA symptoms in healthy women, as well as improvement in measures of sexual wellbeing[158]. At a dose of 60 mg per day, ospemifene significantly reduced the severity of dyspareunia, had a beneficial effect on vaginal dryness[159], improved vulvar vestibular symptoms and normalized the vulvar vestibular innervation sensitivity[160], and improved bone mineral density. The levels of estradiol remained within the normal postmenopausal range, with mean estradiol levels similar to baseline at week 12, and seemed to have an anti-estrogenic effect at the endometrial and breast levels[161]. It is approved by The US Food and Drug Administration (FDA) and by The European Medicine Agency (EMA). The NAMS recognize ospemifene as a nonestrogen therapy to improve vaginal symptoms of GSM and sexual dysfunction due to dyspareunia[82].

Coadministration of ospemifene with drugs that inhibit CYP3A4, CYP2C9 CYP2C19 may increase the risk of adverse reactions. Ospemifene has a good safety profile. The most common treatment-emergent adverse events in clinical trials were hot flushes (7.5% *vs* 2.6% for ospemifene *vs* placebo), vaginal

discharge (3.7% *vs* 0.3%) and headache (3.1% *vs* 2.4%)[162]. The safety of using ospemifene concomitantly with estrogens or other SERMs, such as TAM (indicated for BC patients), has not been studied, and its concurrent use is not recommended. Therefore, ospemifene could be used for the treatment of VVA only once BC treatment, including adjuvant therapy, has been completed[82].

The most important property of ospemifene is that preclinical and clinical data demonstrated its antiestrogenic effect on breast tissue[163,164]. There are no clinical data showing that ospemifene would increase the risk of BC, and similar to other SERM, the data suggest that ospemifene acts as an antiestrogen in breast tissue and is more likely to have beneficial than detrimental effects[164]. However, the follow-up periods of these trials were too short to conclude the long-term effects of ospemifene[59,164].

Despite antiestrogenic effects on the breast in preclinical trials, the effects of ospemifene on breast density or breast cancer risk have not been systematically established in healthy women, nor has ospemifene been studied in women with breast cancer. Although it is not contraindicated for women in Europe with a history of breast cancer who have completed treatment[165], the United States Food and Drug Administration (FDA) does not recommend ospemifene for women at risk or with a history of BC or those with known or suspected estrogen-dependent neoplasia[82].

There are no differences in ospemifene-related improvements in symptoms of vulvar and vaginal atrophy in women with and without a history of BC[166], but there was a very small posthoc analysis in which is had an efficacy comparable to that of estrogenic treatments[167]. Bin Cai *et al* (2020)[168], in a retrospective matched cohort study, reported similar BC incidence rates per 1000 person-years of 2.03 (95%CI: 1.06-3.91) for treated patients and 3.53 (95%CI: 2.49-4.99) for controls (RR = 0.58, 95%CI: 0.28-1.21). Moreover, no difference in recurrence was observed between ospemifene-treated and matched untreated patients: 10 (32.3%) treated *vs* 25 (40.3%) controls in the 1:2 matched analysis.

According to the available evidence, ospemifene seems safer from the perspective of breast tissue. Therefore, it is a first-choice treatment in these cases at the end of adjuvant treatment until breast safety studies are conducted in which ospemifene will be directly compared to vaginal or systemic estrogens [167].

Information from three RCTs and one retrospective matched cohort study regarding systemic hormone treatment in BCSs is shown in Table 2.

**Vaginal estrogens:** The use of local hormone therapies (LHT) may be an option for some women who fail to resolve symptoms with nonpharmacologic and nonhormonal treatments after a discussion of risks and benefits plus review with an oncologist (Table 3).

Vaginal estrogen products are the most effective and sole intervention for menopausal symptoms limited to vaginal atrophy[19,50,64] compared to oral hormone menopausal therapy(HMT)[147].

A Cochrane review[169] of 30 randomized controlled trials of low to moderate quality including 6235 postmenopausal women showed that the local estrogenic preparations, in the form of creams, tablets and the estradiol-releasing vaginal ring, appeared to be equally effective in relieving the symptoms of VVA but there was a very small posthoc analysis in which is had an efficacy comparable, and a higher proportion of these women reported improvement in symptoms compared to those who received placebo. Also, adequate estrogen therapy act on the vaginal mucosa increasing its thickness, revascularizing the epithelium and increasing the number of superficial cells, thereby decreasing vaginal pH and restoring the vaginal microflora, increasing vaginal secretions, and decreasing vaginal dryness and resultant dyspareunia[76]. The evidence to support a role of systemic estrogen therapy in the management of urinary tract symptoms was conflicting according to a 2012 Cochrane review[170]. However, the authors suggested that the use of local (vaginal) estrogen therapy for incontinence may be beneficial (RR 0.74; 95%CI: 0.64-1.48), and less frequency and urgency were also reported[170].

Local therapies include estradiol-releasing intravaginal tablets, low-dose estrogen vaginal inserts, estrogen-based vaginal creams, and estradiol-releasing vaginal rings. All forms of vaginal estrogen therapies have similar rates of effectiveness but different levels of systemic absorption[171]. All preparations result in a minor degree of systemic absorption but do not exceed normal postmenopausal levels [172]. Vaginal estrogen absorption is variable and largely depends of potency of estrogenic ingredient, frequency and duration of use and also varies according to the condition of the vagina (atrophic *vs* estrogenized)[171]. The thin, atrophic vagina is highly absorptive, and this diminishes when the epithelium thickens in response to estrogenization of the vaginal mucosa[173]. In an atrophic mucosa, there is increased absorption, decreasing the level of estrogen absorbed once there is improvement in epithelium quality[174]. Whether a very small increase in estradiol exposure will stimulate quiescent, occult breast cancer cells or contribute to the development of breast cancer is not known. Preclinical data have shown that long-term estrogen deprivation can result in a state of estradiol hypersensitivity, to both proliferation and apoptosis[171], but it is not clear which effect would predominate.

The estrogen most commonly used in these preparations is estriol, which is a weak action estrogen. However, while clearance is more rapid, if used in a manner in which serum levels are consistently elevated, estriol can act as a systemic estrogen; therefore, the same cautions as with vaginal estradiol use are applied. Estriol vaginal preparations (gels, creams, and suppositories) are available in many countries but not in the United States. RCTs have found benefits for vaginal symptoms in healthy postmenopausal women[175]. Limited evidence reported in a small RCT suggested that 0.5 mg of

**Table 2 Systemic hormonal treatments in breast cancer survivors: summary of studies and their outcomes**

| Ref. | Yr | n[1] | Design | Treatment | Conclusion |
|---|---|---|---|---|---|
| Holmberg *et al*[147,149] | 2004 2008 | 221 *vs* 221 | Randomized, non-placebo-controlled noninferiority trial | Oral estradiol hemihydrate and Norethisterone (cyclic or continuous) *vs* control | In BCSs, an increased risk of new breast cancer events and adverse events were observed after 2 yr of therapy (HR = 2.4) |
| von Schoultz *et al*[150] | 2005 | 188 *vs* 190 | Randomized, non-placebo-controlled noninferiority trial | 2 mg estradiol for 21 d with addition of 10 mg medroxyprogesterone acetate for last 10 d; or 2 mg estradiol for 84 d with 20 mg medroxyprogesterone acetate for last 10 d; or 2 mg estradiol valerate daily | No increased risk of breast cancer recurrence; trial was closed early. So, HT doses of estrogen and progestogen and treatment regimens for menopausal hormone therapy may be associated with the recurrence of breast cancer |
| Kenemans *et al*[153] | 2009 | 1556 *vs* 1542 | Prospective randomized placebo controlled | Tibolone 2.5 mg daily or placebo | Trial was closed early. Tibolone had a significantly increased risk of breast cancer recurrence |
| Cai *et al*[168] | 2020 | 1728 *vs* 3456 | Retrospective matched cohort study | Incidence rate in ospemifene users *vs* untreated patients | No differences were observed in the BC incidence and recurrence rates in ospemifene users compared with matched controls |

[1]Cases *vs* control. BC: Breast cancer, BCSs: Breast cancer survivors.

vaginal estriol cream may also prevent recurrent urinary tract infection (UTIs)[176].

The use of estriol rather than estradiol has been suggested for BCSs since its metabolic clearance is more rapid[177]. Dew *et al*[178] in a retrospective cohort study with a follow-up of 5.5 years, administered estriol 0.5 mg cream and pessaries or estradiol 25 μg tablets in a study group of confirmed BC patients with VVA or without VVA as a control, among whom 48% were using TAM, and found that vaginal estrogen therapy does not seem to be associated with an increased relative risk (HR = 0.57; 95%CI: 0.20-1.58, *P* = 0.28) [Qa = Poor]. Biglia *et al*[179] in a prospective study (12 wk) with 31 postmenopausal BCSs not using AIs (TAM or Gn-RH analogs were permitted) and 18 receiving vaginal estrogen therapy (VET) (estriol 0.25 mg, estradiol 12.5 ng or 2.5 g Replens), concluded that VET was effective in improving symptoms and objective evaluations in BCSs, but they did not describe any results on safety [Qa = Good]. In a prospective, randomized study of 10 postmenopausal women with breast cancer who were taking AIs, a two-wk span of daily 0.5 mg vaginal estriol did not increase serum estrogen or estradiol levels but significantly decreased gonadotropin levels, indicating that the systemic effects have to be kept in mind when offering vaginal estriol to BCSs receiving an AI[180]. In one 12-week, open-label pilot study of 16 women with a history of breast cancer taking AIs, a 0.03 mg estriol tablet in combination with lactobacilli improved vaginal symptoms in 100% of patients (effective), and no changes in estradiol or estrona with a small transient increase in estradiol levels were found (safe) [Qa = poor][181,182]. Estriol is not FDA approved for any indication and must be used as an off-label hormone option.

There were no associations between the use of local low potency estrogen therapy and different breast cancer histologies, ductal or lobular, in a population-based case-control study. Only the estimates for tubular cancer were not significantly above unity, with no trend of increased estimates for longer vaginal estrogen use[183].

According to the current recommendations of the North American Menopause Society, the use of low-dose vaginal estrogen treatment is accepted if there is no improvement when using nonhormonal treatments in BCSs with VVA. The lowest effective dose must be administered, starting with the so-called "ultra-low-dose", which has shown efficacy in healthy postmenopausal women[184]. However, the use of low-dose vaginal estrogen in BCSs receiving AIs has been discouraged by the American Cancer Society/American Society of Clinical Oncology[81]. Therefore, currently there is some reluctance to use local estrogen therapy in BCSs because of its potential adverse effects, with up to 70% of oncologists managing BCSs not prescribing hormone therapies. There is fear of interferences with adjuvant treatments, such as TAM or AIs, which may result in an increased risk of BC recurrence[31].

Observational studies have suggested the relative safety of local estrogen treatment, although definitive placebo-controlled RCT data are lacking. A large Finnish observational study identified no elevated risk of de novo breast cancer associated with the use of vaginal ET[185]. Crandall *et al*, in 2018, reported no increased breast cancer risk in healthy participants in the Women's Health Initiative (WHI) observational study despite a very large sample size and duration of follow-up[186].

The results of observational studies are reassuring, at least when vaginal estrogen was administered concurrently with TAM[178,187,188]. Therefore, vaginal estrogens may be appropriate for women with severe urogenital symptoms who use TAM because competitive interaction with the estrogen receptor prevents mild serum estradiol elevations from increasing the risk of breast cancer[189]. Le Ray *et al*[187] conducted a retrospective, nested case-control study of women with breast cancer (*n* = 13479) who used concomitant TAM (*n* = 1 0806) or AIs (*n* = 2673) and local estrogen. Overall, the risk of recurrence in cases treated with local estrogen was not increased compared to the control group (RR: 0.78, 95%CI,0.48-

**Table 3 Local hormonal treatments in breast cancer survivors: summary of studies and their outcomes**

| Ref. | Yr | *n*[1] | Design | Treatment | Conclusion |
|---|---|---|---|---|---|
| Dew *et al* [178] | 2003 | 69 | Retrospective Cohort study | Estriol 0.5 mg cream and pessaries (33); Estradiol 25 µgtablets (*n* = 33) | VET does not seem to be associated with increased RR of BC |
| Kendall *et al*[190] | 2005 | 7 | Prospective before-after analysis | Estradiol 25 mg daily for 2 wk | Vaginal estradiol tablet significantly raises systemic estradiol levels. This reverses the estradiol suppression achieved by AIs in women with BC and is contraindicated |
| Biglia N *et al*[179] | 2010 | 26 | Prospective study | Estriol cream 0.25 mg (*n* = 10) or estradiol tablets 12.5 microg (*n* = 8) polycarbophil-based moisturizer 2.5 g (Replens®) (*n* = 8) | VET is effective in improving symptoms and objective evaluations in BCSs |
| Pfeifer *et al* [180] | 2011 | 10 | Prospective before-after analysis | 0.5 mg vaginal estriol daily for 2 wk | Increase in FHS and LH may indicate systemic estradiol effects |
| Whiterby *et al*[201] | 2011 | 21 | Phase I/II pilot Before-After study | Testosterone cream daily for 28 d. 300/ 150 µg | Vaginal testosterone was associated with improved signs and symptoms of vaginal atrophy related to AI therapy without increasing estradiol or testosterone levels |
| Wills *et al* [49] | 2012 | 24 *vs* 24 | Prospective clinical trial | 25 mcg estradiol vaginal tablet or ring *vs* control | VET treatment increases E2 levels. Should be used with caution |
| Le Ray *et al* [187] | 2012 | 13479TAM (*n* = 10806) or AIs (*n* = 2673) | Retrospective, nested case-control study | Vaginal cream and tablets containing estrogen | Use of VET is not associated with increase in BC recurrence in those treated with TMX or AI |
| Dahir *et al* [202] | 2014 | 13 | Pilot before-after study | Testosterone cream daily for 28 d, 300 µg | Improvement in FSFI scores |
| Donders *et al*[181] | 2014 | 16 | Open label bicentric phase I pharma-cokinetic study | 0.03 mg Estriol + Lactobacillus | Estriol + Lactobacillusis safe in BCpatients andimprovessymptoms |
| Melisko *et al*[204] | 2016 | 69 | Randomised non-comparative study | Estradiol ring 7.5 ng *vs* Testosterone cream at 1% concentration: 1.5 mg/wk | Transient increase in E2 that finally reached normal levels. Meets the primary safety endpoint |
| Davis *et al* [203] | 2018 | 44 | Double-blind, randomised, placebo-controlled trial | Testosterone cream daily for 26 week/ 300 µg *vs* placebo | Testosterone improves sexual test items compared to placebo |

[1]Cases *vs* control. BC: Breast cancer, BCSs: Breast cancer survivors; TAM: Tamoxifen; AIs: Aromatase inhibitors; VET: Vaginal estrogen treatment; FSFI: Female Sexual Function Index.

1.25). In stratified analyses, the risk was likewise not increased in those women on TAM (RR: 0.83, 95%CI,0.51-1.34). In women taking AIs, the risk was not estimable as no women experienced a recurrence. It is important to highlight the retrospective design and the short follow-up of 3.5 years of this trial, which may be too short to show survival outcomes, and thus, lead to uncertainty regarding the data.

Regarding the use of low-dose vaginal estradiol in BCSs receiving AIs, Kendall *et al*[190] in a prospective study, measured serum estrogen levels in patients on adjuvant AIs therapy for BC (*n* = 7) and using 25 mcg estradiol vaginal tablets for severe symptoms of atrophic vaginitis daily for 2 wk. At 2 wk of analysis, estradiol increased 83%, and at 10 wk., it increased by 66%. The authors concluded that vaginal estradiol tablets significantly raised systemic estradiol levels, at least in the short term. This effect would reverse the estradiol suppression achieved by AIs in women with breast cancer and is contraindicated [Qa = Fair]. Similarly, Wills *et al*[49], conducted a prospective clinical trial of postmenopausal women with estrogen receptor-positive breast cancer or at high risk of breast cancer (*n* = 24) who were taking AIs or SERM and VET (25 mcg estradiol vaginal tablet or ring) for ≥ 90 d for atrophic vaginitis and 24 controls taking AIs only. They concluded that VET, regardless of type, resulted in elevated circulating E2 Levels in this population, even with cornification of tissue, and should be used with caution [Qa = Fair]. Therefore, these studies do not provide robust evidence regarding the safety of vaginal estrogens in BCSs taking AIs, whose efficacy is due to markedly suppressed estrogen levels[49, 190]. Nevertheless, Santen *et al*[191] reported that the increased levels of serum estradiol resulting from vaginal estrogen use may not exceed the normal range of postmenopausal serum estradiol. But, there is a lack of clarity regarding whether higher levels within a narrow postmenopausal range associate with increased risk for breast cancer recurrence, and similarly, whether lower levels are reassuring[49]. In addition, unmeasurable levels by commercially available estrogen assays can still mediate changes in distant tissues (*i.e.*, bone or liver).

Conversely, Hirschberg *et al*[192], in sixty-one BCS patients receiving AIs (50 received estriol vaginal gel and 11 received placebo), found that ultra-low-dose 0.005% estriol vaginal gel showed efficacy in improving the symptoms and signs of vulvovaginal atrophy and that estriol levels increased initially and normalized by week 12, while estradiol and estrone remained mostly undetectable throughout the study. They concluded that the negligible impact of the product on the levels of estrogens, FSH, and LH supported the safe use of this ultra-low-dose estriol vaginal gel as a treatment option for vulvovaginal atrophy in BCSs receiving AIs [Qa = Good].

This year (2021), Streff *et al*[193] in a prospective trial to measure the change in blood estradiol levels in only 8 postmenopausal women with ER(+)-BC undergoing treatment with AIs when treated with vaginal estrogen preparation for their urogenital symptoms, found that there was no significant difference between the baseline and week 16 estradiol levels ($P$ = 0.81). In addition, patients in the prospective group reported subjective improvement in their vaginal dryness symptoms questionnaires. Therefore, VET did not cause persistent elevations in serum estradiol levels and might be a safer option for women with hormone receptor-positive breast cancer who have persistent urogenital symptoms [Qa = Poor].

In estrogen/progesterone negative tumors (ER-/PR-), the North American Menopause Society 2013 Position Statement[40] supports that topical vaginal estrogen can be prescribed. To date, there is no data that specifically separates groups of ER+PR+ or ER-PR- tumors in studies of the effectiveness, feasibility, or safety of estrogen in these groups. Based on the results of this review there is clear controversy on this topic, with some studies reporting no recurrence of BC, while others suggest caution due to a possible increase of serum estrogen levels that could lead to an increased risk of BC recurrence, specially in AIs users. Further studies are needed to evaluate these results.

In summary, taking into account the controversy, it is recommended that the risks and benefits be explained, individualizing each case with oncologists before using local estrogen therapies in BCSs. Without evidence to support value in clinical decision making, clinicians should be discouraged from measuring serum estrogen levels to assess systemic absorption of local estrogens as an indirect measure of risk for breast cancer recurrence[65].

BCS should use the lowest effective dose of vaginal estrogen as recommended by American College of Obstetricians and Gynecologists[73], American Cancer Society/American Society of Clinical Oncology[81], the Endocrine Society [72] and North American Menopause Society[82].

**Vaginal promestriene:** Promestriene (3-propyl ethyl, 17β-methyl estradiol) is a synthetic estrogen analog with reported minimal systemic absorption that has been suggested for topical treatment of vaginal atrophy. Low doses of topical vaginal estrogen therapy, because of its limited systemic absorption, are believed to have little or no effect on the breasts[194]. Therefore, as promestriene does not alter hormone levels, it should not modify the risk of breast cancer. Promestriene is an effective treatment for relieving the symptoms of VVA in BCSs with very poor vaginal absorption[195]. Furthermore, the absence of a systemic effect of promestriene has been confirmed with accurate and sensitive mass spectrometry and even after up to 4-6 mo. of therapeutic doses in clinical studies that included women with estrogen-sensitive malignancies[196].

Thus, it could be a first-line option for those who need minimal or ideally no vaginal absorption, particularly in symptomatic cancer patients. There are little data available in the literature, mostly consisting of small, open-label, short duration studies, and few RCTs. After a long-term market experience (almost 40 years), in 34 countries, and millions of pieces prescribed, the side effects were very rarely reported in pharmacovigilance data, whereas the effectiveness to relieve atrophy was good. To further improve the safety of promestriene, especially in estrogen-sensitive cancer patients, a very low dose is used from the beginning, starting with half or less of the usual dose, and then gradually increased until the minimum effective dose, which could further reduce its already minimal vaginal absorption[196]. However, *in vitro* studies[197] concluded that the potential estrogen-like properties of promestriene to stimulate the growth of estrogen receptor-responsive breast cancer cell lines, especially in estrogen-deprived conditions, suggest caution when prescribing for vaginal atrophy in postmenopausal BCSs on AIs. Its ability to activate growth and gene expression in ER-BC cells warrants further study.

**Vaginal testosterone:** Other options, such as intravaginal androgens, are gaining attention as a potential treatment for VVA in BCSs, since androgen receptors have been identified in the vaginal mucosa[198].

In one trial, treatment of 80 healthy postmenopausal women for 12 wk with a compounded vaginal cream containing 300 mg of testosterone propionate improved vaginal signs and symptoms[199].

Testosterone administration at the vaginal level seemed to trigger the activation of estrogen and androgen receptors in the vaginal epithelium layers without activating estrogen receptors in other tissues due to the lack of aromatase at this level[200].

Testosterone can induce proliferation of the vaginal epithelium, but testosterone's conversion to estrogen is blocked by AIs and therefore may be effective in reversing atrophic changes without raising circulating estrogen levels and compromising aromatase inhibitor therapy[201].

Up to 2020, three clinical trials evaluating the safety and efficacy of intravaginal testosterone (IVT) in BCSs were found[201-203] (Table 3). All were conducted in patients on adjuvant AI therapy for BC. The

longest follow-up was 26 wk. Only one clinical trial by Witherby *et al*[201], with 21 BCSs, measured serum estradiol levels. They assessed the use of daily vaginal testosterone to treat vaginal atrophy in women with breast cancer receiving AIs. Testosterone cream in one of two dosages, 150 mcg ($n$ = 10) or 300 mcg ($n$ = 10) was applied to the inner labia minora, introitus, and internal vaginal mucosa for 28 d. Both dosages of testosterone improved symptoms of vaginal atrophy including dyspareunia ($P$ = 0.001) and vaginal dryness ($P$ < 0.001), although only the 300 mcg decreased vaginal pH (*e.g.*, 5.5-5.0), and improved the vaginal maturation index (*e.g.*, 20%-40%). This study did not show any significant elevation ($P$ = 0.91) in serum estradiol levels (remained less than 8 pg/mL) at either dose of testosterone at 4 wk. of therapy. They concluded that a 4-wk course of vaginal testosterone was associated with improved signs and symptoms of vaginal atrophy related to AI therapy without increasing estradiol or testosterone levels, but longer-term trials are warranted.

Melisko *et al*[204] in a randomized, noncomparative trial, analyzed 69 patients on adjuvant AI therapy for BC who completed 12 wk. of estradiol ring 7.5 ng *vs* intravaginal testosterone cream at a 1% concentration 1.5 mg/week treatment. They found a persistent estradiol elevation in no women with vaginal estradiol ring and in 12% with IVT. Vaginal atrophy and sexual interest and dysfunction improved for all patients. This study supported the efficacy and safety of using intravaginal testosterone or estradiol-releasing vaginal rings in patients with breast cancer receiving AI therapy to treat vulvovaginal atrophy. However, persistent estradiol elevation was seen in the intravaginal testosterone group, suggesting that a lower dose of testosterone cream can be used. Therefore, the International Society for the Study of Women's Sexual Health (ISSWSH) concluded that open-label studies that have used high doses of intravaginal testosterone in the presence of AIs for breast cancer have resulted in supraphysiological serum testosterone levels and have been reported to lower vaginal pH, improve the vaginal maturation index, and reduce dyspareunia[205].

Clinical use of vaginal testosterone therapies is limited because no currently available local (or systemic) testosterone formulations are FDA-approved for administration to women.

**Vaginal dehydroepiandrosterone:** Vaginal dehydroepiandrosterone (DHEA) (prasterone®) 6.5 mg/d, a steroid prohormone with the ability to transform into testosterone and estradiol, is currently FDA-approved for the treatment of GSM. It induces local effects in tissues due to its intracrine or intracellular transformation to reproductive steroids and theoretically provides a nonsystemic hormonal approach. Two 12-week, randomized, double-blinded, placebo-controlled efficacy trials in women using 6.5 mg of DHEA nightly showed significant improvement *vs* placebo in vaginal cell maturation, pH, and dyspareunia because of GSM[206,207]. Intravaginal DHEA tested for 52 wk. showed improvement in all domains of sexual function on the Female Sexual Function Index (FSFI)[208,209].

Martel *et al*[210], with highly sensitive and specific mass spectrometry assays, suggested a slight but statistically significant increase in plasma estradiol and testosterone when using intravaginal DHEA, although they concluded that this rise was within the normal range of estradiol concentrations for postmenopausal women. Therefore, longer studies are required to evaluate the safety of this treatment.

Prasterone has been studied as a treatment for GSM in cancer survivors. Barton *et al*[209], in 2018, conducted a phase III randomized clinical trial that evaluated two doses (3.25 and 6.5 mg/d) of vaginal DHEA gel compared to plain moisturizer (PM) for the improvement of vaginal symptoms (dryness or dyspareunia) in postmenopausal women ($n$ = 464) with a history of breast (97%) or gynecologic cancer who could be receiving endocrine therapy. In peripheral blood analyses ($n$ = 345), estradiol was significantly increased in those on 6.5 mg/d DHEA but not in those on 3.25 mg/d DHEA ($P$ < .05 and $P$ = .05, respectively) and not in those on AIs. They concluded that DHEA resulted in increased hormone concentrations, although the levels were still within the lowest half or quartile of the postmenopausal range, and provided more favorable effects on vaginal cytology than PM.

Prasterone label includes a warning against this use in BCS. There are no studies directly comparing vaginal DHEA to vaginal estrogen in efficacy or hormone levels, and for this reason, there can be no recommendation of one over the other in BCS.

### *Pilocarpine*

Pilocarpine, a cholinergic agonist used to treat Sjögren´s syndrome, was investigated for this indication. Two hundred and one postmenopausal women with a history of breast cancer (currently without evidence of active breast cancer) or did not want to take vaginal estrogen for a fear of an increased risk of breast cancer were randomized to receive a target oral pilocarpine hydrochloride dose of 5 mg two times a day, or a target pilocarpine dose of 5 mg four times a day or identical appearing placebos (half with a target dose of two times a day while the other half with a target dose of four times a day). The authors did not find improvements invaginal dryness compared with placebo. Thus, pilocarpine cannot be recommended for use in the treatment of vaginal dryness, despite the preliminary pilot information that suggested that it might have been beneficial[211].

### *Vaginal laser (Fractional CO2 laser/erbium laser)*

Laser and other energy-based devices have been marketed for the treatment of vulvovaginal atrophy, but the safety and efficacy of these devices remain uncertain[212]. Laser therapy typically consists of three laser treatment sessions over a specified time period (usually one session every four to six weeks).

**Table 4 Vaginal laser therapy in breast cancer survivors: Summary of studies and their outcomes.**

| Ref. | Yr | *n*[1] | Design | Treatment | Conclusion |
|---|---|---|---|---|---|
| Pieralli *et al*[223] | 2016 | 50 | Prospective Before-after study | 3 sessions of Fractional Microablative CO2 Laser every 30 d | The treatment seems to be feasible and effective |
| Pagano *et al*[221] | 2016 | 26 | Observational retrospective study | 3 sessions of Fractional Microablative CO2 Laser every 30 d | The treatment seems to be effective and with good tolerance |
| Gambacciani *et al*[218] | 2017 | 43 | Pilot before-after study | 3 sessions of Vaginal Erbium Laser every 30 d | The treatment seems to be effective |
| Pagano *et al*[214] | 2018 | 82 | Observational retrospective study | 3 sessions of Fractional Microablative CO2 Laser every 30 d | The treatment seems to be effective |
| Mothes *et al*[225] | 2018 | 16 | Retrospective study | 1 session of Vaginal Erbium YAG Laser | The treatment seems to be effective |
| Pearson *et al*[222] | 2019 | 26 | Single-arm pilot study Before-After study | 3 sessions of Fractional Microablative CO2 Laser every 30 d | The treatment seems to improve sexual function and vaginal atrophy |
| Areas *et al*[224] | 2019 | 24 | Open, prospective study | 3 sessions of Vaginal Erbium YAG Laser every 30 d | The treatment seems to improve sexual function and vaginal atrophy |

[1]Cases.

The first studies evaluating the effectiveness of vaginal lasers were performed in 2015 using a fractional microablative carbon dioxide laser approved by the FDA as a therapy for GSM in healthy women[213-215]. In recent years, another laser, the nonablative vaginal Erbium YAG laser (VEL), has also been tested in these women[216-218]. Although the CO2 Laser appears to target more superficial tissue, VEL appears to remodel deep collagen and promote collagen synthesis. This effect may promote the production of new collagen that ultimately could result in improved tissue integrity and elasticity. This therapy improves the vascularization of vaginal mucosa by stimulating remodeling of the underlying connective tissue, thereby enlarging the vaginal epithelium and allowing it to accumulate glycogen. The accumulation of glycogen allows restoration of the vaginal flora, a reduction in vaginal pH and improvement in GSM symptoms caused by estrogen deficit[219]. In addition, vaginal lasers (CO2 or VEL) have been shown to improve stress urinary incontinence and vaginal prolapse and to improve vaginal dryness and dyspareunia. Nonetheless, the available data are short term, and the efficacy and safety of repeated applications are not clear[212]. Also, CO2 Laser treatment is very expensive ($1800 to $3000) and it is a procedure that is not yet widely performed by gynecologists, and thus access may be limited by a patient's geographic location.

When treating GSM in women with or at high risk of breast cancer, CO2 or VEL lasers are options that avoid hormone interventions, which is a potential advantage over pharmacologic therapies. Bercopi *et al*, 2018[220], found nonsignificant changes in the vaginal microbiome in BCSs and a high remodeling status in the vaginal epithelium after CO2 vaginal laser, mediated by significant changes in inflammatory and modulatory cytokine patterns. Eight recent studies[214,216,218,221-225] were found on the use of vaginal lasers in BCSs (3 single-arm pilot studies; 2 prospective, open, cohort studies; and 3 retrospective cohort studies) (Table 4). All the studies concluded that laser therapy improves VVA symptoms (FSFI, the Vaginal Health Index (VHI) and the Visual Analog Scale (VAS)) and reported no side effects in short-term follow-up. However, clinical assays evaluating the efficacy and safety of the use of erbium laser are needed, since all the studies included in this review were observational; some were prospective while others were retrospective, with a short follow-up and assessed only subjective variables regarding VVA improvement. There is a lack of data regarding safety and BC relapse, since no study provided information about recurrence during follow up, and serum estradiol levels were not measured.

Pagano *et al*[214] published a retrospective case series of 82 BCS patients who failed to achieve adequate relief of their GSM symptoms with nonestrogenic local treatments. These women were treated with three cycles of a CO2 Laser at 30- to 40-day intervals and demonstrated significant improvements in genital sensitivity during intercourse and vaginal dryness, as well as decreased itching/stinging, dyspareunia, dysuria, bleeding, and movement-related pain when assessed after the three treatments. These benefits were significant regardless of the woman's age or type of adjuvant breast cancer therapy. The authors noted that the optimal number of treatment cycles, as well as the need for and number of retreatments remained to be defined and have called for randomized, prospective comparative trials [216].

The longest follow-up period was that of a pilot study by Gambacciani *et al*[218] in which BCSs were followed for up to 18 mo. Pieralli *et al*[223] evaluated 50 cases of BCSs presenting VVA who were treated with an erbium laser. Of these, 52% were satisfied with the results after an average 11-month follow-up time. A very current (2021) RCT with only 18 gynecologic cancer survivors concluded that fractional CO2 Laser therapy is feasible in these patients, with preliminary evidence of safety and improvement in

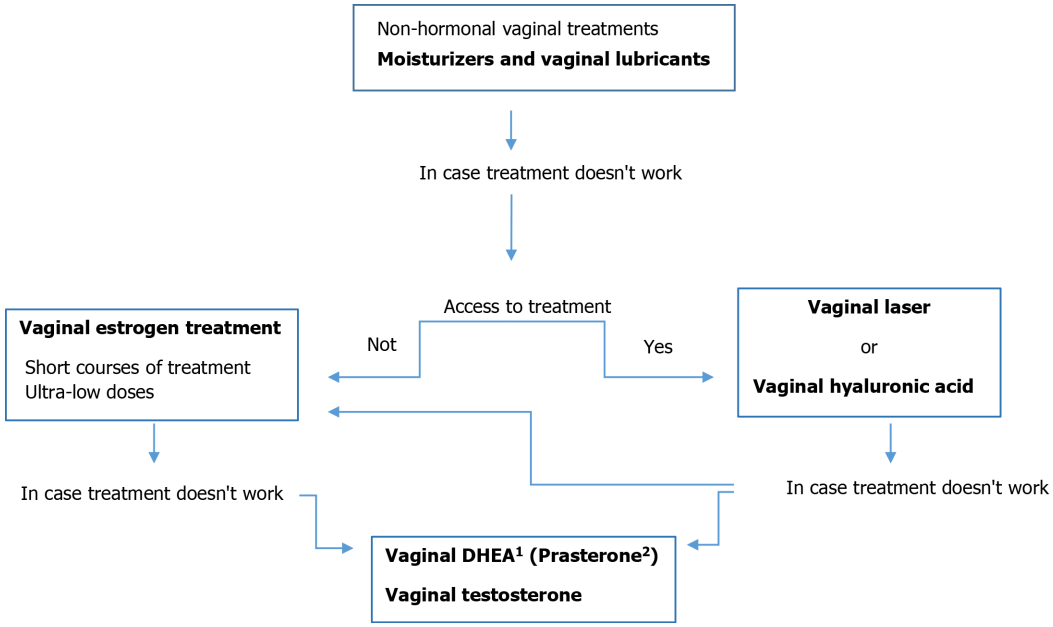


**Figure 1 Treatment of genitourinary syndrome of menopause in women undergoing adjuvant treatment for breast cancer.** [1]Dehydroepiandrosterone; [2]Prasterone label includes a warning against this use in breast cancer survivors.

sexual function compared with those of sham treatment[226]. Although large, sham-controlled RCTs have not been completed to date in women with breast cancer, one ongoing Greek clinical trial with 50 BCSs with GSM and with microablative fractional CO2 Laser therapy (Vaginal Laser Therapy for the Management of Genitourinary Syndrome of Menopause of Breast Cancer Survivors: NCT03738605) had an estimated study completion date of August 2020,but the conclusions are not yet available[227].

Laser or energy-based devices have not been cleared or approved by the FDA for the treatment of VVA. In 2018, the FDA issued safety communication warning patients about the risks associated with the use of these devices, which include vaginal burns, scarring, pain during sexual intercourse, and recurring/chronic pain[228]. In 2020, the American College of Obstetricians and Gynecologists advised that additional data from randomized trials are needed to further assess the efficacy and safety of this procedure[229]. In the same year, a clinical consensus statement by the American Urogynecologic Society concluded that while energy-based therapies had shown treatment promise, long-term outcomes were not yet understood[230]. Therefore, additional large clinical trials are needed to determine the benefits, risks, and cost-effectiveness of laser therapy for vulvovaginal atrophy in healthy women and in BCSs.

## MANAGEMENT OF GENITOURINARY SYNDROME OF MENOPAUSE IN SPECIFIC PATIENT POPULATIONS

In Table 5, we provide consensus recommendations of The North American Menopause Society (NAMS) and The International Society for the Study of Women's Sexual Health (ISSWSH) Expert Consensus Panel[65] for an approach to the management of GSM in specific patient populations, including women at high risk of breast cancer, women with estrogen receptor-positive breast cancers, women with triple-negative breast cancers, and women with metastatic disease.

## SUMMARY OF THE RECOMMENDATIONS ON THE TREATMENT OF GENITOURINARY SYNDROME OF MENOPAUSE IN BREAST CANCER SURVIVORS

A diagram for the treatment of GSM in women undergoing adjuvant treatment for breast cancer is shown in Figure 1. Figure 2 shows a schematic diagram for the treatment of GSM in women who have completed their adjuvant treatment for breast cancer.

**Table 5 Treatment options for management of genitourinary syndrome of menopause in specific patient populations: Consensus recommendations of the The North American Menopause Society[65]**

| General guidelines |
|---|
| Individualize treatment, taking into account risk of recurrence, severity of symptoms, effect on QoL, and personal preferences |
| Moisturizers and lubricants, pelvic floor physical therapy, and dilator therapy are firstline treatments |
| Involve treating oncologist in decision making when considering the use of local hormone therapies[1] |
| Ospemifene, an oral SERM, has not been studied in women at risk for breast cancer and is not FDAapproved for use in women with or at high risk for breast cancer |
| Offlabel use of compounded vaginal testosterone or estriol is not recommended |
| Laser therapy may be considered in women who prefer a nonhormonal approach; women must be counseled regarding lack of longterm safety and efficacy data |
| Women at high risk for breast cancer[2] |
| Local hormone therapies are a reasonable option for women who have failed nonhormonal treatment |
| Observational data do not suggest increased risk of breast cancer with systemic or local estrogen therapies beyond baseline risk |
| Women with ERpositive breast cancers on tamoxifen |
| Tamoxifen is a SERM that acts as an ER antagonist in breast tissue; small transient elevations in serum hormone levels noted with local hormone therapies in women on tamoxifen are less concerning than in women on AIs |
| Women with persistent, severe symptoms who have failed nonhormonal treatments and who have factors suggesting a low risk of recurrence may be candidates for local hormone therapy |
| Women with ERpositive breast cancers on AI |
| AIs block conversion of androgen to estrogen, resulting in undetectable serum estradiol levels; transient elevations in estradiol levels may be of concern |
| GSM symptoms are often more severe |
| Women with severe symptoms who have failed nonhormonal treatments may still be candidates for local hormone therapies after review with the woman's oncologist vs consider switching to tamoxifen |
| Women with triplenegative breast cancers |
| Theoretically, the use of local hormone therapy in women with a history of triplenegative disease is reasonable, but data are lacking |
| Women with metastatic disease |
| QoL, comfort, and intimacy may be a priority for many women with metastatic disease |
| Use of local hormone therapy in women with metastatic disease and probable extended survival may be viewed differently than in women with limited survival when QOL may be a priority |

[1]Local hormone therapies are vaginal estrogen and intravaginal DHEA (prasterone).
[2]Lifetime risk > 20%, carriers of the BRCA mutation, atypical ductal hyperplasia, lobular carcinoma in situ, or ductal carcinoma in situ. AI: Aromatase inhibitor; ER: Estrogen receptor; GSM: Genitourinary syndrome of menopause; QoL: Quality of life; SERM: Selective estrogen-receptor modulator.

## CONCLUSION

GSM in BCSs is the leading cause of sexual dysfunction and severely limits the QoL of these patients. The current recommendations are that nonhormonal approaches are the first-line choices for managing mild-moderate urogenital symptoms experienced by women during or after treatment of breast cancer, which seem to be safe but present limited efficacy and short-term effects. Despite current evidence and the cautious support of multiple medical societies of the use of local ET for the management of GSM refractory to other nonpharmacologic and nonhormonal treatments, the safety of these therapies in women with or at high risk of breast cancer has not been definitively established, and recommendations for use remain controversial. Only vaginal estrogen administration is approved for BCSs and always with the lowest possible dose. Current data do not show an increase in cancer recurrence with VET; however, some studies have revealed concerns regarding elevated serum estradiol levels with estradiol vaginal rings and creams, which may reverse the effects of AIs. There is confusion about what specific estradiol or estrone levels should raise concern for postmenopausal BCSs. Due to several contradictions in published studies, a large, randomized, placebo-controlled study investigating the changes in serum levels of estrogen from varying doses and forms of topical vaginal estrogen therapies is warranted.

The decision to use vaginal hormonal therapy must be made on an individual basis with discussions between the treating physician and the patient, but we should keep in mind that the beneficial effects of VET for BCSs with severe GSM without response to nonhormonal therapies could outweigh the risks

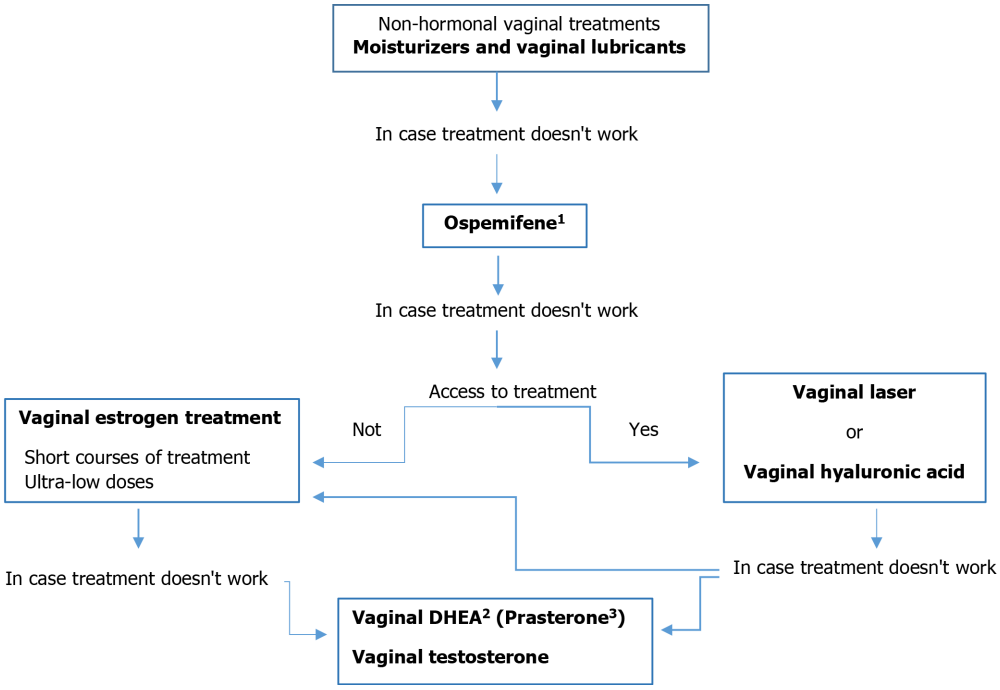


**Figure 2 Treatment of genitourinary syndrome of menopause in women who have completed their adjuvant treatment for breast cancer.** [1]Food and Drug Administration does not recommend ospemifene for women at risk or with history of breast cancer or those with known or suspected estrogen-dependent neoplasia[84]; [2]Dehydroepiandrosterone; [3]Prasterone label includes a warning against this use in breast cancer survivors.

and provide an overall improvement in QoL. Engaging clinicians caring for this population to ask about and treat GSM is important for QoL and requires consensus about treatment because clinical data are lacking.

The duration of therapy with all of these therapies is currently unknown, and at this time, we recommend individualizing the duration of therapy based on symptom improvement and quality of life. We suggest avoiding routine use of VET for women who are on AIs for adjuvant treatment of breast cancer. However, given the emerging data, laser or use of low-dose vaginal prasterone in select women with breast cancer who are at low risk of recurrence is reasonable if they are on AIs. Promestriene and ospemifene must be considered as alternative options. Ospefimine is a nonhormonal estrogen agonist/antagonist with promising results for BCSs when adjuvant treatment has been concluded; however, additional investigation is warranted to ensure the safety in this population. Finally, further research to define the safety and efficacy of intravaginal DHEA and different types of vaginal lasers, as well as to develop new therapies is critical.

## FOOTNOTES

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*MINIREVIEWS*

# Single-fraction stereotactic ablative body radiation therapy for primary and metastasic lung tumor: A new paradigm?

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## Abstract

Stereotactic ablative body radiotherapy (SABR) is an effective technique comparable to surgery in terms of local control and efficacy in early stages of non-

small cell lung cancer (NSCLC) and pulmonary metastasis. Several fractionation schemes have proven to be safe and effective, including the single fraction (SF) scheme. SF is an option cost-effectiveness, more convenience and comfortable for the patient and flexible in terms of its management combined with systemic treatments. The outbreak of the severe acute respiratory syndrome coronavirus 2 pandemic has driven this not new but underutilized paradigm, recommending this option to minimize patients' visits to hospital. SF SABR already has a long experience, strong evidence and sufficient maturity to reliably evaluate outcomes in peripheral primary NSCLC and there are promising outcomes in pulmonary metastases, making it a valid treatment option; although its use in central locations, synchronous and recurrencies tumors requires more prospective safety and efficacy studies. The SABR radiobiology study, together with the combination with systemic therapies, (targeted therapies and immunotherapy) is a direction of research in both advanced disease and early stages whose future includes SF.

**Key Words:** Stereotactic body radiotherapy; Sterotactic ablative body radiotherapy; Radiosurgery; Non-small cell lung cancer; Lung cancer; Lung metastases



**Core Tip:** There is strong evidence (two phase II prospective studies) to support using single-fraction stereotactic ablative body radiotherapy schemes in early stage peripheral non-small cell lung cancer. In pulmonary oligometastatic disease, there are promising outcomes and publication of one randomized prospective phase II study is pending. The association of this scheme with new systemic therapies looks promising for the future.

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## INTRODUCTION

Stereotactic ablative body radiotherapy (SABR) is an important development in the early stages of non-small cell lung cancer (NSCLC). An effective, non-invasive and well-tolerated treatment which, by delivering high and precise doses over several sessions, improves the survival outcomes of these medically inoperable patients compared with conventional fractionation schemes[1,2]. It achieves a high level of local control in stages I and IIA, and a similar survival to surgery[3] in both primary tumors and lung metastases[4].

In spite of an increasingly widespread use of SABR over the past two decades, no consensus has been reached about the most suitable fractionation schemes, as several have proven to be safe and effective[5-7], including a single fraction scheme (SF)[8].

SF SABR was first utilized in intracranial stereotactic radiosurgery (SRS)[9,10] and showed promising efficacy that was comparable to surgery. Pioneering extracranial developments of SF included the treatment of thoracic malignancies[11], although in clinical practice or research it has been adopted much less than fractionated SABR[12].

The outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in 2019 has resulted in an urgent need to reduce the number of patients' face-to-face visits. There is, therefore, renewed interest in SF as a viable treatment option for primary and metastatic lung cancer[13,14], as it delivers a radical treatment dose in just one hospital visit. In fact, oncological guidelines[15-17] now recommend using SF in these patients.

Moreover, recent studies reporting the use of SABR in carefully-selected patients with sustained metachronic extracranial oligometastases[18-22], will increase the number of indications for this approach, and SF could also be an attractive option in this setting.

Other possible applications for SF could include synchronous or oligorecurrent tumors, after a first treatment.

However, SF differs from other treatments in two important ways. One concerns the radiobiological principles and the other refers to a possible different immunogenicity than with multifraction SABR.

The clinical efficacy of SABR is greater than would be expected by the linear-quadratic model. This is because, in addition to the directly ablative effect of SABR, it also has indirect effects that induce

vascular endothelial lesion and immune activation[23,24].

Apart from reoxygenation, perhaps, the other radiobiological principles of the 4Rs are not applicable to SABR. Tumoral hypoxia can persist after vascular lesions caused by SABR[25]. Moreover, it is unlikely that switching from 1 to 5 fractions will permit the initially hypoxic tumor cells to become sufficiently reoxygenated, and could explain the small number of local failures observed in fractionated SABR[8]. To date, no clinical study has measured the effect of SABR on tumoral hypoxia in patients with NSCLC, to determine whether the efficacy of SABR depends on reoxygenation[25].

In the present review, we examine current evidence for the safety and efficacy of SF, its benefits and limitations to use. We also examine possible future directions for new systemic treatments and immunotherapies.

## EARLY-STAGE PERIPHERAL NSCLC

In 2005[26,27], the first published experiences began to appear using single fraction radiation therapy in lung, in which doses of 30-34G achieved local response rates at one-year of 93%, with a G3 toxicity of 2%.

The first prospective studies in dose-escalation (Table 1) were published by Stanford University[28] in 2003. Later, the authors presented the outcomes for different doses[29]. This was a Phase I trial in dose-escalation with a study design with 4 doses of SF increasing from 15 Gy to 30 Gy, by increments of 5 Gy. The primary end-point was to identify the maximum tolerated dose (MTD) three months after dose delivery by SF. A total of 32 inoperable patients were recruited, of whom 20 had NSCLC and 12 were metastatic with lesions smaller than 5 cm. After 5-6 mo, the patients with central tumors and with a PTV > 50 cc presented pneumonitis G2-3. On the other hand, delivery of 25 Gy to patients with prior radiotherapy (RT) produced a significant increase in toxicity effects. Therefore, an addendum was applied for the 30 Gy dose to exclude the population with PTV > 50 cc who had received prior RT. The three G5 toxicities reported all corresponded to centrally located tumors, in patients with prior chemotherapy, one before SABR and two as adjuvant therapy to SABR, and two patients had a PTV > 50 cc. Local control (LC) at one-year was 91% for those delivered a dose higher than 20 Gy and 54% for doses lower than 20 Gy. Local control was significantly less in metastatic lesions than in primary tumors. The authors conclude that SF SABR of 25 Gy is well-tolerated in patients with prior thoracic radiotherapy with a PTV < 50 cc. However, central lesions and the population receiving prior chemotherapy, before or after SABR, could be at greater risk.

After this experience in dose-escalation, two prospective studies were published. The first was the Radiation Therapy Oncology Group (RTOG) 0915 study, published by Videtic *et al*[30] in 2015. This is a phase II study that analyzed 84 patients with a median follow up of 30.2 mo. Patients had T1-T2 N0 peripheral NSCLC and were randomized into one of two arms: SF 34 Gy (Arm A) *vs* 48 Gy delivered in 4F (Arm B). The aim of the study design was to identify the schedule that produced the least G3 adverse events in one year. The results showed a Grade 3 toxicity of 10.3% in Arm A and of 13.3% in Arm B. One G toxicity was recorded in each Arm. This was not related to SABR in Arm A, whereas it was related to treatment in Arm B. Local control at one-year was 97% in Arm A and 92.7% in Arm B with a tendency towards increased overall survival (OS), although this was not statistically significant with the 34 Gy dose.

The study conducted by Singh *et al*[31] at the Roswell Park Cancer Institute and published in 2019 was a phase II study that recruited 98 patients with T1/T2 primary peripheral lung cancer, randomized to receive a SF of 30 Gy (Arm 1) *vs* 60Gy delivered in 3 fractions, not correcting for heterogeneity (Arm 2). The primary endpoint of the study was to determine the incidence of toxicity of G3 or higher, with secondary endpoints of LC, survival and quality-of-life. With a mean follow-up of 53.8 mo, no significant differences were found between the two arms in G3 toxicity, LC at two years, which was 94.9% in Arm 1 and 97.1% in Arm 2, or in OS or progression free survival (PFS). A statistically significant improvement was only observed in social functioning in the 30Gy arm.

The results show that SF presents a comparable toxicity profile to multi-fraction radiotherapy without differences in LC. It would, therefore, seem pertinent to propose a phase III trial[8] that compares SF with Timmerman's classical fractionation schedules of 54 Gy in 3 fractions[32]. Possible limitations to this phase III study would be the problem of obtaining a sufficient sample size, and a possible excess toxicity to the ribs in extreme peripheral lesions.

Because of the SARS-CoV-2 pandemic, the use of hypofractionated schedules are being considered and, specifically, for NSCLC the use of a SF of SABR with a 30 Gy or 34 Gy dose, as both these doses have been reported to produce similar outcomes[33].

## CENTRAL TUMORS

Central tumors are defined in the clinical trial protocol of the cooperative group of the RTOG 0236 as those located less than 2cm away from the proximal bronchial tree (PBT)[34]. The initial experience in

**Table 1 Prospective data, single fraction stereotactic ablative body radiotherapy early-stage peripheral non-small cell lung cancer**

| Ref. | Design | Arms | *n* | Toxicity rates > GIII | LC | PFS | OS | FU[3] | SABR technique/prescription |
|---|---|---|---|---|---|---|---|---|---|
| Le *et al* [29], 2006 | Phase I, *n* = 32 | 15 Gy (1fr) | 9 | 0 | 54 | NSCLC[1]: 67% | NSCLC[1]: 85% | 18 | Cyberknife<br>Gold fiducials |
| | | 20 Gy (1fr) | 1 | 0 | | | | | Breathold or Synchrony (Accuray) respiratory tracking system/Isodose coverage: 95% of PTV |
| | | 25 Gy (1fr) | 20 | 1p (GIII)3p (GV) | 91 | Metastatic[1]: 25% | Metastatic[1]: 56% | | |
| | | 30 Gy (1fr) | 2 | 0 | | | | | |
| Videtic *et al*[30], 2015 | Phase II, *n* = 84 | 48 Gy (4fr) | 45 | 6 (13.3%) | 92.7%[1] | 71.1%[2] | 77.7%[2] | 30.2 | Abdominal compression, gating with the respiratory cycle, tumor tracking, and active breath-holding techniques were allowed. Image guidance was required/prescription isodose surface ≥ 60% and < 90% of the maximun dose. |
| RTOG 0915 | | 34 Gy (1fr) | 39 | 4 (10.3%) | 97%[1] | 56.4%[2] | 62.3%[2] | | |
| Singh *et al*[31], 2019 | Phase II, *n* = 98 | 60 Gy (3fr) | 49 | 6 (15%) | 97.1%[1] | 50%[2] | 62%[2] | 53.8 | Body Fix (Elekta) immobilizer. Real-Time Position Management by Varían Medical System or abdominal compression. 3D-CRT was preferred. Image guidance was required/tumor coverage and normal tissue dose constraints followed RTOG 0915 |
| | | 30 Gy (1fr) | 49 | 8 (17%) | 94.9%[2] | 65%[2] | 73%[2] | | |

[1]At 1 yr.
[2]At 2 yr.
[3]Median follow-up months.
Fr: Fraction; RTOG: Radiation Therapy Oncology Group.

centrally located tumors treated with SABR but following protocols for non-central targets, showed a high toxicity, including deaths from complications[35,36]. Ultra-central tumors[37], in which the margin is reduced to within 1 cm of the boundary of the PBT, and the lesion touches or immediately invades one of the organs at risk, such as the mediastinum, trachea, bronchus or esophagus, are at greater risk of treatment-related death with SABR, associated with necrosis of the respiratory tract. However, for small (T1, T2) ultra-central lesions, SABR has been used quite safely.

There is growing interest in the treatment of central and ultra-centrally located targets by SABR, and in identifying the optimum dosing schedule that is both effective and safe to administer[38].

The Phase I/II RTOG 0813 study[39] evaluated the maximum tolerated dose, efficacy and safety in 120 patients with NSCLC cT1-2N0 of central location. The maximum tolerated dose was 12 Gy/fraction, and was associated with 7.2% of dose-limiting toxicity and high control rates. Local control rates at two years for the 71 evaluable patients in cohorts of 11.5 and 12.0 Gy/fraction were 89% and 88%per cent, respectively. Analysis of ultra-central *vs* central locations is still pending.

The fractionation schedules most used in centrally-located tumors are: 45-50 Gy delivered in 4-5 fractions following recommendations of the American Society for Radiation Oncology[6] or 60 Gy in 8 fractions according to the UK SBRT consortium[40].

Ongoing radiation studies in ultra-central tumors are attempting to elucidate the ideal dosing schedule. These include the Canadian trial SUNSET[41] and the EORTC LungTech study[42], which use the 60 Gy scheme delivered in 8 fractions.

SF SABR schedules of 30-34 Gy in phase II trials have been validated in peripheral tumors[30,31] but not in central targets. The Phase I dose-escalation study of Standford[29], which did include centrally-located tumors, reported a greater toxicity in these patients, as mentioned in the previous section. The remaining studies focusing on the use of SF on central targets are retrospective.

One retrospective study published by the Roswell Park Cancer Institute analyzed 42 patients with central tumors, and compared treatment outcomes in 11 patients delivered a single fraction of 26-30 Gy *vs* 31 patients treated with 52.6-60 Gy in 5 fractions. They found no significant differences in OS, PFS or in local, lymph node, or distant failure at 18 mo[43]. In spite of the higher rate of grade ≥ 3 toxicity ($P$ = 0.28) in the cohort of patients treated with the single fraction, in the univariant analysis dose had no significant effect on risk of toxicity ≥ 3. Local control at one year was 100% in patients treated with SF and 96% in the multiple fraction group.

A retrospective review by Siva *et al*[44] that included 65 patients with 1-3 pulmonary metastases compared SF (26 Gy to peripheral lesions and 18 Gy to central lesions) *vs* delivery of multiple fractions (48 Gy in 4 fractions and 50 Gy in 5 fractions). With a mean follow-up of 25 mo they found no significant

differences in OS, local or distant progression, or toxicity. There were no cases of grade ≥ 3 toxicity.

To conclude, the treatment of centrally-located pulmonary tumors with SABR is still controversial owing to greater toxicity risks associated with central compared with peripheral locations. Evidence from published studies for SF in central or ultra-central tumors shows a higher toxicity risk, as doses exceed tolerance doses for central structures. Therefore, until prospective studies can establish SF as an alternative to multifraction SABR in this location, it cannot be recommended.

## SYNCHRONOUS TUMORS AND RECURRENT DISEASE

There is little solid evidence about the use of SABR, and even less for SF, in synchronous lung tumors. This setting is particularly complex as there is often no anatomical pathology thus complicating therapeutic planning.

A study at Stanford[45] describes the results of a dosing strategy for SABR adapted to tumor volume, in primary and metastatic pulmonary tumors. In one of the groups, patients with a tumoral volume < 12 mL received a SF of 18-30 Gy. This group studied 48 patients with a total of 62 tumors, so an important proportion of patients treated with SF SABR had more than one tumor (between 2 and 4).

With a median follow up of 13 mo, patients with one or more small tumors treated by SF with a BED < 100 Gy, had a high rate of local control and a low toxicity, equivalent to rates recorded in patients treated with multiple fractions of BED >100 Gy.

In 2014, Kumar *et al*[46], of the Cleveland Clinic published the data of their updated series of 445 patients with early stage NSCLC treated with SABR, including 26 patients (5.8%) with synchronous pulmonary tumors confirmed by biopsy and/or PET-CT. Both the group of synchronous and of single pulmonary tumors included patients who had received SF (30 Gy in both groups and 34 Gy in the group of single tumors). At one-year of follow-up, there were no differences in survival or progression between the groups.

In a retrospective analysis by Tekatli *et al*[47] on SABR in both primary and metastatic synchronous pulmonary tumors, out of a total of 84 patients and 188 pulmonary lesions treated, only 7 Lesions (3.7%) were delivered a single session of 34 Gy by multicentric VMAT to simultaneously treat lesions some distance apart. A toxicity ≥ G3 was only recorded in 2% of the patients.

Another setting for which few studies have been published is rescue therapy by SABR, either in cases of tumoral recurrence, or persistence after a first oncological treatment. Most of the published studies of SABR used in tumoral recurrence deliver from 3 to 8 fractions[48-50]. A retrospective series published by Pennathur *et al*[51] analyzed 100 patients receiving SABR treatment for tumoral recurrence using the following regimens: surgery ± radio/chemotherapy, chemo-or radiochemotherapy, RT or radiofrequency. Of these, 31% were given 20 Gy as SF SABR, whereas the remaining patients were given 45 to 60 Gy in 3-5 fractions. With an important median follow up of 51 mo, the OS estimated for the whole sample at 1, 2 and 5 years was 74%, 49% and 31%, respectively. Although these data are from a retrospective study, they are the best data published to date in the setting of SABR for oligorecurrent or persistent lung cancer after a first treatment. No severe toxicity was reported.

Ultimately, there are few published experiences of SABR delivered in a single session for synchronous tumors, or for tumoral recurrence. Further studies are required to establish the viability of this treatment modality in these settings.

## PULMONARY METASTASES

The lung is the second most frequent location of metastases[52]. Although metastectomy is the standard treatment[4], not all patients are candidates for pulmonary resection.

The efficacy and safety of SF SABR in primary or metastatic pulmonary tumors has been known since 2000[11].

Studies and data on SF SABR for the treatment of pulmonary metastases are summarized in Table 2. For series that also include patients treated with fractionated SABR, only data referring to the single fraction treatment are included. Nakagawa *et al*[11] also include pleural and costal metastases. Hara *et al*[26], Fritz *et al*[53], Le *et al*[29] and Wulf *et al*[54] combine patients with primary and those with metastatic pulmonary tumors, although only two studies assess local control and distinguish between that achieved in primary *vs* metastatic tumors. The phase I trial at Standford of Le *et al*[29] , also mentioned previously, found a lower LC rate at one-year in metastases of 58%, compared to 78% with primary tumors, whereas the prospective series by Fritz *et al*[53], found no significant differences in LC ( 80% 5 years) or OS (mean survival between 20 and 26 mo) in metastases *vs* primary tumors.

Treatment with SF SABR has been used for pulmonary metastases for over 20 years, in over 1000 cases. In seven publications the lesions included for analysis exceed 90[54-60].

In these series, the mean dose delivered to peripheral lesions was 27.03 Gy (range: 12-30 Gy), and for centrally-located tumors was 18.75 Gy (range: 16-23 Gy). The lowest doses are found in publications of the first exploratory studies of SABR and dose-escalation. In more recent publications (from 2010

**Table 2 Single fraction stereotactic ablative body radiotherapy for pulmonary metastases**

| Ref. | Study design | Total lesions (*n*)/LM (*n*) | Mean, Dose Gy (range)/Location | SABR technique/prescription | Mean GTV (cc) (range) failing this, cm | FU (mo), median | LC | Toxicity ≥ GIII | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Nakagawa *et al* [11] | P | 22/12 | 22.8 (18-25)[1]/NR | Rotational or StaticTherapy 3D-CRT. Abdominal compression/PTV enclosing isodose. | 4.8 (0.8-13) | 10 | 100%[1] | 0 | Non actuarial LC |
| Hara *et al*[26] | P | 59/48 | 30(20-34)/Periph | Static 3D-CRT. Gating/Minimal dose to GTV | 5 (1-19) | 12(mean) | 1-yr 93%<br>2-yr 78% | 1 GIII | LC 52% < 30 Gy<br>LC 83% ≥ 30 Gy<br>*P* = 0.068 |
| Wulf *et al*[54] | R | 92/31 | 26/Central | Static 3D-CRT. Abdominal compression/65-80%-isodose enclosing PTV | NR | 14 | 100% | NR | SF data are shown |
| Fritz *et al*[53] | P | 64/31 | 30/Periph | Static 3D-CRT. Abdominal compression/Isocenter, 90% isodose enclosing GTV, 80% isodose enclosing PTV | Median: 6 (2.8-55.8)[1] | 22[1] | 5-yr 80%[1] | 0 | No difference LC and OS LM *vs* primary lung cancer |
| Le *et al* [29] | Phase I | 32/11 | 22.34 (15-30)/Periph | Cyberknife. Gold fiducials.Breathold or Synchrony (Accuray) respiratory tracking system / Isodose coverage: 95% of PTV | Median: 17.1 (2-103) | 18 | 1-yr 91% (≥ 20 Gy)<br>1-yr 54% (< 20 Gy) | 1 GIII (pn)<br>3 GV (central) | LC primary *vs* LM: 78% *vs* 58%<br>And OS (85% *vs* 56%)<br>Higher toxicity in central tumors |
| Hof *et al* [63] | P | 0/71 | 24.35 (12-30)/NR | Static 3D-CRT. Abdominal compression/Isocenter: 80% isodose enclosing PTV | 10 (1-53) | 14 | 1-yr 88.6%<br>2-yr 73.7%<br>3-yr 63.1% | 3 GIII (pn) | LC 3 yr 78% 26-30 Gy |
| Gandhidasan *et al* [56] | R | 186/95 | 18/Central26 or 28/Periph | Static 3D-CRT or IMRT/80% isodose enclosing PTV | NR | 22 | 2yr 84% | 0 | |
| Osti *et al* [57] | P | 0/103 | 23Gy/Central30 Gy/Periph | Static 3D-CRT. 4DCT. 80% isodose enclosing PTV | NR | 15 | Central *vs* peripheral:1-yr 79.4% *vs* 94.7%<br>Global: 1-yr 89.1%, 2-yr 82.1% | 2 GIII (pn) | Prognostic factors for LC: sex and histology |
| Filippi *et al*[58] | R | 0/90 | 26Gy/Periph | Static 3D-CRT or IMRT or VMAT. Abdominal compression/80% isodose enclosing PTV | < 5 cm | 24 | 1-yr 93.4%<br>2-yr 88.1% | 8 GII-IIIlate radiological toxicity<br>6 GII-IIIchest wall toxicity | They suggest not to use a SF in lesions close to the chest wall |
| Siva *et al* [44] | R | 0/41 | 18/Central26/Periph | Static 3D-CRT or IMRT or VMAT. /70-80% isodose enclosing PTV | < 5 cm | 25 | 2-yr 93% | 0 | LC, OS and toxicity rates between SF and multi-fraction SABR |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Osti *et al* [59] | R | 0/166 | 30/Periph | Static 3D-CRT. 4DCT/95% isodose enclosing PTV | 3.46 (0.03-47.48) | 38 | 3-yr 80.1%<br>5-yr 79.2% | 6 GIII (pn)<br>11 GIIIlung fibrosis<br>1 GV at 15 mm PBT | Lesions ≤ 15 mm from mediastinum were not included in the study |
| Sharma *et al* [61] | R | 32 | 30/Periph | Cyberknife. Radiopaque markers Tumor traking.70-90% isodose enclosing PTV | < 3 cm | 22 | 2-yr 68%<br>3-yr 63%<br>4-yr 59% | No details for SF | $BED_{10}$ < 100, delivery of pre-SBRT chemo. and synchronous metastasis: independently < LC |
| Sogono *et al* [60] | R | 167 (95% peripher) | 16-18/Central26-28/Periph | Static 3D-CRT or IMRT or VMAT. 4DCT/99% isodose enclosing PTV | NR | 37 | 1-yr 96%<br>2-yr 92%<br>5-yr 92% | NR | Several locations |
| Siva *et al*[55] | Phase II | 133 | 28/NR | Static 3D-CRT or IMRT or VMAT. Abdominalo compression/70-80% isodose enclosing PTV | 2.2 cm (mean) | 12 | 1-yr 93% | 2 GIII | Preliminary results (TROG 13.01 SAFRON II)<br>1-3 metastases non-central targets < 5 cm |

[1]Data refer to subgroup pulmonary metastases; when not specified otherwise, data refer to the whole series.

FU: Follow up; LC: Local control; OS: Overall survival; G: Grade; LM: Lung metastases; P: Prospective; R: Retrospective; NR: No reported; pn: Pneumonitis; periph: Peripheral; 3D-CRT: Tridimensional conformal radiotherapy. 4DCT: Four-dimensional CT; IMRT: Intensity-modulated radiotherapy; VMAT: Volumetric-modulated arc therapy.

onwards), the most frequently used dosing interval in peripheral tumors is from 26 to 30 Gy. Recently, central tumors have also been included in SF SABR protocols[44,54,56,57,60].

With an estimated mean follow up of 22 mo, the mean local control at one- and two-years is 87.1% and 84.2%, respectively; only Osti *et al*[59] and Sogono *et al*[60] provide data for LC at 5 years, of 79% and 92%, respectively.

Sharma *et al*[61] obtained particularly poor results (LC at 2 years of 68%, at 3 years of 63% and at 4 years of 59%). They attribute this to the dose calculation algorithm used[62], and suggest that the real dose delivered was lower than the theoretical dose. Although Filippi *et al*[58] advise against using SF schemes in tumors close to the chest wall , Sogono *et al*[60] and Siva *et al*[44] report no toxicities when dosing limits are of organ at risk are respected.

As shown in Table 2, grade 3 toxicity is very rare in all the cited studies. A total of 4 deaths were reported, all in patients with centrally-located tumors treated with non-adapted regimens. Three of these were reported in the phase I dose-escalation trial at Stanford[29] mentioned in previous sections, and one of them located at 15mm PBT in the retrospective series of Osti *et al*[59].

As mentioned in the section on centrally-located tumors, in the retrospectrive review of Siva *et al*[44], with appropriate dose constraints, no significant differences are observed in LC or toxicity compared with peripheral pulmonary tumors in retrospective series.

The phase II multicentric prospective study TROG 13.01 SAFRON II of Siva *et al*[55] is currently addressing the equivalence of a SF SABR schedule of 28 Gy and a schedule of 48 Gy delivered in four fractions for peripheral pulmonary oligometastases smaller than 5 cm. The prespecified primary evaluation criterion relating to safety was satisfied. Preliminary results point to an equivalence of both schedules for LC, OS and DFS (disease free survival), although more time is required to verify these, and other secondary endpoints such as quality-of-life and cost-effectiveness.

## BENEFITS AND CONSTRAINTS TO IMPLEMENTATION

SF SABR schemes are an attractive option in terms of more convenience for the patient, reduced costs (direct and indirect) and greater flexibility for combinations with systemic treatments[58]. These features have become even more critical during the pandemic, to minimize patients´ visits to hospital, and hospital stay.

However, some constraints have prevented the widespread implementation of this technique such as: a fear of severe toxicity (especially in early studies and central tumors[29]), the scarcity of long-term studies compared with fractionated SABR (a scheme the specialist is already familiar with), and the possibility of errors in geographical positioning (which can be fatal in SF-SABR), requiring a high quality SABR control and appropriate technical capability[8,17] , among others (Table 3).

As in fractionated SABR, motion management methods should be used in SF, at planning and/or treatment; depending on available technology and previous experience (Figure 1). The treatment and prescription techniques of the studies mentioned in this article are shown in (Tables 1 and 2).

Regarding the benefits of this therapy, there is now strong evidence (two phase II prospective studies), and of sufficient maturity to reliably evaluate outcomes (5 years), to support using SF SABR schemes in early stage peripheral NSCLC[30,31].

In pulmonary oligometastatic disease, prospective and retrospective studies (Table 2) describe promising outcomes for LC, acceptable toxicity and emphasize benefits for patient adherence, more convenience and less associated costs. Publication of the randomized prospective phase II study, which is also studying cost-effectiveness, is pending[55,63].

Published data on SF-SABR in centrally-located and large-volumed primary tumors (> 50 cc), are controversial, and its use in these settings is not recommended [29,35].

There is some uncertainty about the combined use of some systemic therapies (especially with gemcitabine) due to a possible rise in cases of *recall pneumonitis*, more associated with higher doses per fraction[29].

Radiobiologically, single fraction schemes use a similar biologically effective dose (BED) to fractionated schemes (BED > 100 Gy). Therefore, theoretically both should have the same effect on the tumor (> 90%). The BED for healthy tissues suggests a possible rise in toxicity, although this has not been demonstrated in prospective studies (Table 4)[30,31,64]. Moreover, toxicity could be mitigated by increasing the precision of the irradiation, with a high dose gradient between the tumor and healthy tissues, adequate inmolibilization to minimize motion and account for intra-fraction movement[17].

The use of single fraction schedules has been found to be 40% less costly than 3 fraction schedules, according to Medicare 2009 rates, approximately 9000$ *vs* 150000$), although the reimbursement per fraction scheme has been a barrier in countries that implement it (US)[65]. The combination of greater patient comfort, with fewer hospital visits and shorter duration of treatments (one day *vs* one week), less burden on accelerators, and guarantees of acceptable toxicity and effectiveness[8,66], have all contributed to making SF SABR a valid treatment option to consider.

## RECOMMENDATIONS OF SF SABR DURING THE COVID-19 PANDEMIC

The SARS-CoV-2 has posed a major challenge for the practice of radiation oncology, especially in lung cancer patients that represents one of the greatest risk groups[67].

The first results of the Thoracic Cancers International COVID-19 Collaboration (TERAVOLT), the first registry created to establish the effects of SARS-CoV-2 infection in patients with thoracic cancers, report a higher mortality in this group of patients and less access to intensive care units, although 74% of cases corresponded to Stage I patients[68].

During the pandemic, we have had to evaluate alternative dose fractionation schemes and RT techniques, with two main goals: (1) To reduce the number of hospital visits and limit exposure to SARS-CoV-2 of patients receiving RT of curative intent for lung cancer; and (2) To make room, in the radiotherapeutic oncology services, to treat operable lung cancer patients who cannot receive surgery during the pandemic.

Several guidelines have been published (Table 5) in order to provide an objective and transparent framework with which to classify patients according to the stage of the pandemic and the healthcare resources available.

**Table 3 Benefits and constraints to using single fraction stereotactic ablative body radiotherapy schemes**

| Benefits | Constraints |
|---|---|
| Low medium-long term toxicity | Fear of severe toxicity in initial studies |
| Prospective efficacy and toxicity data | Insufficient long-term data |
| Convenience for patient, fewer hospital visits (indirect costs), shorter treatment times | |
| Less occupation of accelerators | |
| Reduced positioning errors between fractions | Greater risk of positioning errors |
| Peripheral tumors | Central tumors |
| Reduction in direct costs | |
| Less interference with systemic therapies | Cases of *Neumonitis recall* with some systemic therapies |
| Convenience for COVID-19 pandemic | |

**Table 4 Biologically effective dose**

| | Early tumor effects $\alpha/\beta = 10$ | Late tumor effects $\alpha/\beta = 3$ |
|---|---|---|
| 28 Gy in 1 fraction | 106 Gy | 289 Gy |
| 48 Gy in 4 fractions | 105 Gy | 240 Gy |

**Table 5 Summary of indications for stereotactic ablative body radiotherapy in pandemic COVID-19 in patients with early stage non-small cell lung cancer**

| ESTRO-ASTRO | UK | GOECP/SEOR |
|---|---|---|
| 45-54 Gy in 3 fx, 48 Gy in 4 fx; Maximum hypofractionation supported, 30-34 Gy in 1 fx (90% support if choosing hypofractionation) | Safe zone: 34 Gy in 1 fx<br>Tumours within 2.5 cm of the Chest Wall: 48-54 Gy in 3 fx<br>Moderately central: 50 Gy in 5 fx<br>Ultra-central: 45-50 Gy in 4-5 fx, 60 Gy in 8 fx<br>Central/ultra-central early stage tumours not suitable for stereotactic ablative radiotherapy: 50-60 Gy in 15 fx | Safe zone: 30-34 Gy, 1 fx (first option); 54 Gy in 3 fx<br>Peripheral lesions: 48 Gy in 4 fx (first option)<br>Central tumour: 50-60 Gy in 5 fx, 60 Gy in 8 fx |

ESTRO: European Society for Radiotherapy and Oncology; ASTRO: American Society for Radiation Oncology; GOECP: Oncologic Group for the Study of Lung Cancer; SEOR: Spanish Society of Radiation Oncology; UK: United Kingdom.

There is unanimous agreement about recommending SABR in operable patients with early stage NSCLC or oligometastatic lesions, owing to closed operating theatres or delayed surgical interventions [15-17].

Some teams have adopted an approach called SABR-BRIDGE (Stereotactic ABlative Radiotherapy Before Resection to avoId Delay for early-stage lunG cancer or oligomEts) in which SABR is used as a bridge to provide a radical treatment based on a combination of immediate SABR followed by programmed surgery 3 to 6 mo later[69].

Of the different SABR schemes available, the guidelines support administration of a SF treatment to reduce the number of visits during the pandemic. The preferred option is SF of 30-34 Gy for tumors ≤ 2 cm and > 1 cm distant from the chest wall that are outside the no-fly zone. However, the timing and the ability to implement changes in doses/fractionation schedules will depend upon the healthcare resources and technology available (for example, daily CBCT, 4 DCT *etc.*), and previous experience in SABR is preferable if SF dosing schemes are to be implemented.

## FUTURE DIRECTIONS

New systemic treatments have changed the paradigm for lung cancer, benefitting both OS and DFS.

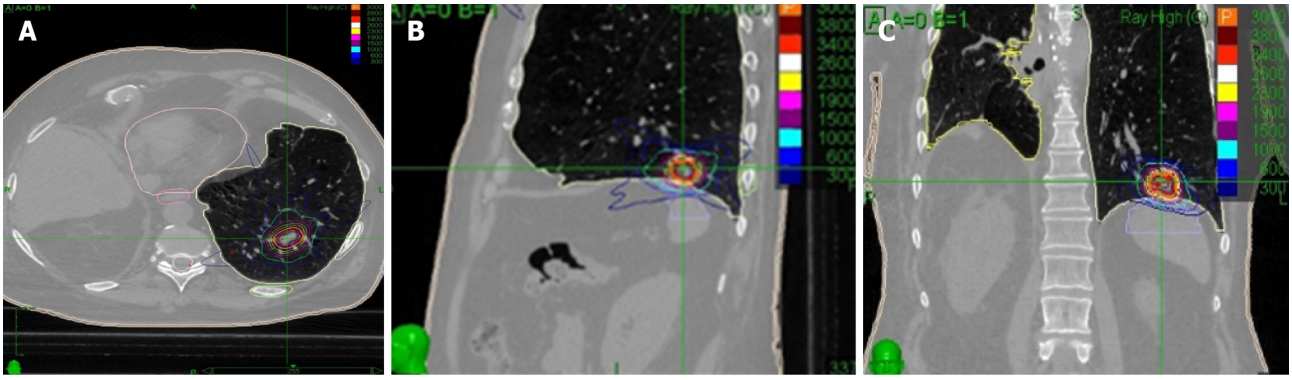


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**Figure 1 Stereotactic ablative body radiotherapy dose distribution for an oligometastasis from non-small cell lung cancer.** Treatment was delivered by means of the CyberKnife. A: Axial view; B: Sagittal view; C: Coronal view.

Immune checkpoint inhibitors (ICI) are a standard procedure of locally-advanced and metastatic NSCLC[24]. The use of targeted therapies in carriers of actionable mutations (EGFR, ALK, ROS1, BRAF, TRK, RET and MET) has also changed the course of advanced disease[70]. Unfortunately, platinum-based chemotherapy doublets produce low response rates[71]. Moreover, new treatments can present primary and/or secondary resistances that limit their efficacy in most patients. The exclusive use of ICI in monotherapy produces a clinical benefit in fewer than 30% of patients, and 20% of those receiving targeted therapies develop acquired resistance during the first year[24,72].

Several studies have shown that systemic treatment is effective at controlling the microscopic disease, but largely ineffective macroscopically[20]. This has led to studies exploring combinations of systemic treatments with local therapies such as SABR. The clinical benefit of this combination has been demonstrated in two randomized phase II studies in oligometastatic patients with NSCLC[21,22]. In both of these, the patients received induction ChT and were then randomized to receive SABR or surgery *vs* systemic treatment exclusively. Similar outcomes were obtained, and PFS was three times greater in the group receiving local consolidation therapy.

Randomized retrospective and prospective studies on the combined use of SABR and targeted therapies in stage IV NSCLC have also reported a clinical benefit for LC, PFS and OS[73,74]. This was confirmed in the Phase III randomized study (SINDAS), which showed an increase in PFS and OS[75].

The combination of ICI and SABR (I-SABR) is attracting even more interest. This is because SABR can induce an effective immunogenic death that can reactivate the antitumoral immune response[24]. A systematic review of stage IV NSCLC found that I-SABR increased the objective response rate (ORR) in 40% and also the PFS[76]. The PEMBRO-RT study (phase II randomized) used SABR (24 Gy in 3 fractions) prior to starting pembrolizumab, and reported an ORR, PFS and OS of 36%, 6.6 mo and 15.9 mo in favor of the combination[77]. Bauml *et al*[78] (phase II study of one arm) evaluated the combination of local ablative therapies with pembrolizumab and found a PFS of 19 mo and an OS of 77.5% at two years. A pooled analysis of the PEMBRO-RT and MDACC trials reported better outcomes for I-SABR with a median PFS and OS of 9 mo and 19.2 mo, respectively[79].

In the light of these promising results for I-SABR in advanced disease, current research is focusing on its benefits in early stages. One example is the PACIFIC-004 study, a multicentric phase III trial that combines SABR with durvalumab in stage I-II[80].

Although current evidence tends to favor hypofractionation, there is still controversy regarding the optimum fractionation schedule. Some ongoing studies are attempting to evaluate the role of single fraction SABR combined with immunotherapy. One example is the NCT03217071 trial that uses induction SABR at 12 Gy associated with pembrolizumab in stages I-IIIA. In advanced disease, the NCT02639026 trial evaluates the 17Gy scheme associated with durvalumab + tremelimumab[81].

Carbon ion radiotherapy (CIRT) has also proven effective in NSCLC. The use of CIRT in single fraction has achieved LC rates of 95% at 5 years with doses higher than 48 GyE[82]. Several possible synergistic mechanisms have been proposed for combinations with immunotherapy, but this research is still ongoing[83].

## CONCLUSION

SF SABR is a valid treatment option in patients with lung cancer owing to an increased convenience of this approach, its lower costs and greater flexibility for combining with systemic therapy. During the SARS-CoV-2 pandemic, there has been renewed interest in hypofractionated and ultra-short schedules including SF, which has transformed the paradigm of radiation oncology.

Results reported in the literature reveal comparable local control, PFS and OS, late onset toxicity and quality-of-life for both SF SABR and multifraction SABR in primary NSCLC and there are promising outcomes in lung metastases.

However, there are some settings in which SF could entail too high a toxicity risk such as: patients who have received prior RT, when PTV > 50 cc, or in peripheral locations where noncompliance of SF with dosing limits for healthy tissues could endanger structures such as the chest wall. Moreover, the use of this scheme in centrally-located tumors with SABR is still controversial owing to toxicity risks and the current evidence so should be used in a clinical trial scenario.

The radiobiology of SF and combinations of this technique with immunotherapy are still under investigation, and studies focusing on high dose ablative regimens will continue.

Combining SABR with systemic treatments is safe and effective. Preclinical trials have reported an immune effect for SABR in a SF, and this is also easier to deliver between one systemic treatment and the next. However, the clinical application of SF with immunotherapy to trigger synergistic effects is still being investigated.

## FOOTNOTES

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*MINIREVIEWS*

# Optimal timing of thoracic irradiation for limited stage small cell lung cancer: Current evidence and future prospects

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## Abstract

Lung cancer is a global health concern as the leading cause of cancer related mortality worldwide. Small cell lung cancer (SCLC) poses a formidable challenge to the treating physicians with the worst prognosis among all lung cancers. However, limited stage SCLC (LS-SCLC) has a relatively better outcome with multimodality management. Efforts have been focused on optimal integration of treatment modalities to achieve an improved therapeutic ratio for patients with LS-SCLC. While chemotherapy and thoracic radiation therapy (TRT) are primary components of initial management for LS-SCLC, there is no consensus on optimal timing of TRT. Within this context, we herein provide a concise overview of current evidence and future prospects regarding the optimal timing of thoracic irradiation for LS-SCLC in light of the literature.

**Key Words:** Small cell lung cancer; Thoracic irradiation; Limited stage small cell lung cancer; Timing of thoracic radiation therapy; Thoracic radiation therapy

**Core Tip:** There has been extensive effort to establish optimal timing of thoracic radiation therapy (TRT) in limited stage small cell lung cancer (LS-SCLC) management. While late TRT may have utility for management of LS-SCLC patients who may not tolerate curative-intent upfront chest irradiation due to excessive tumor burden at the outset, early TRT allows for exploiting the synergistic effect of chemoradiotherapy to eradicate as many tumor cells as possible in a shorter timeframe. Admittedly, differences in trial designs, definition of early and late TRT, patient selection criteria, administered chemotherapy regimens, treatment compliance, TRT dose and fractionation may affect treatment outcomes.

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## INTRODUCTION

Lung cancer presents a major and global health concern as a leading cause of cancer related mortality worldwide[1,2]. The 2 major histological types of lung cancer include small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). While NSCLC is the most common type, SCLC is typically associated with worse prognosis due to short doubling time and high growth fraction[3-7]. SCLC has been traditionally staged as limited stage SCLC (LS-SCLC) and extensive stage SCLC (ES-SCLC) by the Veterans' Administration Lung Study Group (VALSG) two-stage classification scheme, however, International Association for the Study of Lung Cancer staging with tumor, node, metastasis classification may also be used[8-10]. According to VALSG system, LS-SCLC is defined as disease confined to one hemithorax which can be adequately encompassed in a reasonable radiation portal. ES-SCLC refers to disease extending beyond one hemithorax which can not be encompassed within a tolerable radiation portal and may include presence of malignant pleural or pericardial effusions, contralateral hilar or supraclavicular lymph nodes, and hematogenous metastases[9,10]. While the overall prognosis of SCLC is typically poor, a subgroup of patients with LS-SCLC may have relatively more favorable treatment outcomes[11]. In light of high level evidence from systematic reviews, guidelines, and metaanalyses, current standard management of LS-SCLC includes combination of chemotherapy and thoracic radiation therapy (TRT)[12-16]. While there is consensus on combined modality management for LS-SCLC, controversies remain regarding target volumes, dose fractionation regimens and optimal sequencing of chemotherapy and TRT[17,18]. Herein, we provide a concise overview of current evidence and future prospects regarding the optimal timing of thoracic irradiation for LS-SCLC in light of the literature.

## COMBINED MODALITY MANAGEMENT FOR LS-SCLC

Addition of TRT to chemotherapy has been shown to improve survival of patients with LS-SCLC as demonstrated by high level evidence[15,16]. In this context, combined modality management with chemotherapy and TRT has been standard treatment for LS-SCLC. Since the mechanism of action is different between these 2 modalities, there is potential for additive and synergistic effects which may lead to improved therapeutic outcomes[18]. SCLC is well known for its propensity to disseminate early in the course of the disease. From this standpoint, it may be feasible to consider the potential of combining 2 different therapeutic modalities for eradication of tumor clonogens to achieve both local and systemic control. In addition to eradication of tumor cells by different mechanisms, synchronous administration of chemotherapy may also play a radiosensitizer role which may enhance the overall effect of combined modality management[18,19].

Main rationale of combined modality management is to eradicate as many tumor cells as possible in a shorter timeframe by exploiting the synergistic effect of chemoradiotherapy. SCLC has tendency for early systemic dissemination, however, there is great potential for achieving good response from chemoradiotherapy given the radiosensitivity and chemosensitivity of tumor cells. Combined modality management may also offer a judicious strategy to overcome accelerated repopulation which is an important cause of treatment failures[18].

## OPTIMAL TIMING OF THORACIC IRRADIATION FOR LS-SCLC

Optimal TRT timing in LS-SCLC management has been the subject of several studies, systematic reviews and metaanalyses over the years[20-41]. Selected studies of early and late TRT for LS-SCLC management are summarized in Table 1.

Murray *et al*[20] reported outcomes of a randomized National Cancer Institute of Canada Clinical Trials Group study including 308 eligible patients with LS-SCLC. The study included 155 patients in the early TRT arm (starting in day 22) and 153 patients in the late TRT arm (starting in day 106). Administered chemotherapy regimen included cyclophosphamide, doxorubicin, and vincristine alternating with etoposide and cisplatin, delivered for 3 cycles each every 3 wk. Dose of TRT was 40 Gy delivered in 15 daily fractions over 3 wk. Median progression free survival (PFS) was 15.4 mo in early TRT arm and 11.8 mo in late TRT arm. There was statistically significant improvement in 3 year PFS (26% *vs* 19%, $P = 0.036$), 3 year overall survival (OS) (29.7% *vs* 21.5%, $P = 0.006$), and median survival (21.2 mo *vs* 16 mo, $P = 0.008$) in favor of early TRT[20].

Work *et al*[21] conducted a randomized study of initial *vs* late chest irradiation combined with chemotherapy in LS-SCLC on behalf of the Aarhus Lung Cancer Group from Denmark. A total of 199 consecutive patients were randomly assigned to receive initial chest irradiation or late chest irradiation given 18 wk delayed. There were 99 patients in early TRT arm and 100 patients in late TRT arm all receiving the same 9 cycles of combination chemotherapy including 3 cycles of cisplatin and etoposide and 6 cycles of cyclophosphamide, doxorubicin, and vincristine. Median survival was 10.5 mo in early TRT arm and 12 mo in late TRT arm. Timing of TRT was not found to affect on the incidence of in field recurrences, CNS recurrences, or OS in the study[21]. Inferior outcomes in this study may be partly explained by the reduced chemotherapy doses in the concurrent chemoradiation arm and changing of the TRT schedule from 40 Gy in 20 fractions to 45 Gy in 22 fractions during the study period. Admittedly, initially delivered TRT doses of 40 Gy in 20 fractions may be considered low in comparison with current management standards and may have contributed to inferior outcomes in the study.

Jeremic *et al*[22] reported outcomes of a randomized study on initial *vs* delayed accelerated hyperfractionated TRT and concurrent chemotherapy for LS-SCLC. The study was conducted at the Department of Oncology, University of Kragujevac, Yugoslavia. Out of the total 103 eligible patients, 52 patients were allocated to receive early TRT (starting on day 1) and 51 patients were allocated to receive late TRT (starting on day 43). All patients received a total TRT dose of 54 Gy delivered twice daily fractions of 1.5 Gy. Chemotherapy schedule consisted of concurrent daily carboplatin/etoposide (C/E) (30 mg each) and 4 sequential cycles of cisplatin/etoposide (PE) (30 mg/m$^2$ and 120 mg/m$^2$, respectively, on days 1 to 3). Median survival was 34 mo in early TRT arm and 26 mo in late TRT arm, and the Kaplan-Meier 5-year survival rates were 30% *vs* 15%, in favor of early TRT[22].

Gregor *et al*[23] conducted the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group randomized trial of alternating *vs* sequential radiotherapy/chemotherapy in LS-SCLC. A total of 335 eligible patients were randomized to 5 courses of cyclophosphamide, doxorubicin, and etoposide (CDE) chemotherapy followed by TRT and same total dose of chemotherapy and TRT split into 4 courses of 5 daily fractions delivered on days 14 to 21 of the second and subsequent chemotherapy courses. No significant difference was found between the 2 arms in terms of median survival (14 *vs* 15 mo in early *vs* late TRT arms), 1-year survival (60% *vs* 64% in early *vs* late TRT arms), 2 year survival (26% *vs* 23% in early *vs* late TRT arms), and 3-year survival (12% *vs* 15% in early *vs* late TRT arms)[23]. The study failed to confirm the superiority of an alternating schedule of delivery which may be partly explained by hematologic toxicity with this combination of chemotherapy and TRT.

Perry *et al*[24] reported the 10 year update of the experience of the Cancer and Leukemia Group B 8083 study assessing addition of TRT to chemotherapy in LS-SCLC. In the study, a total of 399 patients with LS-SCLC were randomized to receive TRT starting on day 1 (arm I) or day 64 of chemotherapy treatment (arm II), or chemotherapy alone with cyclophosphamide, vincristine, and etoposide (later, doxorubicin). Total TRT dose was 50 Gy delivered in daily fractions of 2 Gy over 5 wk. Median survival was 13.04 mo, 14.54 mo, and 13.58 mo in arm I, arm II, and arm III, respectively with statistical significance ($P = 0.0072$). The authors concluded that the 2 arms including TRT remained to be superior to chemotherapy alone with 10 years of follow-up[24].

Skarlos *et al*[25] conducted the randomized phase II Hellenic Cooperative Oncology Group (HeCOG) study assessing the timing of hyperfractionated TRT (early *vs* late) when given concurrently with chemotherapy. A total of 81 eligible patients with LS-SCLC were randomized to receive hyperfractionated TRT either concurrently with the first cycle of chemotherapy (early TRT group) or with the fourth cycle of chemotherapy (late TRT group). Chemotherapy included carboplatin delivered at an area under the curve of 6 as intravenous infusion followed by etoposide at a dose of 100 mg/m$^2$ intravenously for 3 consecutive days every 3 wk up to a total of 6 cycles. Overall response rate was 76% in early TRT group and 92.5% in late TRT group. Complete response rate was 40.5% and 56.5% in early and late TRT groups, respectively. Overall median survival was 17.5 and 17 mo, 2 year survival was 36% and 29%, 3 year survival was 22% and 13% in early and late TRT groups, respectively without statistical significance[25].

**Table 1 Selected randomized studies of early and late thoracic radiation therapy for limited stage small cell lung cancer management**

| Ref. | Period | Number of patients | Age | Performance status | Timing of RT (start of TRT) (d) | RT dose fractionation schedule | Chemotherapy Schedule | PCI | Survival | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|
| Murray *et al*[20], 1993, National Cancer Institute of Canada Clinical Trials Group Study | 1985-1988 | Total number of patients 308; 155 patients in early TRT group; 153 patients in late TRT group | Median age 61.8 yr in early TRT group; Median age 61.6 yr in late TRT group | ECOG 0-1 87% in early TRT group; ECOG 0-1 90% in late TRT group | Day 22 in early TRT group; Day 106 in late TRT group | 40 Gy/2.67 Gy daily RT (hypofractionation) | Platinum based chemotherapy | 86% of patients received PCI (2.5 Gy × 10 fractions) | Median survival 21.2 mo in early TRT group; 2-yr survival 40% in early TRT group; 3-yr survival 29.7% in early TRT group; Median survival 16 mo in late TRT group; 2-yr survival 34% in late TRT group; 3-yr survival 21.6% in late TRT group | 0.006 in favor of early TRT |
| Work *et al*[21], 1997, Aarhus Lung Cancer Group Study | 1981-1989 | Total number of patients 199; 99 patients in early TRT group; 100 patients in late TRT group | Age range 36-70 yr in early TRT group; Age range 36-69 yr in late TRT group | KPS 80-100 82% in early TRT group; KPS 80-100 80% in late TRT group | Day 1 in early TRT group; Day 120 in late TRT group | 40-45 Gy/2 Gy daily (conventional fractionation) split course RT over 7 wk | Platinum based chemotherapy | All early RT patients received PCI; 58% of late RT patients received PCI | Median survival 10.5 mo in early TRT group; 2-yr survival 20.2% in early TRT group; 3-yr survival 13.1% in early TRT group; Median survival 12 mo in late TRT group; 2-yr survival 19% in late TRT group; 3-yr survival 12% in late TRT group | Not statistically significant |
| Jeremic *et al*[22], 1997, University of Kragujevac, Yugoslavia study | 1988-1992 | Total number of patients 103; 52 patients in early TRT group; 51 patients in late TRT group | Age range 40-67 yr in early TRT group; Age range 44-66 yr in lateTRT group | KPS 90-100 52% in early TRT group; KPS 90-100 47% in late TRT group | Day 1 in early TRT group; Day 43 in late TRT group | 54 Gy 1.5 Gy BID (hyperfractionation) | Platinum based chemotherapy | All patients with complete or partial response received PCI (2.5 Gy × 10 fractions) | Median survival 34 mo in early TRT group; 2-yr survival 71.2% in early TRT group; 3-yr survival 48.1% in early TRT group; Median survival 26 mo in late TRT group; 2-yr survival 52.9% in late TRT group; 3-yr survival 39.2% in late TRT group | 0.027 in favor of early TRT |
| Gregor *et al*[23], 1997, EORTC Lung Cancer Co-operative Group Study | 1989-1995 | Total number of patients 335 | Median age 61 yr (range: 33-75 yr) | ECOG 0-1 in 311 patients | Day 42 in early TRT group; Day 91 in late TRT group | 12.5 Gy/2.5 Gy daily (1 wk on, 3 wk off) × 4 in early TRT group (hypofractionation); 50 Gy/2.5 Gy daily in late TRT group (hypofractionation) | No platinum based chemotherapy | PCI was not a formal part of the study, however, all patients with complete response were eligible | Median survival 14 mo in early TRT group; 2-yr survival 26% in early TRT group; 3-yr survival 12% in early TRT group; Median survival 15 mo in late TRT group; 2-yr survival 23% in late TRT group; 3-yr survival 15% in late TRT group | Not statistically significant |
| Perry *et al*[24], 1998, Cancer and Leukemia Group B (CALGB) study | 1981-1984 | Total number of patients 270; 125 patients in early TRT group; 145 patients in late TRT group | Age range 32-79 | ECOG 0-1 86% in early TRT group; ECOG 0-1 87% in late TRT group | Day 1 in early TRT group; Day 64 in late TRT group | 50 Gy/2 Gy daily conventionally fractionated RT over 5 wk | No platinum based chemotherapy | All patients received PCI (3 Gy × 10 fractions) | Median survival 13.04 mo in early TRT group; 2-yr survival 24% in early TRT group; 3-yr survival 7.2% in early TRT group; Median survival 14.54 mo in late TRT group; 2-yr survival 31.7% in late TRT group; 3-yr survival 13.8% in late TRT group | 0.0072 in favor of lateTRT |
| Skarlos *et al*[25], 2001, Hellenic | 1993-1999 | Total number of patients 81; 42 | Age range 40-76 yr in early | ECOG 0-1 76% in early TRT group; | Day 1 in early TRT | 45 Gy 1.5 Gy BID (hyperfractionation) | Platinum based chemotherapy | All patients with complete or near | Median survival 17.5 mo in early TRT group; 2-yr survival 36% in | Not statistically significant |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Cooperative Oncology Group (HeCOG) study | | patients in early TRT group; 39 patients in late TRT group | TRT group; Age range 38-79 yr in late TRT group | ECOG 0-1 85% in late TRT group | group; Day 56 in late TRT group | | | complete response received PCI (1.5 Gy BID × 6) | early TRT group; 3-yr survival 22% in early TRT group; Median survival 17 mo in late TRT group; 2-yr survival 29% in late TRT group; 3-yr survival 13 % in late TRT group | |
| Takada *et al*[26], 2002, Japan Clinical Oncology Group (JCOG) Study | 1991-1995 | Total number of patients 228; 114 patients in early TRT group; 114 patients in late TRT group | Age range 39-74 yr in early TRT group; Age range 30-74 yr in late TRT group | ECOG 0-1 95% in both early and late TRT groups | Day 2 in early TRT group; Day 85 in late TRT group | 45 Gy 1.5 Gy BID (hyperfractionation) | Platinum based chemotherapy | All patients with complete response received PCI (4 Gy × 6) | Median survival 27.2 mo in early TRT group; 2-yr survival 54.4% in early TRT group; 3-yr survival 29.8% in early TRT group; Median survival 19.7 mo in late TRT group; 2-yr survival 35.1% in late TRT group; 3-yr survival 20.2% in late TRT group | 0.097 in favor of early concurrent TRT but not statistically significant |

TRT: Thoracic radiation therapy; PCI: Prophylactic cranial irradiation.

Takada *et al*[26] reported the results of the Japan Clinical Oncology Group phase III study 9104 assessing concurrent *vs* sequential TRT in combination with cisplatin and etoposide for LS-SCLC. Total dose of TRT was 45 Gy delivered in twice daily fractions of 1.5 Gy over 3 wk. Patients were randomized to sequential or concurrent TRT arms. All patients received 4 cycles of cisplatin plus etoposide every 3 wk in the sequential arm or 4 wk in the concurrent arm. TRT was started on day 2 of the first cycle of chemotherapy in concurrent arm and after the fourth cycle in the sequential arm. Concurrent TRT conferred improved survival compared to sequential TRT ($P$ = 0.097, not statistically significant). Median survival was 19.7 mo *vs* 27.2 mo in the in the sequential and concurrent TRT arms, respectively. The 2, 3, and 5 year survival rates were were 35.1%, 20.2%, and 18.3% *vs* 54.4%, 29.8% and 23.7% for patients receiving sequential *vs* concurrent TRT, respectively[26].

While all these randomized studies have addressed sequencing of chemotherapy and TRT in multimodality management of LS-SCLC, there are several critical points to consider in interpretation of the results from the perspective of TRT timing. Trial designs and protocols, patient selection criteria, definition of early and late TRT, administered chemotherapy regimens and compliance, TRT doses and fractionation schemes, follow up durations and outcome measures show significant diversities which emphasizes the need for vigilance in interpretation of the results. Administered TRT dose and treatment delivery techniques, dose and content of chemotherapy regimens in some of these studies may be considered inadequate and outdated as compared to current treatment standards.

There have also been more recent studies and metaanalyses addressing timing of TRT in LS-SCLC. Huncharek and McGarry[27] conducted a metaanalysis of timing of chest irradiation in combined modality treatment of LS-SCLC. Eight randomized trials including 1574 patients were analyzed, and 60% relative benefit was found in 2 year OS for early TRT which increased to 81% when only trials using cisplatin/etoposide based chemotherapy were included[27].

Bayman *et al*[28] assessed impact of early *vs* late TRT on survival for patients with LS-SCLC. A total of 70 consecutive patients receiving chemoradiotherapy for LS-SCLC were retrospectively analyzed. Administration of TRT was either after 1 to 2 cycles of chemotherapy (early TRT) or after 3 to 6 cycles of chemotherapy (late TRT). At a median follow-up duration of 2 years, late TRT was found to provide

improved response rate[28].

A metaanalysis by Pijls-Johannesma *et al*[29] used a different definition for early TRT as starting within 30 days of chemotherapy initiation. Seven randomized trials were included in the metaanalysis, and no statistically significant difference was found in 2-year OS rates ($P$ = 0.18). However, a statistically significant survival improvement was observed in favor of early TRT when the only trial using non-platinum based chemotherapy was excluded ($P$ = 0.01). The authors emphasized that the results should be interpreted with caution given the potential influence of patient selection, systemic treatment, and compliance rates[29].

American Radium Society Thoracic Appropriate Use Criteria Committee reported consensus recommendations for LS-SCLC[30]. The panel reaffirmed that early delivery of TRT was supported by high level evidence and suggested that it was appropriate for TRT to be incorporated in combined modality management of LS-SCLC no later than second cycle of chemotherapy[30].

Sun *et al*[35] conducted aphase III trial of concurrent TRT with either first or third cycle chemotherapy for LS-SCLC. TRT dose was 52.5 Gy in 25 daily fractions of 2.1 Gy delivered over 5 wk. Chemotherapy consisted of 4 cycles of etoposide/cisplatin which was delivered every 21 d. Median OS and PFS did not significantly differ between early and late TRT arms. Also, significantly lower rate of neutropenic fever was observed in the late TRT arm which could be partly explained by relatively smaller postchemotherapy TRT treatment volumes[35].

De Ruysscher *et al*[36] assessed impact of earlier or later TRT and shorter or longer TRT in LS-SCLC by conducting an individual patient data metaanalysis on behalf of the RadioTherapy Timing in SCLC (RTT-SCLC) Collaborative Group. Importance of using individual patient data was emphasized. Data from 9 trials including 2305 patients were available for the analysis. Median follow-up duration was 10 years. OS was not significantly effected by earlier or shorter *vs* later or longer TRT when all trials were analyzed together. Nevertheless, earlier or shorter TRT resulted in improved OS when trials including similar proportion of patients in both arms with respect to chemotherapy compliance were analyzed. Absolute gain in 5-year OS was 7.7% with earlier or shorter TRT when trials with similar chemotherapy compliance in both arms were analyzed, albeit with a higher incidence of severe acute esophagitis[36].

Wong *et al*[37] examined the National Cancer Data Base to evaluate practice patterns and survival for TRT timing in association with chemotherapy for non metastatic SCLC. A total of 8391 patients were included, and early TRT was found to improve survival compared to late TRT particularly when hyperfractionated TRT was used. Multivariate analysis revealed that hyperfractionated TRT was associated with reduced mortality[37].

Zhao *et al*[38] assessed effects of TRT timing and duration on PFS in LS-SCLC. A total of 197 patients receiving chemoradiotherapy for LS-SCLC were retrospectively analyzed. Early and short TRT was found to be correlated with longer PFS on univarite analysis. The study confirmed that early and short TRT had a positive prognostic role in LS-SCLC particularly for patients receiving hyperfactionated TRT and etoposide/cisplatin chemotherapy[38].

Results of a survey among 309 US Radiation Oncologists on timing of TRT with chemotherapy in LS-SCLC by Farrell *et al*[39] revealed that adherence to guidelines was excellent. When delivering TRT concurrently with chemotherapy, 71%, 25%, and 4% of participants preferred beginning TRT in cycle 1, cycle 2, cycle 3 or later of chemotherapy, respectively[39].

Hu *et al*[40] compared standard hyperfractionated TRT with hypofractionated TRT in combination with concurrent chemotherapy for LS-SCLC in a retrospective study. Analysis of patients enrolled in 2 independent prospective studies revealed that both hyperfractionated and hypofractionated TRT delivered with concurrent EP chemotherapy may confer good locoregional control and OS. The authors concluded that early commencement of TRT and utilization of a short course TRT schedule should be considered[40].

Hasan *et al*[41] evaluated optimal timing of TRT in LS-SCLC with daily fractionation using the National Cancer Database (NCDB). Trends in timing of TRT in LS-SCLC treated with daily fractionation, the significance of 30 day window to start TRT in this patient population, as well as optimal duration and completion times of TRT were assessed. Three and 5-year actuarial survival rates were 32.7% and 22.9% *vs* 28% and 18.4% when TRT was initiated within 30 d and beyond 30 d of chemotherapy, respectively ($P$ < 0.001). Multivariable analysis revealed that commencement of TRT beyond 30 d of chemotherapy was associated with reduced survival[41].

To summarize, the literature includes conflicting results regarding the optimal timing of TRT in multimodality management of LS-SCLC. Different results between the studies may be partly explained by differences in trial designs, definition of early and late TRT, patient selection criteria, administered chemotherapy regimens, treatment compliance, TRT dose and fractionation.

## CONCLUSION

There has been extensive effort to establish optimal timing of TRT in LS-SCLC management. The debate continues despite the accumulating data from randomized studies, systematic reviews, and metaanalyses. While late TRT may have utility for management of LS-SCLC patients who may not

tolerate curative-intent upfront chest irradiation due to excessive tumor burden at the outset, early TRT allows for exploiting the synergistic effect of chemoradiotherapy to eradicate as many tumor cells as possible in a shorter timeframe. Admittedly, differences in trial designs, definition of early and late TRT, patient selection criteria, administered chemotherapy regimens, treatment compliance, TRT dose and fractionation may affect treatment outcomes.

It appears that thorough individualized patient assessment gains critical importance in decision making for optimal TRT timing in combined modality management of LS-SCLC. Nevertheless, early TRT may be suggested to overcome accelerated repopulation and improve treatment outcomes particularly when compliance with chemotherapy is high. Future trials should focus on optimal TRT dose and fractionation, incorporation of immunotherapy approaches, adaptive TRT strategies and contemporary image guidance techniques to improve the toxicity profile of radiation delivery.

### *Article highlights*

Lung cancer presents a major and global health concern as a leading cause of cancer related mortality worldwide. While chemotherapy and TRT are primary components of initial management for LS-SCLC, there is no consensus on optimal timing of TRT.

While several randomized studies have addressed sequencing of chemotherapy and TRT in multimodality management of LS-SCLC, there are several critical points to consider in interpretation of the results from the perspective of TRT timing. Trial designs and protocols, patient selection criteria, definition of early and late TRT, administered chemotherapy regimens and compliance, TRT doses and fractionation schemes, follow up durations and outcome measures show significant diversities which emphasizes the need for vigilance in interpretation of the results.

While late TRT may have utility for management of LS-SCLC patients who may not tolerate curative-intent upfront chest irradiation due to excessive tumor burden at the outset, early TRT allows for exploiting the synergistic effect of chemoradiotherapy to eradicate as many tumor cells as possible in a shorter timeframe. It appears that thorough individualized patient assessment gains critical importance in decision making for optimal TRT timing in combined modality management of LS-SCLC. Nevertheless, early TRT may be suggested to overcome accelerated repopulation and improve treatment outcomes particularly when compliance with chemotherapy is high.

Future trials should focus on optimal TRT dose and fractionation, incorporation of immunotherapy approaches, adaptive TRT strategies and contemporary image guidance techniques to improve the toxicity profile of radiation delivery.

## FOOTNOTES

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*MINIREVIEWS*

# Artificial intelligence and cholangiocarcinoma: Updates and prospects

Hossein Haghbin, Muhammad Aziz

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## Abstract

Artificial intelligence (AI) is the timeliest field of computer science and attempts to mimic cognitive function of humans to solve problems. In the era of "Big data", there is an ever-increasing need for AI in all aspects of medicine. Cholangiocarcinoma (CCA) is the second most common primary malignancy of liver that has shown an increase in incidence in the last years. CCA has high mortality as it is diagnosed in later stages that decreases effect of surgery, chemotherapy, and other modalities. With technological advancement there is an immense amount of clinicopathologic, genetic, serologic, histologic, and radiologic data that can be assimilated together by modern AI tools for diagnosis, treatment, and prognosis of CCA. The literature shows that in almost all cases AI models have the capacity to increase accuracy in diagnosis, treatment, and prognosis of CCA. Most studies however are retrospective, and one study failed to show AI benefit in practice. There is immense potential for AI in diagnosis, treatment, and prognosis of CCA however limitations such as relative lack of studies in use by human operators in improvement of survival remains to be seen.

**Key Words:** Artificial intelligence; Machine learning; Cholangiocarcinoma; Diagnosis; Treatment; Prognosis

**Core Tip:** The wide array of modalities available to treat cholangiocarcinoma (CCA) in addition to the diversity of the tumor urges us to use individualized therapy. To establish the proper approach to diagnose, treat, and prognose CCA, analysis of available data is the key to achieve the individualized care. Artificial intelligence can be a potential modality for achieving this goal.

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## INTRODUCTION

The ever-growing rate of technological advancement in medicine has resulted in the era of "Big data". Artificial intelligence (AI) and its various techniques are used to harness the infinite potential of Big data in medical field[1]. AI, the timeliest field of computer science, involves development of computer algorithms attempting to mimic cognitive function of humans in order to learn and solve problems[2]. Since invention of the first operational computer by Alan Turing in 1940s, we have seen a prodigious rise in AI advancement. Machine learning (ML) is a very practical area of AI that enables computers to learn without direct programming. ML helps machines learn from previous data and improve their learning behavior by gaining experience from data patterns, thereby establishing ever improving predictive models[3]. Various AI techniques including representation learning, natural language processing, and different ML techniques, such as regression trees, support-vector machines (SVM), artificial neural networks (ANN) and more recently, deep learning (DL), have been used in medical field [4]. ML and DL have vastly increased the scope of AI and enabled individualized medicine rather than algorithm-only-based care and has resulted in improved accuracy, efficiency, and outcomes[4].

Despite all the benefits of AI, one should be wary of the drawbacks[5]. The field of AI brings enormous potential however it concurrently brings big ethical problems. ML algorithms, to some extent, function as "black-boxes" where there is difficulty in finding the logic behind the decision by the machine. This will have medicolegal consequences which will be more pronounced as the models become more sophisticated and companies behind ML software reluctant to reveal the details of their software. Moreover, AI poses threats to privacy, data security, and patient autonomy. Lastly, ML algorithms do make mistakes and may not provide accurate results across race, gender, and socioeconomic status spectrum[5].

Cholangiocarcinoma (CCA) is the second most common primary malignancy of the liver. CCA originates from the epithelial cells of the bile ducts exclusive of gallbladder and ampulla of Vater. CCA is an aggressive tumor diagnosed sporadically in advanced stages with high mortality[6]. The incidence of CCA is increasing; therefore, there is increased interest in diagnosis, prognosis, and treatment of this malignancy[7]. Both serum markers and radiologic imaging are used for diagnosis of CCA. A combination of serum markers like liver function tests, carbohydrate antigen (CA) 19-9, and carcinoembryonic antigen (CEA) are utilized to diagnose the disease[8]. The presence of the vast array of serum markers has led to utilization of the markers in novel AI tools in combination with imaging. Positron emission tomography with fluorodeoxyglucose (FDG-PET) integrated with computed tomography (CT) and Magnetic resonance imaging (MRI) in combination with magnetic resonance cholangiopancreatography (MRCP) are valuable tools harnessed by AI to assess the extent of tumor and stage the disease[9, 10]. Treatment includes surgical management, neoadjuvant/adjuvant chemotherapy and chemoradiotherapy, hepatic artery radioembolization, and orthotopic liver transplant in selected patients[11-14]. Endoscopic retrograde cholangiopancreatography (ERCP) has two roles of diagnosis and treatment of CCA. Its diagnostic role includes inspecting and providing samples from the biliary system. As palliative treatment, stent placement provides increased quality of life especially in most unresectable cases[15]. Novel AI tools have been able to help in individualizing candidates for each treatment modality.

Increased mortality from CCA in the last decade has coincided with development of AI technology. Figure 1 illustrates how AI can be used to diagnose, treat, and prognose patients with CCA. This review depicts how AI can analyze the radiologic, serologic, and histologic markers of CCA to diagnose, stage, and aid with an individualized treatment plan in addition to giving a prognostic estimate with or without treatment modalities.

AI has shown promise to aid in diagnosis of CCA. AI is particularly helpful in CCA diagnosis as the condition is not common and there is heterogeneity in anatomical location of the tumor and risk factors of the tumor[16]. This makes the traditional algorithms inferior compared to AI. Many AI tools in the field of ML have been utilized for diagnosis of CCA (Table 1). LR is a linear regression model used for binary classification of problems[17]. SVM is an appropriate model for small samples, high-dimensional,

**Table 1 Advantages and disadvantages of artificial intelligence models used for cholangiocarcinoma diagnosis in radiology**

| AI technology | Imaging modalities used in | Advantages | Disadvantages |
|---|---|---|---|
| Logistic regression | US/CT | Interpretable | Low precision |
| Support-vector machine | US/CT/MRI | Avoids overlearning and dimension disaster problems | Prone to missing data |
| Extreme learning machine | CT | Does not need high amount of data for training | Slow processing speed |
| Artificial neural network | CT/MRI | High generalization power | Needs long training time |
| Convolutional neural network | US/CT/MRI | Higher efficacy and speed as there is no need to compute features as first step | Needs large training data |

AI: Artificial intelligence; CT: Computed tomography; MRI: Magnetic resonance imaging; US: Ultrasound.

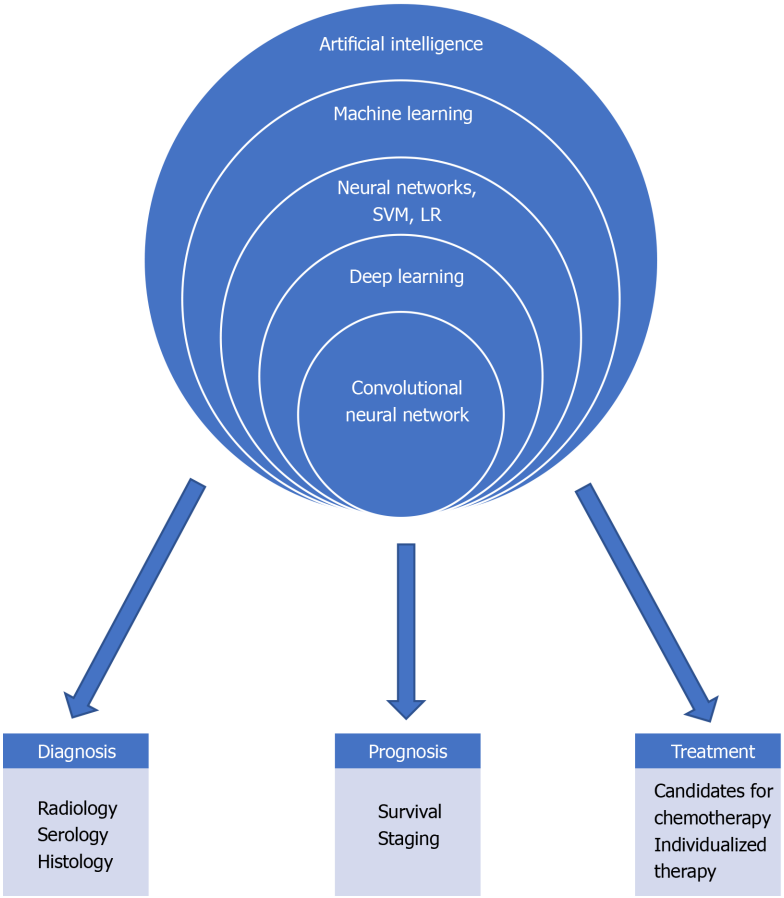


**Figure 1 Application of artificial intelligence in addressing cholangiocarcinoma.** LR: Logistic regression; SVM: Support-vector machine.

and non-linear patterns assigning labels to objects and has advantage of avoiding "over learning" problem[18]. ANN or multilayer perceptron is an attempt to simulate the biologic nervous system with neurons interconnected able to do parallel processing[17]. Developed by Huang *et al*, Extreme Learning Machines (ELM) are a type of feedforward neural network models that have shown superiority over SVMs and traditional feedforward neural networks[19]. Convoluted neural network (CNN), a type of DL consists of multilayer of ANN that results in a superior learning ability of complex tasks and has been used in radiology and imaging of the malignancy and associating the radiological data to the clinicopathologic data[20,21]. Every method has their advantages and drawbacks illustrated in Table 1.

## AI IN THE DIAGNOSIS OF CCA

### *Serum markers*

Evaluation of serum markers is amongst the least invasive and most available data that is present in many patients even before there is a suspicion for diagnosis of CCA. Due to wide availability, these tests are used in adjunct with radiological and other clinical factors in diagnosis of CCA. Sometimes serological models are enough to diagnose the malignancy; for example, Negrini *et al*[22] developed a ML model that analyzed 15 bile acids of the serum and was able to diagnose CCA with good sensitivity of 79% and excellent accuracy, Area Under Curve (AUC), and specificity of 86.4%, 95%, and 100%, respectively. ANN based model using combination CCA associated carbohydrate antigen and alkaline phosphatase showed promise in diagnosing CCA with a sensitivity and specificity of more than 95% [23].

### *Cytology*

ERCP and Cytology of brushings is a valuable tool for diagnosis of CCA. As a common malignant cause of biliary stricture is CCA, cytology can be crucial in early stages of the malignancy when radiology may have limited roles. Urman *et al*[24], using a neural network model studying metabolomic and proteomic profile of bile from 36 CCA patients, was able to satisfactorily distinguish CCA from benign stricture with AUC, sensitivity, and specificity of 98.4%, 94.1% and 92.3%, respectively.

### *Histology*

Histology remains the gold standard for diagnosis of malignancies including CCA. From their Shanghai laboratory, Sun *et al*[25] developed a CNN model for diagnosis of CCA from microscopic hyperspectral pathological slides with promising results. After setting up the first benchmark based on microscopic pathological images consisting of 880 images with pixels manually labeled as tumor or non-tumor for the AI learning, the CNN model was able to diagnose CCA with 88.3% accuracy[25]. AI assistance in histology has not always shown benefits. Stanford University researchers developed an AI diagnostic assistant using DL model to assist pathologists in differentiating hepatocellular carcinoma (HCC) from CCA (26). The model had a good accuracy rate of 84.2% on a set of 80 slides however it failed to improve performance among pathologists [Odds ratio (OR) 1.287, 95%CI: 0.886-1.871]. For all case difficulty levels, the model highly biased the decision of pathologists which led them to wrong diagnosis[26]. The authors concluded that this would question the use of current AI technology for difficult subspecialty tasks[26]. Sometimes CCA can manifest as cancer of unknown primary site (CUP) as it metastasizes to other organs. AI has been used to delineate source of CUP, consisting of 3 to 5% of tumors[27]. CUP-AI-Dx is a CNN model that was trained on more than 18,000 tumors including CCA and has achieved an accuracy of 98.54% in finding the primary site of tumor from the human body system in cross-validation[28].

### *CT*

To elucidate the lesion detected by ultrasound, further workup is required with CT, MRI, and MRCP. As CNN is a DL technique that consists of multilayers of ANN, it has shown great potential especially once it comes to radiology image analysis of pixels. Human yield in diagnosing CCA is limited. Nakai *et al*[29] have developed CNN models factoring in a combination of CT with serum tumor markers including CEA and CA 19-9. Their CNN model was superior to human radiologists in detecting CCA (0.68 *vs* 0.45; $P = 0.04$) [29]. One challenge in diagnosing CCA is differentiating intrahepatic CCA from other intrahepatic malignancies. Xu *et al*[30] have developed an AI model on 28 intrahepatic lymphomas and 101 CCAs. Their model was able to differentiate between the two tumors with AUC and accuracy both more than 85%. Pannoprat *et al*[31] have developed CNN model that can differentiate between CCA and hepatocellular carcinoma (the most common primary liver malignancy) with an 88% accuracy. Zhang *et al*[32] performed a retrospective analysis of contrast enhanced CT of 86 patients with CCA and 46 with combined CCA/HCC tumors, which are difficult to differentiate from CCA necessitating biopsy and surgery. Using ML techniques to classify the lesions as CCA or combined CCA/HCC achieved an AUC of 94.2%[32].

### *MRI and MRCP*

MRI and MRCP have a superior function to diagnose CCA than CT due to ability to illustrate soft tissue, vasculature, and biliary system better than that of CT. ML has been widely utilized in MRI and MRCP. Xu *et al*[33] and Yu *et al*[34] each studied MRI of more than 100 patients with CCA and developed SVM models that showed superiority (validation group AUC 87.0% and 90%, respectively). Logeswaran *et al* [35] in a 2009 study showed 88 to 94% detection rate of Multilayer Perceptron ANN in diagnosis of CCA in MRCP. Yang *et al*[36] developed an AI model for MRI diagnosis and evaluation of extent of lymph node metastasis of CCA patients. After training the model on 100 CCA patients, the model was able to differentiate high *vs* low risk CCA groups and lymph node metastasis with AUCs of 80% and 90% in testing cohorts, respectively[36]. Table 2 lists the studies using AI models to diagnose CCA.

**Table 2 Studies utilizing artificial intelligence in the diagnosis of cholangiocarcinoma**

| Ref. | Year of publication | Title of study | Diagnostic modality | AI model |
|---|---|---|---|---|
| Chu *et al*[44] | 2021 | Radiomics using CT images for preoperative prediction of futile resection in intrahepatic cholangiocarcinoma | CT | LR |
| Ibragimov *et al*[45] | 2020 | Deep learning for identification of critical regions associated with toxicities after liver stereotactic body radiation therapy | CT | CNN |
| Liu *et al*[46] | 2021 | Can machine learning radiomics provide pre-operative differentiation of combined hepatocellular cholangiocarcinoma from hepatocellular carcinoma and cholangiocarcinoma to inform optimal treatment planning? | MRI, CT | SVM |
| Logeswaran[35] | 2009 | Cholangiocarcinoma--an automated preliminary detection system using MLP | MRCP | ANN |
| Midya *et al*[47] | 2018 | Deep convolutional neural network for the classification of hepatocellular carcinoma and intrahepatic cholangiocarcinoma | CT | CNN |
| Nakai *et al*[29] | 2021 | Convolutional neural network for classifying primary liver cancer based on triple-phase CT and tumor marker information: a pilot study | CT, tumor markers | CNN |
| Negrini *et al*[22] | 2020 | Machine Learning Model Comparison in the Screening of Cholangiocarcinoma Using Plasma Bile Acids Profiles | Serum bile acids | ML |
| Pattanapairoj *et al*[23] | 2015 | Improve discrimination power of serum markers for diagnosis of cholangiocarcinoma using data mining-based approach | Tumor markers | ANN |
| Peng *et al*[48] | 2020 | Preoperative Ultrasound Radiomics Signatures for Noninvasive Evaluation of Biological Characteristics of Intrahepatic Cholangiocarcinoma | US | SVM |
| Peng *et al*[49] | 2020 | Ultrasound-Based Radiomics Analysis for Preoperatively Predicting Different Histopathological Subtypes of Primary Liver Cancer | US | Radiomics |
| Ponnoprat *et al*[31] | 2020 | Classification of hepatocellular carcinoma and intrahepatic cholangiocarcinoma based on multi-phase CT scans | CT | CNN |
| Selvathi *et al*[50] | 2013 | Automatic segmentation and classification of liver tumor in CT images using adaptive hybrid technique and Contourlet based ELM classifier | CT | ELM |
| Sun *et al*[25] | 2021 | Diagnosis of cholangiocarcinoma from microscopic hyperspectral pathological dataset by deep convolution neural networks | Histology | CNN |
| Urman *et al*[24] | 2020 | Pilot Multi-Omic Analysis of Human Bile from Benign and Malignant Biliary Strictures: A Machine-Learning Approach | Bile acids, lipids | ANN |
| Uyumazturk *et al*[26] | 2019 | Deep learning for the digital pathologic diagnosis of cholangiocarcinoma and hepatocellular carcinoma: evaluating the impact of a web-based diagnostic assistant | Histology | DL |
| Wang *et al*[51] | 2020 | SCCNN: A Diagnosis Method for Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma Based on Siamese Cross Contrast Neural Network | CT | ANN |
| Wang *et al*[52] | 2019 | Deep learning for liver tumor diagnosis part II: convolutional neural network interpretation using radiologic imaging features | MRI | DL |
| Xu *et al*[33] | 2019 | A radiomics approach based on support vector machine using MR images for preoperative lymph node status evaluation in intrahepatic cholangiocarcinoma | MRI | SVM |
| Xu *et al*[30] | 2021 | Differentiation of Intrahepatic Cholangiocarcinoma and Hepatic Lymphoma Based on Radiomics and Machine Learning in Contrast-Enhanced Computer Tomography | Contrast enhanced CT | ML |
| Yang *et al*[36] | 2020 | Radiomics model of magnetic resonance imaging for predicting pathological grading and lymph node metastases of extrahepatic cholangiocarcinoma | MRI | Radiomics |
| Yao *et al*[34] | 2020 | A Novel Approach to Assessing Differentiation Degree and Lymph Node Metastasis of Extrahepatic Cholangiocarcinoma: Prediction Using a Radiomics-Based Particle Swarm Optimization and Support Vector Machine Model | MRI | SVM |
| Yasaka *et al*[53] | 2018 | Deep Learning with Convolutional Neural Network for Differentiation of Liver Masses at Dynamic Contrast-enhanced CT: A Preliminary Study | CT | CNN |
| Zhang *et al*[32] | 2020 | Differentiation combined hepatocellular and cholangiocarcinoma from intrahepatic cholangiocarcinoma based on radiomics machine learning | CT | Radiomics |
| Zhao *et al*[28] | 2020 | CUP-AI-Dx: A tool for inferring cancer tissue of origin and molecular | Tissue biopsy | CNN |

| | | | | |
|---|---|---|---|---|
| | | subtype using RNA gene-expression data and artificial intelligence | | |
| Zhou *et al*[54] | 2021 | Automatic Detection and Classification of Focal Liver Lesions Based on Deep Convolutional Neural Networks: A Preliminary Study | Multiphasic CT | CNN |

AI: Artificial intelligence; ANN: Artificial Neural Network; CCA: Cholangiocarcinoma; CNN: Convolutional neural network; CT: Computed tomography; DL: deep learning; ML: machine learning; ELM: Extreme learning machine; LR: Logistic regression; MRCP: Magnetic resonance cholangiopancreatography; MRI: Magnetic resonance imaging; SVM: Support-vector machine, US: Ultrasound.

## TREATMENT AND PROGNOSIS OF CCA

ML techniques have also been used for treatment and prognosis of CCA. Almost all studies use a combination of radiological, histological, serological, and clinical data for the best results in predicting the survival of the patients and their response to treatment. Table 3 illustrates the studies using AI models to treat and prognose CCA. The fact that such sophisticated models are needed is proof to the complexity of the CCA pathophysiology and ever developing variety of treatment protocols that makes decision making impossible without help of AI technology. One example of such potential is studied by Tsilimigras *et al*[37]. They constructed a ML model that predicted survival of CCA patients after surgery based on preop serological and radiological data[37]. They conducted an international multi-institutional study on 826 CCA patients, clustering them into groups based on CA 19-9, neutrophil-to-lymphocyte ratio, and tumor size. Their machine learning model showed an excellent agreement with cluster (k = 0.93, 95%CI: 0.90-0.96). This study shows that ML models detect patterns and clusters not detectable to humans using traditional statistical techniques[38]. In this study, AI was able to detect a group of high-risk patients otherwise undetectable. These groups benefit the most from additional neoadjuvant therapy prior to resection as they have a high recurrence[37,38].

### *CT imaging*

Another example of tight interrelation between prognosis and treatment is by Jeong *et al*[39] who elaborated a ML algorithm using the combination of serology, patient characteristics, and CT images of 1421 CCA patients to classify patients to stable and latent risk group. The model was able to predict the disease-free survival between latent and stable groups and response to adjuvant therapy in latent group with excellent ability proven by hazard ratios (HR) of 3.56 and 0.46, respectively ($P < 0.001$ for both) [39]. Tang *et al*[40] drew up a predictive model of CCA survival after studying 101 patients with CCA. Their AI model analyzed radiologic characteristics of the CT scan, tumor markers, and past clinical history like cirrhosis with AUC of 78% and 75% for 3-year and 5-year overall survival, respectively[40].

### *CA 19-9*

CA 19-9 as a tumor marker has shown promise in prognosis of CCA. Li *et al*[41] and Müller *et al*[42] each validated an AI model to prognosticate the CCA tumors based on clinical, tumor markers such as CA 19-9, serologic like albumin level, and clinical data like nodal metastasis. Li *et al*[41] model retrospectively studied a total of 1390 patients and achieved a Concordance Index (C-index) superior to the staging system proposed by the 8$^{th}$ edition of the American Joint Committee on Cancer (C-index: 0.693, 95%CI: 0.663-0.723). Müller *et al*[42] model was able to predict the 1-year survival of patients with an AUC of 89% and 80% for the training and validation sets, respectively.

### *Palliative measures*

Palliative measures like stent placement recommended for inoperable hilar CCAs, are also analyzed by AI models. Shao *et al* developed an ANN model based on data of 288 CCA patients requiring stent placement that can predict stent occlusion with high AUC of 96% (95%CI: 94-99%)[43].

## FUTURE DIRECTIONS

The literature review showed a wealth of studies utilizing AI in CCA, however there is room for much improvement. First, there is need for larger prospective studies including different races, nationalities, and socioeconomic statuses to validate role of AI in diagnosis, treatment, and prognosis of CCA. As study from Stanford showed the AI may not prove to be beneficial in all cases in real life; therefore, in some cases there is need for prospective studies showing AI effectiveness in practice[26]. This precaution is accentuated since there was a lack of negative studies in our review of the literature which can potentially bias toward increased efficacy of AI. Furthermore, the prognostic data should be validated by implementing the data into treatment strategies and seeing an increase in not only survival but also quality of life in CCA patients. One last recommendation for medical field is that healthcare professionals' education should be improved to prepare them for the ever-increasing role of AI in daily diagnosis, treatment, and prognosis of CCA and at the same time informing them of the current limits

**Table 3 Studies utilizing artificial intelligence in the treatment and prognostication of cholangiocarcinoma**

| Ref. | Year of publication | Title of study | AI variables | AI model |
|---|---|---|---|---|
| Jeong *et al*[39] | 2020 | Latent Risk Intrahepatic Cholangiocarcinoma Susceptible to Adjuvant Treatment After Resection: A Clinical Deep Learning Approach | CT, albumin, platelets, Diabetes, CA 19-9 | ML |
| Ji *et al*[55] | 2019 | Biliary Tract Cancer at CT: A Radiomics-based Model to Predict Lymph Node Metastasis and Survival Outcomes | CT reported LN features | ANN |
| Li *et al*[41] | 2020 | A Novel Prognostic Scoring System of Intrahepatic Cholangiocarcinoma With Machine Learning Basing on Real-World Data | CEA, CA 19-9, tumor stage | ML |
| Muller *et al*[42] | 2021 | Survival Prediction in Intrahepatic Cholangiocarcinoma: A Proof-of-Concept Study Using Artificial Intelligence for Risk Assessment | Tumor size, tumor boundary, serology | ANN |
| Shao *et al*[43] | 2018 | Artificial Neural Networking Model for the Prediction of Early Occlusion of Bilateral Plastic Stent Placement for Inoperable Hilar Cholangiocarcinoma | Tumor size, nodal involvement | ANN |
| Tang *et al*[40] | 2021 | The preoperative prognostic value of the radiomics nomogram based on CT combined with machine learning in patients with intrahepatic cholangiocarcinoma | Tumor size, cirrhosis in CT | Radiomics |
| Tsilimigras *et al*[37] | 2020 | A Novel Classification of Intrahepatic Cholangiocarcinoma Phenotypes Using Machine Learning Techniques: An International Multi-Institutional Analysis | Tumor size, nodal involvement, serology | ML |

AI: Artificial intelligence; ANN: Artificial Neural Network; CA 19-9: Carbohydrate antigen 19-9; CCA: Cholangiocarcinoma; CEA: Carcinoembryonic antigen; CT: Computed tomography; ML: Machine learning.

and future potentials of the AI technology.

## CONCLUSION

In the recent years, we have seen an increase in CCA incidence and, in parallel, a more exponential rise in AI utilization in medicine. AI will be able to utilize the vast amount of data to assist healthcare professionals in addressing CCA. Currently the AI models are showing potential in diagnosis, treatment, and prognosis of CCA. Nonetheless, AI has limits that should be considered; further research is needed to validate use of AI models in real life in use by medical professional to determine their effectiveness and acceptance as auxiliary tools to augment human intelligence. Finally, ethical issues regarding AI including equity and transparency will also need to be addressed to improve acceptance of the technologies by healthcare industry and, more importantly, the patients.

## FOOTNOTES

**Author contributions:** Haghbin H and Aziz M designed and performed the research study. Haghbin H and Aziz M wrote the manuscript; all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

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# Neurotrophic receptor tyrosine kinase family members in secretory and non-secretory breast carcinomas

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## Abstract

***BACKGROUND***

Breast cancer is the most common female cancer and a major cause of morbidity and mortality. Progress in breast cancer therapeutics has been attained with the introduction of targeted therapies for specific sub-sets. However, other subsets lack targeted interventions and thus there is persisting need for identification and characterization of molecular targets in order to advance breast cancer therapeutics.

***AIM***

To analyze the role of lesions in neurotrophic receptor tyrosine kinase (NTRK) genes in breast cancers.

***METHODS***

Analysis of publicly available genomic breast cancer datasets was performed for identification and characterization of cases with fusions and other molecular abnormalities involving *NTRK1*, *NTRK2* and *NTRK3* genes.

***RESULTS***

NTRK fusions are present in a small number of breast cancers at the extensive GENIE project data set which contains more than 10000 breast cancers. These cases are not identified as secretory in the database, suggesting that the histologic characterization is not always evident. In the breast cancer The Cancer Genome Atlas (TCGA) cohort the more common molecular lesion in NTRK genes is amplification of *NTRK1* observed in 7.9% of breast cancers.

***CONCLUSION***

Neurotrophin receptors molecular lesions other than fusions are observed more often than fusions. However, currently available NTRK inhibitors are effective

mainly for fusion lesions. Amplifications of *NTRK1*, being more frequent in breast cancers, could be a viable therapeutic target if inhibitors efficacious for them become available.

**Key Words:** Neurotrophic receptor tyrosine kinases; Breast cancer; Amplifications; Fusions; Tropomyosin related kinases



**Core Tip:** Molecular lesions in neurotrophic receptor tyrosine kinase (NTRK) receptors have been brought to the forefront of cancer therapy with the introduction of specific inhibitors which are effective in cancers with fusions involving the family of receptors. In breast cancer fusions involving the NTRK receptors are rarely seen and concern exclusively the secretory sub-type. In non-secretory breast carcinomas amplifications are observed in a minority of cases.

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## INTRODUCTION

Breast cancer is the most common neoplasm in women and a significant cause of morbidity and mortality. In United States alone, an estimated 284000 cases of breast cancer will occur in 2021, with more than 44000 resulting deaths[1]. Breast cancers represent about 30% of all cancers diagnosed in women. Despite recent advances in breast cancer therapies produced by an improved understanding of molecular pathogenesis, the disease remains difficult to treat when metastatic. It is currently well established that breast cancer does not represent a single entity, but several sub-types exist with implications for prognosis and treatment[2]. The most frequent sub-type is estrogen receptor (ER) positive and negative for the epidermal growth factor receptor (EGFR) family receptor 2, known as human EGFR receptor 2 (HER2) and is further divided in a more indolent disease corresponding with the genomic luminal A sub-type and a more aggressive, less estrogen-dependent disease aligning with the genomic luminal B classification[3]. Another breast cancer sub-type is positive for the HER2 receptor, while the triple negative sub-type is negative for both ER and HER2, as well as the receptor for Progesterone, PR, which is positive in most ER positive cases. Treatments for each sub-type has evolved to differ significantly and therapeutic decisions in breast cancer depend on the sub-type. HER2 positive cancers, for example, are treated with monoclonal antibodies, small molecule kinase inhibitors and antibody drug conjugates targeting HER2[4].

Several other receptor tyrosine kinases have been implicated in cancer pathogenesis and progression and treatments targeting some of them exist. These include the angiogenesis kinase receptor vascular endothelial growth factor receptor (VEGFR) and its ligand VEGF, EGFR, fibroblast growth factor receptor (FGFR) and c-Met, the receptor for hepatocyte growth factor (HGF). In breast cancer, besides HER2, no receptor tyrosine kinase inhibitors have been approved. Recently, inhibitors of the neurotrophic kinase family of tyrosine kinase receptors have become available and confirmed to be effective in cancers with fusions involving these receptors[5]. These fusions are observed in the majority of rare histologic types of cancers such as mammary analogue secretory carcinomas of the salivary glands and secretory breast cancers but are exceedingly rare in more common histologic subtypes of cancers[6]. The current analysis examines fusions and other molecular lesions of neurotrophin receptors in secretory and non-secretory carcinomas of the breast using publicly available genomic data.

## MATERIALS AND METHODS

### *Study design and data collection*

Published genomic studies of molecular lesions in neurotrophic receptor tyrosine kinases (NTRKs) in breast cancer were interrogated in the cBioportal platform (http://www.cbioportal.org). cBioportal is a platform freely available to investigators containing molecular studies and corresponding clinical data [7,8]. The platform allows for a multi-dimensional interrogation of genomic data from publicly available studies. cBioportal also provides the opportunity to associate data of molecular lesions (mutations, fusions, copy number alterations and mRNA hyperexpression or hypo-expression) of any gene of

interest in studies from the Cancer Genome Atlas (TCGA) and other studies with patient clinical characteristics and survival outcomes[7]. The current analysis is based on the TCGA breast cancer study and on the project GENIE study, both included in the cBioportal and providing open access to their data[9, 10]. The analysis of copy number alterations (CNAs) in TCGA is performed with the algorithm Genomic Identification of Significant Targets in Cancer (GISTIC) [11]. In GISTIC, putative amplification of a given gene is defined as a score of 2 or above. TCGA provides an aneuploidy score (AS) as a measure of chromosomal instability of each sample. AS is calculated as the sum of the number of chromosome arms in each sample that have copy number alterations (gains or losses). A chromosome arm is considered copy number altered, either gained or lost, if there is a somatic copy number alteration in more than 80% of the length of the arm as calculated by an algorithm called ABSOLUTE based on Affymetrix 6.0 SNP arrays[12]. Chromosomal arms with somatic copy number alterations in 20% to 80% of the arm length are considered not evaluable and chromosomal arms with somatic copy number alterations in less than 20% of the arm length are considered not altered. mRNA expression grids in cBioportal are constructed and normalized using the RSEM (RNA-Seq by Expectation Maximization) algorithm[13].

Expression of NTRK proteins in breast cancer were evaluated using publicly available data from the Human Protein Atlas (www.proteinatlas.org), a database of protein expressions in human normal and neoplastic tissues[14]. The Human Protein Atlas contains a semi-quantitative immunohistochemistry-based evaluation of the expression of proteins of interest.

The effect of mRNA expression level of *NTRK1* gene on survival of breast cancer patients was examined with data derived from the online publicly available platform Kaplan Meier Plotter (www.kmplot.com)[15]. The cut-off of amplified and non-amplified samples for each gene was set at the higher quartile of amplification, which is the closer cut-off provided by the platform to the percentage of breast cancer cases with *NTRK1* amplifications.

### Statistical analysis

The Fisher's exact test or the $\chi^2$ test and the *t* test, respectively, are used to compare categorical and continuous data. Kaplan-Meier survival curves were compared using the Log Rank test. All statistical comparisons were considered significant if $P < 0.05$.

## RESULTS

Among 11,886 patients with breast cancer in the project GENIE cohort, 27 patients (0.22%) had fusions in one of the three NTRK genes. Two male patients were included among the 27 NTRK fusion positive breast cancer patients. Most patients with information for race were White, while 2 patients were Black and one was Asian. Histologically, 25 patients were diagnosed with ductal carcinomas or breast carcinomas not otherwise specified and one patient had an invasive lobular carcinoma. Interestingly, only one case was diagnosed as juvenile secretory carcinoma, in a male patient. A total of 32 fusions involving the 3 NTRK genes were present in the 27 patients (5 patients had more than one different fusions). The most frequent fusions involved *NTRK3*, in 16 samples, followed by *NTRK1* in 13 samples and *NTRK2* in 3 samples. Fusions in seven cases were intragenic and a variety of partners were involved in other fusions. Recurring partner genes include *ETV6* with *NTRK3* and *LMNA* with *NTRK1*. Frequent mutations observed in breast cancers such as in *TP53*, *PIK3CA* and *GATA3* genes are also observed in cases with NTRK gene fusions. with a frequency not statistically significant different compared with cases without NTRK fusions. Similarly, common amplifications in breast cancers of *CCND1* at 11q13.3, *ERBB2* at 17q12, *NSD3* at 8p11.23 and *c-MYC* at 8q24.21 are encountered in cases with NTRK fusions in frequencies comparable to cancers without NTRK fusions.

In TCGA breast cancer cohort, no fusions involving the 3 NTRK genes were observed. The most common molecular lesions were amplifications that were observed in 9.8% of patients, most commonly in NTRK1 (7.9%) and more rarely in NTRK3 (1.9%) and in NTRK2 (0.2%). NTRK amplified cancers have a distribution of histologic types (ductal, lobular, mixed, other) that is similar to non-amplified cases. NTRK amplified cancers are basal more commonly than NTRK non-amplified cancers (31.1% *vs* 14.1%, $\chi^2$ $P < 0.001$) but less commonly of the luminal B phenotype (11.3% *vs* 18.9% in non-amplified cancers, $\chi^2$ $P = 0.05$) (Figure 1). Total tumor mutation burden (TMB) was not different between NTRK amplified and non-amplified breast cancers with about 10% of cases in each group displaying a TMB above 120. In contrast, NTRK amplified cancers had more commonly chromosomal instability as measured by an AS of 4 or greater ($\chi^2$ $P < 0.001$) (Figure 2). Among cancer-associated genes frequently mutated in breast cancer, tumor suppressor *TP53* was mutated in 41.5% of NTRK amplified cancers and in 31.6% of non-amplified cancers ($\chi^2$ $P = 0.03$) (Figure 3). In contrast, oncogene *PIK3CA* was more often mutated in NTRK non-amplified cases (33.5% *vs* 23.6% in NTRK amplified cases), although the difference did not reach statistical significance ($\chi^2$ $P = 0.06$). Amplifications of oncogene *c-MYC* were more common in NTRK amplified cases (24.5% *vs* 14% in NTRK non-amplified cases, $\chi^2$ $P = 0.005$).

In breast cancer cases with amplifications of NTRK genes, expression of the respective mRNAs is not increased, except in rare cases. However, breast cancers with increased NTRK1 mRNA expression at the upper quartile tend to have a better overall survival (OS) than cancers with low NTRK1 mRNA

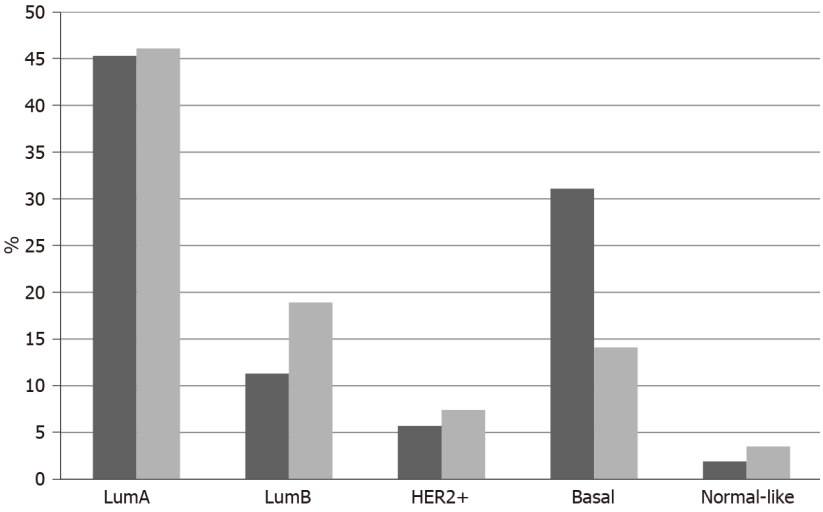


**Figure 1 Percentage of patients with different breast cancer molecular sub-types among the neurotrophic receptor tyrosine kinase amplified and non-amplified groups.** Data are from TCGA breast cancer cohort. Black columns: Neurotrophic receptor tyrosine kinase amplified; Grey columns: Neurotrophic receptor tyrosine kinase non-amplified.

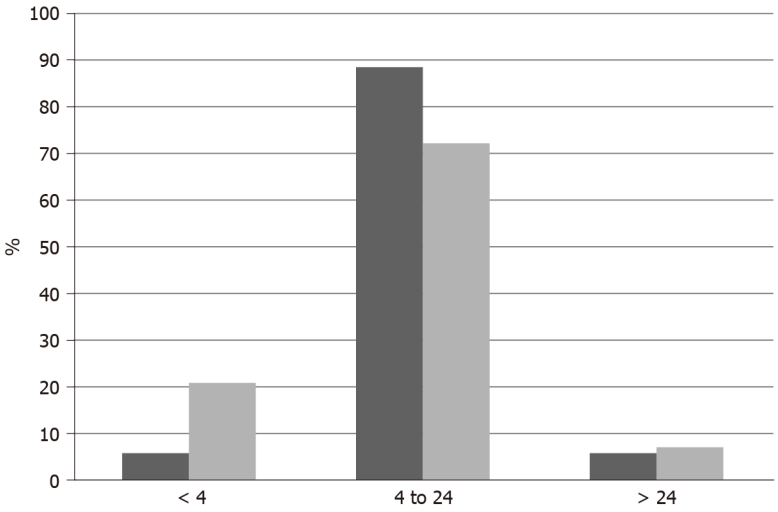


**Figure 2 Percentage of patients with different aneuploidy score levels in breast cancer groups with and without neurotrophic receptor tyrosine kinase amplifications.** Data are from TCGA breast cancer cohort. Black columns: Neurotrophic receptor tyrosine kinase amplified; Grey columns: Neurotrophic receptor tyrosine kinase non-amplified.

expression, falling in the three lower quartiles (Figure 4A). This holds true also for an analysis restricted to basal breast cancers (Figure 4B).

Protein expression of TrkA is present in most breast cancers as evaluated by immunohistochemistry. The Human Protein Atlas has found moderate to high expression of the protein in 72.7% (8 of 11 samples) and 63.6% (7 of 11 samples) using two different antibodies (HPA035799 rabbit polyclonal antibody from Sigma-Aldrich and CAB004606 mouse monoclonal antibody from Santa Cruz Biotechnology). One and three additional cases have shown a low intensity of staining. In contrast, almost all cases of breast cancer examined showed low or absent staining for TrkB and TrkC in the Human Protein Atlas.

## DISCUSSION

The human neurotrophin system consists of four ligands, nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3) and neurotrophin 4/5 (NT-4/5), and three Trk receptors, TrkA, TrkB, TrkC, as well as two additional non-Trk receptors, $p75^{NTR}$ and sortilin[16]. NGF is the ligand for receptor TrkA, encoded by gene *NTRK1*, BDNF and NT-4/5 are the ligands for TrkB encoded by gene *NTRK2* and NT-5 is the ligand for TrkC, encoded by gene *NTRK3*. NT-5 can also ligate

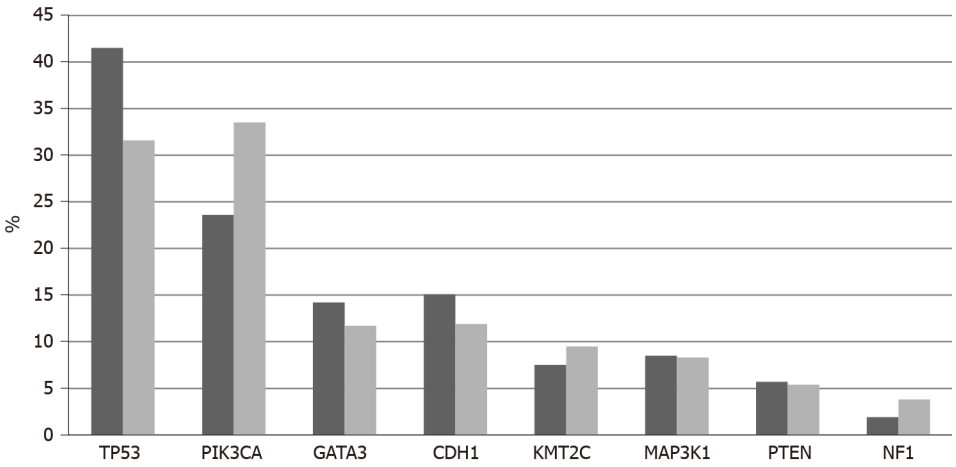


**Figure 3 Percentage of mutations in the most common breast cancer associated genes in breast cancers with and without neurotrophic receptor tyrosine kinase amplifications.** Data are from TCGA breast cancer cohort. Black columns: Neurotrophic receptor tyrosine kinase amplified; Grey columns: Neurotrophic receptor tyrosine kinase non-amplified.

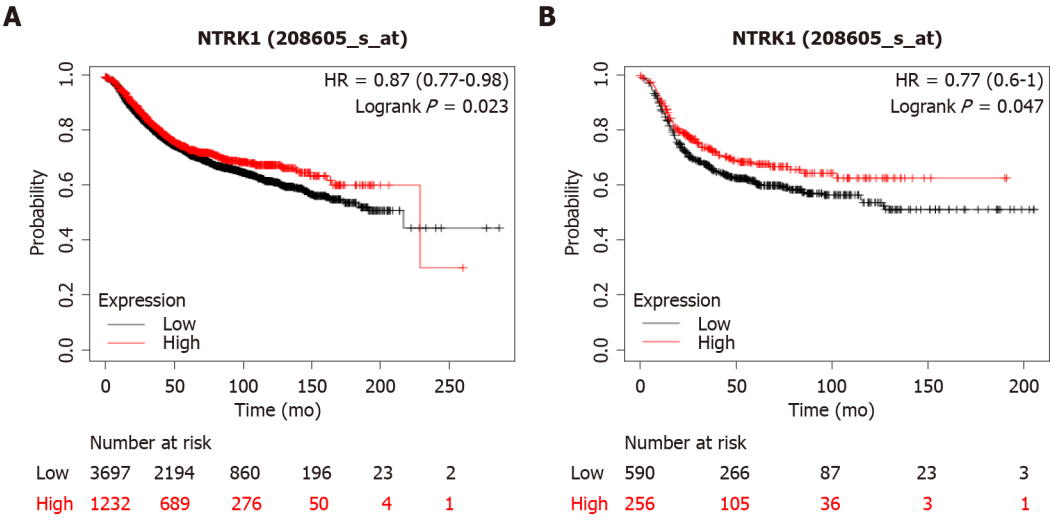


**Figure 4 Overall survival of breast cancers according to *NTRK1* mRNA expression.** A: Overall survival curves of all breast cancer patients with high *NTRK1* mRNA expression *vs* low *NTRK1* mRNA expression, across sub-types. Log-rank *P* = 0.02; B: Overall survival curves of basal sub-type patients with high *NTRK1* mRNA expression *vs* low *NTRK1* mRNA expression. Log-rank *P* = 0.04.

the two other Trk receptors. All four ligands ligate the common neurotrophin receptor p75$^{NTR}$, which also serves as a receptor for the precursor forms of the four ligands pro-NGF, pro-BDNF, pro-NT-3 and pro-NT-4/5 and possesses an intracellular death domain[17]. All precursor forms ligate, additionally, sortilin, also known as neurotensin receptor 3 (NTSR3). The three Trk kinase receptors have a common structure with an extracellular part consisting of two cysteine-rich domains separated by three leucine-rich repeats. Closer to the cell membrane, the three Trk receptors possess two immunoglobulin-like domains. The intracellular part of the receptors holds the tyrosine kinase domain with five conserved tyrosines, three of which are phosphorylated when the receptors are activated by ligand binding. Downstream of receptors activation, the MAPK and PI3K/Akt kinase cascades are activated transmitting signals of proliferation and apoptosis inhibition. The physiologic role of neurotrophins signaling is best described in the nervous system, both in peripheral nervous system and the brain[18]. In peripheral nervous system, NGF signaling stimulates neurite growth and prevents apoptosis. NGF is also functional in brain where BDNF is also present and involved in signal transduction through binding and induction of phosphorylation of TrkB resulting in neuron survival and differentiation[18,19].

Similarities of downstream signaling between the neurotrophin receptors and the EGFR family of tyrosine kinase receptors, which are well-known oncogenes, have led to the exploration of the role of Trk receptors in cancer[18,20]. Expression of receptor TrkA is observed in breast cancer cell lines and in breast cancer tissues, where it is more prominent than surrounding normal breast epithelium[21]. TrkA signaling enhances breast cancer cell proliferation and anchorage independent growth. Moreover, TrkA

inhibits apoptosis and anoikis in metastatic sites. In breast cancer cells, activation of TrkA transmits signals through the MAPK pathway consistent with the physiologic circuit of the receptor[18]. Pro-NGF derived from cancer cells also binds TrkA and signals in an autocrine manner[22]. TrkA ligation promotes interaction with another receptor kinase EphA2 and downstream activation of Src and Akt kinases, resulting in phosphorylation and activation of these kinases and stimulation of cell growth[22]. In contrast, pharmacologic or small interfering RNA inhibition of TrkA or EphA2 decreases tumor growth and metastases of breast cancer in an *in vivo* mouse model. Immunohistochemical studies showed that Pro-NGF is expressed at higher levels in breast cancer tissues compared with normal breast tissues and benign lesions[23]. Receptor $p75^{NTR}$ is also expressed in breast cancer cells and leads to increased proliferation and inhibition of apoptosis through activation of transcription factor NF-κB[24]. $p75^{NTR}$ interacts with NF-κB through mediator TRADD (TNFR Associated Death Domain) when MCF-7 breast cancer cells are exposed to NGF and absence of TRADD promotes apoptosis in the same conditions[24].

BDNF and its receptor TrkB are expressed in breast cancer cells and promote cell survival and proliferation[25,26]. Knock down of BDNF or pharmacologic inhibition of TrkB reduced the viability of breast cancer cells *in vitro*. TrkB is expressed in cancer stem cells with the CD44 positive phenotype derived from triple negative breast cancers and participates in a paracrine circuit ligated by BDNF derived from differentiated breast cancer cells[27]. BDNF stimulation induces stemness core factor KLF4 and promotes stemness phenotype and stem cell renewal. In addition, TrkB expression predicts relapse of localized triple negative breast cancers[27]. Related to stemness, epithelial to mesenchymal transition (EMT) is a process that promotes cancer cell metastasis[28]. TrkB is a target of micro-RNA miR-200c, which protects against EMT and preserves breast cancer cell epithelial phenotype, further supporting the role of TrkB in breast cancer promotion[29].

Further interest in neurotrophin family receptors in cancer was stimulated by the discovery of rare fusions involving the receptor genes *NTRK1*, *NTRK2* and *NTRK3* that act as oncogenic drivers and can be neutralized by NTRK inhibitors[30]. Fusions involving most frequently NTRK3 were confirmed to be the underlying molecular mechanism of secretory mammary carcinomas but were absent in other more common breast cancer histologies[30,31]. The carcinogenic mechanism of the fusion involves deregulated activation of the RAS-MAPK and PI3K-Akt pathways that are the physiologic targets of neurotrophic kinases signaling[32]. In contrast, these fusions do not affect the differentiation programs of cells, as suggested by their presence in diverse cancers, in addition to secretory breast carcinomas, including nephromas, infant fibrosarcomas, mammary analogue secretory carcinomas of the salivary glands and acute myeloblastic leukemias[33,34].

Breast secretory carcinoma is a rare type of breast cancer malignancy, accounting for 0.15% to 0.2% of all breast cancers[35]. It has generally an indolent clinical behavior, with late local recurrence and prolonged survival, even with lymph node involvement, that occurs at nearly 30% of cases[36]. It was initially described by Mc Divitt and Stewart as a variation of mammary carcinoma in the pediatric population, also called "juvenile carcinoma"[37]. In 1980, Tavassoli and Norris[38] reported several cases presenting at variable ages and recommended to replace the previous definition with the term "secretory carcinoma". Secretory breast cancer displays a particular phenotype related to the presence of large amounts of intracellular and extracellular secretory material. Although it has been described as a sub-family of basal-like triple negative breast cancers with cytokeratin 5/6 expression and no expression of either hormone receptors or HER2, this tumor has a unique immunophenotypic profile among triple negative breast carcinomas. It stains diffusely for mammaglobin and gross cystic disease fluid protein (GCDFP) and displays strong and diffuse SOX10 and S-100 Labeling[39,40]. The hallmark genetic alteration of this cancer is a t(12;15) translocation, resulting in the ETV6-NTRK3 gene fusion which is pathognomonic, detected in more than 90% of secretory breast carcinomas. The same translocation is also identified in the mammary analog secretory carcinoma, its salivary gland counterpart[30,39,41]. Given that NTRK3 protein expression is not detected in breast epithelial cells physiologically, immunohistochemical analysis using pan-Trk antibodies has been shown to constitute a sensitive and specific approach for the detection of NTRK3 rearrangements in breast secretory carcinomas[42]. Absence of Trk receptor expression in non-secretory breast cancer was also observed in a micro-array study of 339 breast cancer patients, using a pan-Trk rabbit monoclonal antibody[43]. However, since TrkA is expressed in a sub-set of non-secretory breast cancers, as shown in the human Protein Atlas, the intensity of staining should be taken into consideration and confirmatory molecular detection of fusions should be standard practice.

Patients with tumors that harbor NTRK fusions as a specific molecular alteration may benefit from treatment with selective tyrosine kinase inhibitors or antagonistic monoclonal antibodies. There is accumulating evidence for the efficacy of Trk inhibitors in the control of the disease in these patients. Two Trk inhibitors, larotrectinib and entrectinib, are both approved by the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Larotrectinib is a selective inhibitor of the Trk proteins (including TrkA, TrkB, and TrkC) approved for the treatment of locally advanced and metastatic solid tumors with NTRK fusions, in both adult and pediatric cancer patients. Its efficacy and safety have been studied in three multicenter, phase 1/2, open-label, single-arm clinical trials[44-46]. An objective response rate (ORR) of 78% [95% confidence interval (CI): 71%-84%] regardless of histology, age, and type of NTRK fusion was shown in the joint analysis of these studies. The median

progression-free survival (PFS) was 36.8 months [95%CI: 25.7 mo - not estimated (NE)] with 90% (95%CI: 75%-90%) of patients being alive at 1 year. A specific adult population analysis, that included 5% with breast cancers, has showed an ORR of 71% (95%CI: 62%-79%), a median PFS of 25.8 mo (15.2 mo to NE), and 87% of patients alive at 1 year. The most frequent fusion transcripts were NTRK3 (54%) and NTRK1 (43%), and only 3% had NTRK2[47]. Impressive responses have also been observed in locally advanced disease highlighting the potential utility of Trk inhibition as neoadjuvant therapy in the non-metastatic setting. The most common side effects were fatigue (30%), constipation (27%), cough (27%), elevation of liver enzymes (24%), dizziness (25%) and nausea (24%), mainly grade 1-2. Only 2% of patients had to discontinue treatment and 16% had grade 3-4 toxicity related to treatment, predominantly elevation of transaminases (3%), decreased neutrophil count (2%) and anemia (2%).

Entrectinib, a multikinase inhibitor of the TrkA, TrkB, TrkC, ROS1, and ALK proteins was tested in three clinical trials, two phase 1 and one "basket" phase 2 trial in the adult population with tumors harboring NTRK fusions[48]. Breast cancer represented the 11% of the tumors in these trials. In the analysis of the first 54 patients included, an ORR of 59% (95%CI: 45%-72%), a PFS of 11.2 mo (95%CI: 8.0-14.9 mo), and an OS of 23.9 mo (95%CI: 16.8 mo to NE) were observed. Entrectinib crosses the blood-brain barrier and has showed activity at the CNS level. In the 22% of patients with brain metastases the intracranial ORR was 55% (95%CI: 23%-83%)[48,49]. The activity of Trk inhibitors in the CNS is crucial because cancers that harbor NTRK fusions can present with primary or metastatic intracranial disease. The tolerability of the inhibitors was acceptable with the most frequent adverse events being anemia (10%), weight gain (14%), dyspnea, and asthenia (25%)[50,51]. The majority of adverse events encountered were grade 1-2. These side effects are manageable with drug dose modifications.

Despite the marked efficacy of Trk inhibitors and, in many cases, long-lasting responses, resistance may occur leading to progression. Several potential mechanisms of resistance have been described, including through the development of mutations in the NTRK genes, mutations of mitogen-activated protein kinase (MAPK) pathway genes such as BRAF (V600E) and KRAS (G12D), and the amplification of MET[52]. Razavi *et al*[53] identified lesions in the MAPK pathway that were responsible for resistance to endocrine therapy. The same findings were supported by Ross *et al*[54], who aimed at characterizing kinase fusions within a large cohort of 4857 patients with advanced breast cancer. In total, 56% with fusion-positive breast cancers had a history of previous endocrine therapy and none of the fusion-positive breast cancer samples harbored *ESR1* hotspot mutations. Two patients with acquired LMNA-NTRK1 fusions and metastatic disease received larotrectinib and demonstrated clinical benefit[54]. The kinase fusions, even if they are rare in breast cancer, they are enriched in hormone-resistant, metastatic carcinomas and mutually exclusive with *ESR1* mutations. These data expand the spectrum of genetic alterations activating MAPK signaling that can substitute for *ESR1* mutations in this setting. Thus, molecular testing in metastatic breast cancer at progression after endocrine therapy should include fusion testing, especially in case of absence of *ESR1* hotspot alterations. Specific mutations in NTRK1 producing substitutions at position p.G595R and p.G667C have been described as associated with resistance to entrectinib in a patient with colon cancer bearing the LMNA-NTRK1 rearrangement[55].

Second-generation Trk inhibitors such as selitrectinib and repotrectinib, have been developed, and have shown activity in these patients, in both adult and pediatric populations, in the first in human dose escalation clinical trials[56,57]. Currently there are ongoing trials evaluation the safety and efficacy of these drugs in solid tumors. Inspired by the resistance of other kinases, dual blocking TRKs or combination inhibitors could be a new treatment approach. The inhibitor foretinib was able to inhibit xenografts with the LMNA-NTRK1 fusion that had become resistance to entrectinib after acquiring the above mentioned mutation p.G667C, suggesting that mutations producing resistance to first generation inhibitors may still be sensitive to second generation inhibitors in development[58].

Regarding NTRK gene amplification, it was shown to result in TRK overexpression in a sub-set of breast cancers[59]. Among the 1250 analyzed tumor specimens, NRTK amplification was detected in 2.2% cases, representing 14.8% of cases with TrkA protein overexpression. The efficacy of TRK inhibitors in tumors harboring NTRK gene amplification is not well characterized. These patients were not included in the trials of TRK inhibitors. Interestingly, two patients with NTRK gene amplification have been described in whom larotrectinib has marked a durable antitumor activity[60,61] suggesting that these therapies may have a role in a sub-set of amplified patients, who remain to be identified. Regarding patients with mutations as a primary abnormality in Trk proteins (as opposed to the discussed above secondary mutations in patients with fusions), TRK inhibitors have not shown activity [61]. It has been suggested that these mutations are not driver lesions in these cancers. However, it is possible that a subset of these mutations are indeed oncogenic[62]. In various hematologic malignancies including AML, ALL, CML and myelofibrosis, NTRK2 and NTRK3 mutations were observed in about 5% of patients and cells bearing some of them were inhibited by entrectinib *in vitro*[63].

## CONCLUSION

The current study confirms the rarity of NTRK fusions in breast cancer with a prevalence rate of less than 1%. Amplifications of NTRK1 are more common and are associated with basal cancers and *TP53*

mutations which are most common in this breast cancer type. Although amplification of the NTRK1 gene does not always lead to mRNA over-expression, TrkA protein is expressed in many breast cancers and thus can be a therapeutic target. In contrast to our results, another study that examined expression of TrkA at the protein level suggested that the receptor is more often expressed in HER2 positive cancers compared to luminal and basal carcinomas[64]. This study also confirmed discrepancies between gene dosage and protein expression. Clearly, transcription and post-transcription regulations are critical for TrkA expression in breast cancer.

## ARTICLE HIGHLIGHTS

### *Research background*

Breast cancer is a common female cancer. It constitutes a major cause of morbidity and mortality. Progress in breast cancer therapeutics has been attained with the introduction of targeted therapies for specific sub-sets. However, other breast cancer subsets lack targeted therapeutics.

### *Research motivation*

Personalized therapies for breast cancer have the potential to improve outcomes. These therapies take consideration of specific molecular abnormalities that could be targeted for optimal results.

### *Research objectives*

This article aims to analyze the landscape of neurotrophic receptor tyrosine kinase (NTRK) abnormalities in breast cancer. These are molecular lesions in a family of receptor tyrosine kinases. Specific drug inhibitors have been developed and have obtained regulatory approval, paving the way for effective patient treatment.

### *Research methods*

An analysis of publicly available genomic breast cancer datasets was performed for identification and characterization of cases with fusions and other molecular abnormalities involving *NTRK1*, *NTRK2* and *NTRK3* genes.

### *Research results*

NTRK fusions are rare in breast cancers as a whole. They are present in a small number of breast cancers at the extensive GENIE project data set which contains more than 10000 breast cancers. These cases are not identified as secretory in the database.

### *Research conclusions*

NTRK lesions other than fusions are more common than fusions in breast cancers. However, confirmation of efficacy for the currently available inhibitors exist only for NTRK fusions.

### *Research perspectives*

Amplifications of NTRK receptor genes are more common than fusions in breast cancers. Inhibitors effective for interfering with the activity of amplified NTRK receptors could advance therapeutics in this subset of breast cancers.

## FOOTNOTES

**Author contributions:** Both authors contributed to the conception of the study, literature review, data analysis, writing of the article and revising the article.

**Institutional review board statement:** No institutional review board approval was required or obtained as the study was not a clinical trial.

**Clinical trial registration statement:** This study was not registered as a clinical trial as it includes only data from publicly available previously published studies and no new patient information.

**Informed consent statement:** No informed consents have been obtained for this study as no new patients were included. The study analyzed publicly available data from previously published studies.

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ORIGINAL ARTICLE

Retrospective Cohort Study

# First-line cisplatin, docetaxel, and cetuximab for patients with recurrent or metastatic head and neck cancer: A multicenter cohort study

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## Abstract

*BACKGROUND*

The targeted therapy cetuximab [directed at the epidermal growth factor receptor (EGFR)] in combination with 5-fluorouracil and platinum-based chemotherapy (the EXTREME regimen) has shown substantial efficacy for patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). Thus, this scheme has been established as the preferred first-line option for these patients. However, more recently, a new strategy combining platinum, taxanes, and cetuximab (the TPEx regimen) has demonstrated similar efficacy with a more favorable toxicity profile in clinical trials.

***AIM***
To evaluate the safety and efficacy of the TPEx scheme as first-line therapy in advanced SCCHN in a multicenter cohort study.

***METHODS***
This retrospective multicenter cohort study included patients with histologically confirmed recurrent or metastatic SCCHN treated with first-line TPEx at five medical centers in Argentina between January 1, 2017 and April 31, 2020. Chemotherapy consisted of four cycles of docetaxel, cisplatin, and cetuximab followed by cetuximab maintenance therapy. Clinical outcomes and toxicity profiles were collected from medical charts. Treatment response was assessed by the investigator in accordance with Response Evaluation Criteria in Solid Tumors (version 1.1). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

***RESULTS***
Twenty-four patients were included. The median age at diagnosis was 58 years (range: 36-77 years). The majority of patients (83.3%) received at least four chemotherapy cycles in the initial phase. In the included group, the overall response rate was 62.5%, and 3 patients achieved a complete response (12.5%). The median time to response was 2.4 mo [95% confidence interval (CI): 1.3-3.5]. With a median follow-up of 12.7 mo (95%CI: 8.8-16.6), the median progression-free survival (PFS) was 6.9 mo (95%CI: 6.5-7.3), and the overall survival rate at 12 mo was 82.4%. Patients with documented tumor response showed a better PFS than those with disease stabilization or progression [8.5 mo (95%CI: 5.5-11.5) and 4.5 mo (95%CI: 2.5-6.6), respectively; $P$ = 0.042]. Regarding the safety analysis, two-thirds of patients reported at least one treatment-related adverse event, and 25% presented grade 3 toxicities. Of note, no patient experienced grade 4 adverse events.

***CONCLUSION***
TPEx was an adequately tolerated regimen in our population, with low incidence of grade 3-4 adverse events. The median PFS were consistent with those in recent reports of clinical trials evaluating this treatment combination. This regimen may be considered an attractive therapeutic strategy due to its simplified administration, decreased total number of chemotherapy cycles, and treatment tolerability.

**Key Words:** Recurrent and/or metastatic head and neck cancer; TPEx schema; Cetuximab; Docetaxel; Cisplatin; First-line



**Core Tip:** We evaluated the safety and efficacy of the combination platinum, taxanes, and cetuximab scheme as a first-line therapy for patients with recurrent or metastatic squamous cell carcinoma of the head and neck in a real-world setting. Among the 24 patients included, the median progression-free survival was 6.9 mo (95% confidence interval: 6.5-7.3), and the overall survival rate at 12 mo was 82.4%, which was consistent with previous clinical trials. Patients with documented tumor response showed statistically better progression-free survival than those with disease stabilization or progression ($P$ = 0.034). The combination platinum, taxanes, and cetuximab regimen was adequately tolerated by most of the analyzed patients, as the incidence of grade 3-4 adverse events was surprisingly lower than expected (25%).

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## INTRODUCTION

Squamous cell carcinoma of the head and neck (SCCHN) cases represent 5% of all newly diagnosed cancer cases, leading to over 300000 deaths per year[1]. Despite appropriate primary treatments, in

approximately 50% to 60% of patients with stage III to IV disease locoregional relapse occurs[2]. Given that a significant proportion of these patients are not suitable for surgery or radiotherapy, systemic treatments and best supportive care are the preferred therapeutic options.

Up to the early 2000s, the median overall survival (OS) of patients with metastatic disease was only 6 mo[3,4]. This poor prognosis encouraged significant research efforts to develop novel drugs in the last 15 years. In this setting, the targeted therapy cetuximab [directed at the epidermal growth factor receptor (EGFR)] has shown substantial efficacy for recurrent or metastatic (R/M) SCCHN treatment in combination with 5-fluorouracil and platinum-based chemotherapy (the EXTREME regimen)[3]. More recently, a new strategy using the immune checkpoint inhibitor pembrolizumab alone or in combination with 5-fluorouracil and platinum has become an appropriate first-line treatment for R/M SCCHN patients[5-7].

Currently, the EXTREME regimen still represents a recommended first-line treatment option in selected scenarios, such as cases with programmed death-ligand 1-negative tumors or when immunotherapy is contraindicated. Notably, this treatment regimen may represent an attractive approach for patients with disease progression after first-line immune checkpoint inhibitors are given as monotherapy[8].

Taxanes have maintained widespread clinical use, particularly in solid tumors since their discovery in the early 1970s, and several clinical trials have shown their antineoplastic activity against SCCHN[9-11]. The addition of fluorouracil to a taxane seeks to take advantage of the potential immunogenic and proapoptotic synergy between cetuximab and docetaxel or paclitaxel[12,13]. Cetuximab-, platinum-, and taxane-based schedules have been associated with promising survival results and cytoreductive properties in clinical studies[14-18]. TPExtreme was the first large, phase 3, randomized trial comparing the TPEx regimen (cetuximab, taxane, and platinum) with the EXTREME scheme in a first-line setting [19]. This trial demonstrated similar efficacy outcomes in 539 R/M HNSCC patients, showing a median OS of 14.5 and 13.4 mo using the TPEx and EXTREME regimens, respectively. Furthermore, the TPEx arm had a more favorable toxicity profile, leading to better compliance of the planned treatment (72% *vs* 44%) and fewer dose interruptions (10% *vs* 27%).

Based on these considerations and given the scarce real-world studies including patients treated with this scheme, we retrospectively evaluated the efficacy and safety of the TPEx regimen as first-line therapy in patients with R/M SCCHN.

## MATERIALS AND METHODS

### *Study population and treatment characteristics*

This retrospective multicenter cohort study included patients seen between January 1, 2017 and April 31, 2020 with a histologically confirmed diagnosis of R/M SCCHN who received TPEx as first-line treatment at five medical centers in Argentina. Chemotherapy consisted of four cycles of docetaxel 75 mg/m$^2$ and cisplatin 75 mg/m$^2$ every 3 wk and cetuximab (400 mg/m$^2$ on day 1 of cycle 1 and then 250 mg/m$^2$ weekly), with systemic granulocyte colony-stimulating factor support during each cycle. Patients with controlled disease continued with weekly cetuximab 250 mg/m$^2$ or cetuximab 500 mg/m$^2$ every 2 wk as maintenance until disease progression or unacceptable toxicity. Demographic and clinicopathological characteristics, including age, Eastern Cooperative Oncology Group performance status, smoking status, alcohol consumption, primary tumor site, and previous treatments, were collected from medical charts and entered into a predefined centralized database. Efficacy and safety information was also retrieved, and treatment strategies, responses, adverse events, and discontinuation were also documented.

Disease progression and treatment response were collected from medical charts. Treatment response was assessed by the investigator using computed tomography or magnetic resonance imaging scans in accordance with Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). The study was reviewed by our expert biostatistician Santiago Duarte, MD.

### *Statistical analysis*

Data are summarized as frequencies and percentages for categorical variables and as medians, ranges, and interquartile ranges for continuous variables. The progression-free survival (PFS) and OS of patients treated with TPEx as first-line treatment were calculated from the date of therapy initiation to first documented relapse (PFS) or death due to any cause (OS). Data were censored at the last follow-up if the patient was alive. The duration of response (DOR) was defined as the time from the first complete response (CR) or partial response to progressive disease or death. Survival curves were generated using the Kaplan-Meier method, and differences between groups were calculated using the log-rank test. Relevant prognostic factors were stratified by univariate Cox regression models for PFS. All statistical analyses were performed using SPSS software version 23.0 (SPSS, Inc., Armonk, NY, United States).

## RESULTS

### Patients characteristics

In this multicenter retrospective study, 24 patients with R/M SCCHN were included from five Argentinian medical centers. All patients received first-line chemotherapy with TPEx. The median age at diagnosis was 58 years (range: 36-77), males made up 62.5% of the population ($n$ = 15), and the majority of patients had an Eastern Cooperative Oncology Group score of 0-1 (22, 91.7%) (Table 1). A smoking history was reported in 13 patients (54.2%), and approximately one-third of the patients reported alcohol consumption. Of note, only 2 patients (8.3%) had a body mass index < 18.5.

Previous treatments included definitive concomitant chemoradiotherapy (33.3%), surgery (20.8%), surgery plus radiotherapy (12.5%), chemoradiotherapy (20.8%), and definitive radiotherapy alone (4.2%). Approximately half of the population had previously received cisplatin ($n$ = 13, 54.2%), and only 2 patients (8.3%) had metastatic disease at diagnosis. The most common reason for treatment discontinuation was disease progression (58.3%), and only 2 patients (8.3%) discontinued treatment prematurely due to unacceptable toxicity. Notably, most patients (83.3%) received at least four chemotherapy cycles during induction therapy.

### Efficacy

A total of 3 patients achieved a complete response (12.5%), and in half of the patients, a partial response was documented (Table 2). Remarkably, most of the patients benefited from TPEx therapy since the overall response rate (ORR) and disease control rate (DCR) were 62.5% and 87.5%, respectively. The median time to response was 2.4 mo [95% confidence interval (CI): 1.3-3.5).

No statistical differences were observed in terms of ORR or DCR between patients with only locoregional recurrence prior to TEPx initiation and the rest of the included patients [ORR 50% (7/14), DCR 85.7% (12/14) and ORR 80% (8/10), DCR 90% (9/10), respectively; $P$ = 0.21 and $P$ = 1.0].

After a median follow-up of 12.7 mo (95%CI: 8.8-16.6), 14 progression events occurred. The median PFS and DOR were 6.9 mo (95%CI: 6.5-7.3) (Figure 1A) and 5.1 mo (95%CI: 3.0-7.2), respectively (Figure 1B). Univariate relevant prognostic factor analyses for first-line TPEx PFS are reported in Table 3. As expected, patients with documented tumor response showed a better PFS than those with disease stabilization or progression [8.5 mo (95%CI: 5.5-11.5) and 4.5 mo (95%CI: 2.5-6.5), respectively; $P$ = 0.042] (Figure 1C). Notably, in 2 out of the 3 patients with documented CR, substantially longer PFS (22.3 and 18.8 mo) and DOR (16.6 and 16.9) were observed. Patients with hypo/oropharyngeal tumors had a better PFS compared to those with other primary sites [22 mo (95%CI: 19.9-25.1) and 6.7 mo (95%CI: 4.7-8.9), respectively; $P$ = 0.038] (Figure 1D). No difference was observed when comparing patients with advanced and metastatic disease ($P$ = 0.953) (Figure 1E). The OS rate at 12 mo was 82.4% (Figure 1F). Remarkably, among the 14 patients who experienced disease progression on TPEx, 13 received second-line treatment with immunotherapy [pembrolizumab ($n$ = 9) and nivolumab ($n$ = 4)].

### Safety and adverse events

Two-thirds of the patients reported at least one treatment-related adverse event, and 25% reported at least one grade 3 adverse event. Of note, no patient experienced grade 4 toxicity. A summary of the safety profile is listed in Table 4. The most commonly reported hematological adverse events were febrile neutropenia (12.5%), anemia (12.5%), and hyponatremia/hypokalemia (12.5%). Among nonhematological events, acne-like rash was the most frequent (33.3%) related adverse event. Grade 3 nausea-vomiting, asthenia, and renal failure were noted in 4.2% of the patients. Only 1 patient experienced a grade 1 hypersensitivity reaction during taxane infusion.

Overall, serious adverse events were reported in 5 patients (20.8%). Three of the patients developed febrile neutropenia, 1 developed acute renal failure, and the remaining patient was hospitalized due to grade 3 vomiting that required intravenous hydration. All patients continued treatment after the toxicity resolved. The median duration of hospitalization among patients with severe adverse events was 6 d (range: 2-22). Additionally, no fatal events were reported. Globally, TPEx was associated with a low rate of adverse events leading to treatment interruption (12.5%), discontinuation (8.3%), or dose reduction (8.3%).

## DISCUSSION

Despite substantial advances in the last decade, R/M SCCHN remains a significant clinical challenge because of its associated high mortality rate. As such, increasing the tumor response rate is an important goal in these patients given its association with symptom improvement and better quality of life.

Over the past years, the EXTREME regimen has become a preferred first-line strategy for R/M SCCHN patients[3]. While significant improvements in OS, PFS, and ORR were demonstrated in the cetuximab plus platinum–fluorouracil arm of a pivotal phase 3 trial, 82% of the included patients experienced grade 3-4 adverse events, mostly related to 5-fluorouracil continuous infusion. Of note, all these findings were observed in fit patients; hence, treatment decisions in this setting should be

**Table 1 Clinicopathological characteristics**

| Characteristics | Number of patients (%) |
|---|---|
| Total | 24 |
| Median age (range), yr | 58 (36-77) |
| Sex | |
| Male | 15 (62.5) |
| Female | 9 (37.5) |
| ECOG at TPEx treatment initiation | |
| 0-1 | 22 (91.7) |
| 2 | 2 (8.3) |
| Smoking history | |
| Never | 6 (25) |
| Current or former | 13 (54.2) |
| NS | 5 (20.8) |
| Alcohol consumption | |
| Occasional or regular | 8 (33.3) |
| None | 7 (29.2) |
| NS | 9 (37.5) |
| Primary tumor site | |
| Larynx | 7 (29.2) |
| Oropharynx | 6 (25) |
| Oral cavity | 5 (20.8) |
| Hypopharynx | 1 (4.2) |
| Other | 5 (20.8) |
| Previous treatment | |
| Concomitant chemoradiotherapy only | 8 (33.3) |
| Surgery only | 5 (20.8) |
| Surgery + concomitant chemoradiotherapy | 5 (20.8) |
| Surgery + radiotherapy | 3 (12.5) |
| Radiotherapy only | 1 (4.2) |
| No | 2 (8.3) |
| Extent of disease at TPEx treatment initiation | |
| Locoregional recurrence only | 14 (58.3) |
| Locoregional recurrence + distant metastasis | 5 (20.8) |
| Metastatic disease | 5 (20.8) |
| Time from initial diagnosis to recurrence(Median, IQR), mo | 16.2 (5.4-37.5) |
| Metastatic or unresectable disease at diagnosis | 11 (45.8) |

NS: Not specified; ECOG: Eastern Cooperative Oncology Group; HPV: Human papilloma virus; IQR: Interquartile range.

analyzed on a case-by-case basis. Clinical comorbidities, performance status, nutritional assessment results, access to infusion pumps, or even availability for patient hospitalization are some of the considerations made in clinical practice before treatment decisions are made.

Given that not all patients can tolerate the EXTREME regimen, alternative treatment protocols have been developed, mostly replacing 5-fluorouracil with taxanes (Table 5). The phase 2 GORTEC study evaluated cisplatin, docetaxel, and cetuximab as a first-line treatment in 54 patients with R/M SCCHN

**Table 2 Summary of treatment response**

| | TPEx (*n* = 24) |
|---|---|
| Type of response, *n* (%) | |
| Complete | 3 (12.5) |
| Partial | 12 (50) |
| Stable disease | 6 (25) |
| Progression | 1 (4.2) |
| Nonassessable | 2 (8.3) |
| Objective response rate - % of patients (95%CI)[1] | 62.5 |
| Disease-control rate - % of patients (95%CI)[2] | 87.5 |
| Time to response – mo[3] | |
| Median (95%CI) | 2.4 (1.3-3.5) |
| Duration of response – mo[4] | |
| Median (95%CI) | 5.1 (3.0-7.2) |

[1]An objective response was considered to be a confirmed complete or partial response, as assessed by the investigator.
[2]The disease-control rate was calculated considering patients with a confirmed complete response, partial response, or stable disease as assessed by the investigator.
[3]The time to response was calculated with the use of the Kaplan-Meier method from the date of TPEx initiation to the date of the first documented partial or complete response.
[4]The duration of response was calculated with the use of the Kaplan-Meier method from the date of the first documented response until the date of documented disease progression, death, or the last response assessment in the absence of disease progression.
CI: Confidence interval.

**Table 3 Univariate prognostic factor analyses for TPEx progression-free survival**

| Variable | HR (95%CI) | *P* value | Median PFS (95%CI) |
|---|---|---|---|
| ECOG(0 *vs* 1-2) | 0.91 (0.30-2.80) | 0.87 | 6.9 mo (5.1-8.8) *vs* 6.8 mo (4.7-8.9) |
| Primary tumor site (Hypo/oropharyngeal *vs* Others) | 0.15 (0.02-1.17) | 0.04 | 22 mo (19.9-25.1) *vs* 6.7 mo (4.7-8.9) |
| Response (Responders *vs* Nonresponders) | 0.34 (0.12–0.97) | 0.04 | 8.5 mo (5.5-11.5) *vs* 4.5 mo (2.5-6.5) |
| Extent of disease at TPEx initiation (Locoregionally advanced *vs* Metastatic) | 0.95 (0.33-2.85) | 0.95 | 6.9 mo (4.2-9.7) *vs* 6.8 mo (5.6-7.8) |
| Relapse-free survival of the primary treatment (≤ 24 *vs* > 24 mo)[1] | 0.37 (0.11-1.21) | 0.09 | 6.1 mo (3.6-8.6) *vs* 8.5 mo (4.5-12.5) |
| Previous treatment[2](Multimodality *vs* Unimodality) | 0.44 (0.14–1.41) | 0.17 | 7.5 mo (6.3-8.7) *vs* 6.1 mo (2.7-9.4) |
| Treatment interruption, discontinuation, or dose reduction (Yes *vs* No) | 1.15 (0.39-3.41) | 0.80 | 6.9 mo (6.4-7.4) *vs* 6.8 mo (5.0-8.5) |
| Adverse events (Grade 1-2 *vs* 3-4) | 0.74 (0.23-2.44) | 0.62 | 6.9 mo (5.2-8.6) *vs* 6.7 mo (0.3-13.9) |

[1]Time from primary definitive treatment to advanced disease and first-line TPEx initiation.
[2]Treatment received as primary intention.
Unimodality included surgery or radiotherapy only. Multimodality included surgery and/or radiotherapy +/- chemotherapy. ECOG: Eastern Cooperative Oncology Group; CI: Confidence interval.

[14]. The median OS, PFS, and ORR were 14 mo, 6.2 mo, and 44.4%, respectively. In this selected population, only 12 patients (22.2%) experienced grade 4 adverse events. In another phase 2 trial, Bossi *et al*[15] randomized 201 patients with R/M SCCHN to receive first-line cetuximab plus cisplatin with or without paclitaxel. The authors reported a median PFS of 7 mo and an ORR of 51.7% in the cetuximab, cisplatin, and paclitaxel arm. With this regimen, 72.5% and 33% of the included patients presented grade ≥ 3 and 4 adverse events, respectively.

Guigay and collaborators[19] have recently published the results of a phase 2 trial that compared TPEx with EXTREME as first-line treatment for 541 patients. PFS and ORR values were 14.5 *vs* 13.4 mo, 6.0 *vs* 6.2 mo, and 57.6% *vs* 57%, respectively, and there were no significant differences between the two

**Table 4 Adverse events of any cause during TPEx treatment**

| Event, *n* (%) | TPEx (*n* = 24) | | |
|---|---|---|---|
| | Any grade | Grade 3 | Grade 4 |
| Any treatment-related adverse event[1] | 18 (75) | 6 (25) | 0 |
| Hematological | | | |
| Febrile neutropenia | 3 (12.5) | 3 (12.5) | 0 |
| Anemia | 3 (12.5) | 0 | |
| Hyponatremia and/or hypokalemia | 3 (12.5) | 2 (8.3) | 0 |
| Hypomagnesemia | 2 (8.3) | 1 (4.2) | 0 |
| Thrombocytopenia | 1 (4.2) | 0 | 0 |
| Nonhematological | | | |
| Acne-like rash | 8 (33.3) | 0 | 0 |
| Nausea - vomiting | 4 (16.7) | 1 (4.2) | 0 |
| Asthenia | 4 (16.7) | 1 (4.2) | 0 |
| Diarrhea | 2 (8.3) | 0 | 0 |
| Renal failure | 1 (4.2) | 1 (4.2) | 0 |
| Hypersensitivity | 1 (4.2) | 0 | |
| Oral mucositis | 1 (4.2) | 0 | 0 |
| Any serious adverse event[2] | - | 5 (20.8) | 0 |
| Treatment-related death | 0 | - | - |
| Event leading to interruption of any treatment component[3] | 3 (12.5) | - | - |
| Chemotherapy | 2 (8.3) | - | - |
| Cetuximab | 1 (4.2) | - | - |
| Event leading to discontinuation of any treatment component[3] | 2 (8.3) | - | - |
| Chemotherapy | 2 (8.3) | - | - |
| Cetuximab | 0 | | |
| Event leading to dose reduction | 2 (8.3) | - | - |

[1]The investigators determined whether adverse events were related to the treatment.
[2]Adverse events that lead to hospitalization.
[3]This category includes patients who experienced cisplatin, docetaxel, or cetuximab treatment interruption or discontinuation because of an adverse event at any time and patients who experienced cetuximab maintenance therapy interruption or discontinuation for an adverse event after completing the chemotherapy cycles.
Events were attributed to the specific treatment by the investigator.

arms. The TPEx regimen was associated with a grade 4 adverse event incidence of 33%, which was significantly lower than the 46% incidence reported with the EXTREME scheme. Furthermore, an exploratory analysis for this trial showed a better quality of life in patients who received TPEx, mainly in terms of global health status, physical functioning, role functioning, and scores of appetite[20].

Remarkably, real-world data in this setting are scarce. Before the GORTEC trial, Even and collaborators[21] presented the results of 30 patients treated with TPEx at Gustave Roussy Institute between 2011 and 2013. In this group of patients, the median PFS and OS were 6.0 and 13.6 mo, respectively. A total of eight grade 3-4 adverse events were documented, including vomiting, mucositis, skin rash, diarrhea, hypersensitivity, and neutropenia. Additionally, Fuchs *et al*[22] reported similar results in a retrospective single-institution study, including 38 R/M SCCHN patients treated with TPEx at the Medical University of Vienna. In this study, the median OS, PFS, and ORR values were 10.8 mo, 6.3 mo, and 50%, respectively.

To the best of our knowledge, our study presents the first multicenter cohort (including data from South America) of patients treated with the TPEx schema. Notably, the PFS and ORR were consistent with those reported in previous clinical trials. Intriguingly, 2 patients with complete responses had

**Table 5 Selected studies that assessed first-line TPEx schema in patients with recurrent or metastatic head and neck cancer**

| Ref. | Study type | *n* | ORR (%) | PFS (mo) | OS (mo) | Grade 3, adverse events (%) | Grade 4, adverse events (%) |
|---|---|---|---|---|---|---|---|
| Guigay *et al*[19] | Phase 2 | 541 | 57.6 | 6.0 | 14.5 | 73 | 33 |
| Guigay *et al*[14] | Phase 2 | 54 | 44.4 | 6.2 | 14 | 93 | 22 |
| Bossi *et al*[15] | Phase 2[1] | 201 | 51.7 | 7.0 | 11 | 73 | 33 |
| Even *et al*[21] | Retrospective | 30 | 87 | 6.0 | 13.6 | 17 | 10 |
| Fuchs *et al*[22] | Retrospective | 38 | 50 | 6.3 | 10.8 | 100 | |

[1]This trial used paclitaxel.

ORR: Overall response rate; PFS: Progression-free survival; OS: Overall survival.

longer PFS, which may support that depth of response could be studied as a prognostic factor in patients with R/M HNSCC.

In our study, the TPEx regimen was adequately tolerated by most of the analyzed patients. The incidence of grade 3-4 adverse events was surprisingly lower than expected (25%), but it should be noted that 5 patients had treatment-related hospitalizations. Fortunately, no fatal toxicities were experienced.

Our experience confirms that the replacement of 5-fluorouracil with docetaxel may be a reasonable treatment strategy for R/M SCCHN patients. TPEx has been incorporated as a standard regimen in our centers, considering that this regimen is associated with a lower duration of treatment infusions and lower total number of cycles and the recent reports of safety and quality of life outcomes. These particular characteristics are essential in low- and middle-income countries with limited access to infusion pumps. Furthermore, the instauration of simplified regimens has become extremely important during the coronavirus disease 2019 pandemic[23].

Our results should be interpreted with caution considering the study limitations. This observational study was conducted in five private care centers, which may have been responsible for the high proportion of patients with access to immunotherapy after disease progression (92.9%). The low number of included patients and the retrospective nature of the study may also hamper the extrapolation of our results to Hispanic and Latino American populations. Additionally, our follow-up was not long enough to analyze adequately OS in our sample. Accordingly, the high response rate and the low incidence of grade 3-4 adverse events and serious toxicity may also be explained by a patient selection bias. Although public and private care centers were invited to register their experience with the TPEX regimen, only private-care physicians reported patients that received this treatment strategy.

Finally, it should also be highlighted that the landscape in R/M SCCHN is evolving. First-line treatment strategies currently include immunotherapy given alone or in combination with chemotherapy[7]. Nevertheless, TPEx represents an adequate alternative for patients with R/M HNSCC without programmed death-ligand 1 expression or as a subsequent treatment after disease progression on immune checkpoint inhibitors given as monotherapy. It should be emphasized that drug combination regimens, such as TPEx, have proven to be associated with a higher ORR, which is particularly beneficial in patients with a high tumor burden.

## CONCLUSION

TPEx was a well-tolerated regimen in our population, showing a lower incidence of grade 3-4 adverse events than previously reported. PFS was comparable to those of recently reported clinical trials using the same treatment scheme. We observed a higher ORR compared to the previous results in phase 2 trials. This regimen may be considered an attractive therapeutic strategy due to its simplified administration, decreased total number of chemotherapy cycles, and treatment tolerability. Overall, quality of life, cost of hospitalization, and adverse event management should be carefully analyzed before deciding the best therapeutic plan for patients with R/M SCCHN.

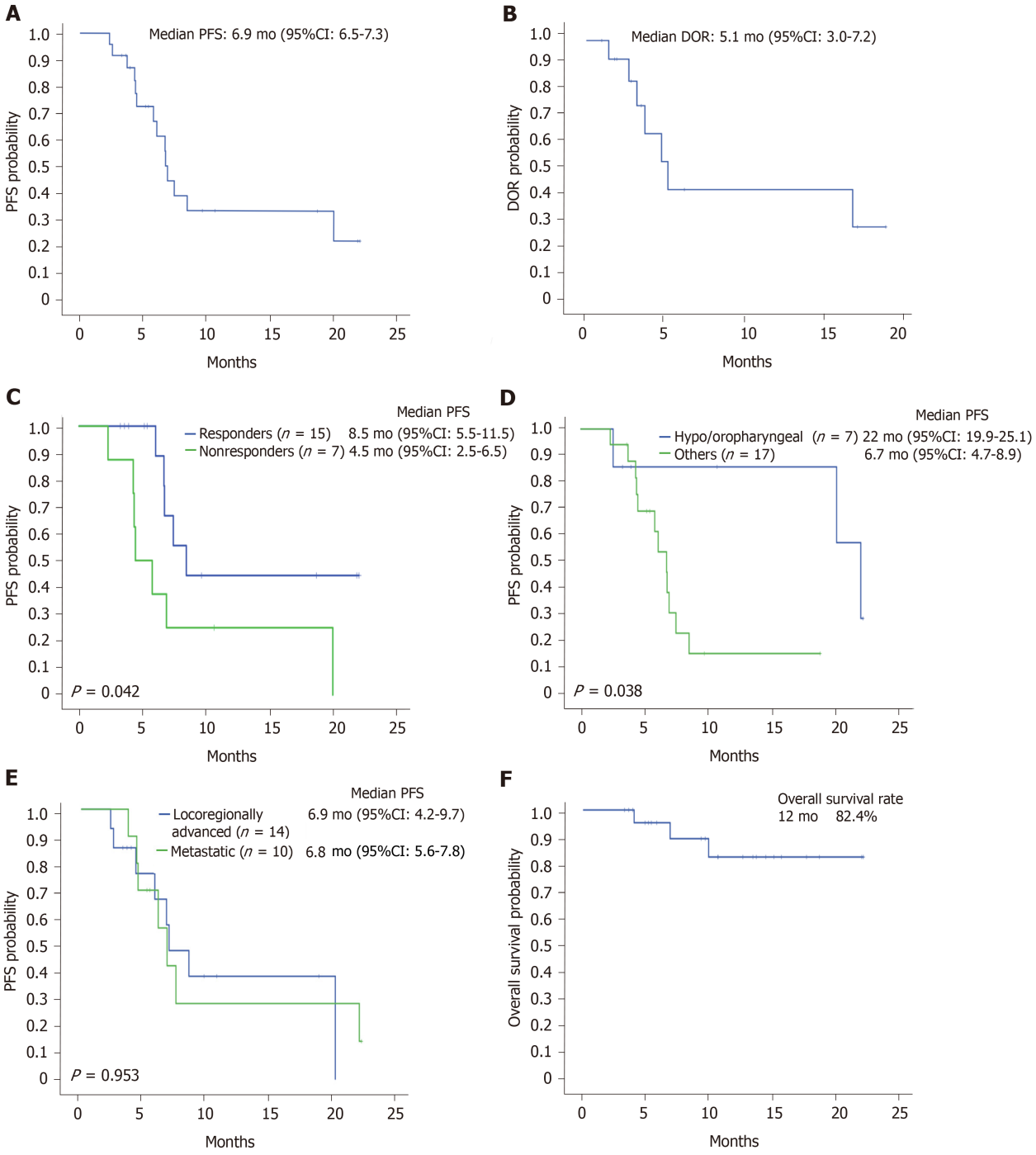


**Figure 1 Kaplan–Meier curves.** A: For progression-free survival (PFS); B: For duration of response (DOR); C: For PFS according to response; D: For PFS according to primary tumor site; E: For PFS according to extent of disease at TPEx initiation; F: For overall survival. PFS: Progression-free survival.

## ARTICLE HIGHLIGHTS

### *Research background*

The targeted therapy cetuximab in combination with 5-fluorouracil and platinum-based chemotherapy (the EXTREME regimen) has shown substantial efficacy for patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). However, a new strategy combining platinum, taxanes, and cetuximab (the TPEx regimen) has demonstrated similar efficacy with a more favorable toxicity profile in clinical trials.

### *Research motivation*

There is scarce evidence outside randomized clinical trials including patients treated with TPEx scheme.

### *Research objectives*

To evaluate the safety and efficacy of the TPEx scheme as first-line therapy in advanced SCCHN in a multicenter cohort study.

### *Research methods*

This retrospective multicenter cohort study included patients with histologically confirmed recurrent or metastatic SCCHN treated with first-line TPEx at five medical centers in Argentina between January 1, 2017, and April 31, 2020. Chemotherapy consisted of four cycles of docetaxel, cisplatin, and cetuximab followed by cetuximab maintenance therapy. Clinical outcomes and toxicity profiles were collected from medical charts. Treatment response was assessed by the investigator in accordance with Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

### *Research results*

Among the 24 patients included, the majority of patients (83.3%) received at least four chemotherapy cycles in the initial phase. The overall response rate was 62.5%, and 3 patients achieved a complete response (12.5%). The median time to response was 2.4 mo (95%CI: 1.3-3.5). With a median follow-up of 12.7 mo [95% confidence interval (CI): 8.8-16.6), the median progression-free survival (PFS) was 6.9 mo (95%CI: 6.5-7.3), and the overall survival rate at 12 mo was 82.4%. Patients with documented tumor response showed a better PFS than those with disease stabilization or progression [8.5 mo (95% CI: 5.5-11.5) and 4.5 mo (95%CI: 2.5-6.6), respectively; $P = 0.042$]. Regarding the safety analysis, two-thirds of patients reported at least one treatment-related adverse event, and 25% presented grade 3 toxicities. Of note, no patient experienced grade 4 adverse events.

### *Research conclusions*

TPEx was a well-tolerated regimen in our population, showing a lower incidence of grade 3-4 adverse events than previously reported. PFS was comparable to those of recently reported clinical trials using the same treatment scheme. We observed a higher overall response rate compared to the previous results in phase 2 trials.

### *Research perspectives*

This regimen may be considered an attractive therapeutic strategy due to its simplified administration, decreased total number of chemotherapy cycles, and treatment tolerability.


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## FOOTNOTES

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**Institutional review board statement:** The study was reviewed and approved for publication by the Institutional Review Board of each center according to the Argentinian ethical norms and regulations for multicenter studies.

**Informed consent statement:** Patients were not required to give their informed consent for this study because the analysis used anonymous data lacking patient names, addresses, dates of birth, wards, bed numbers, and hospital numbers and other private information.

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