Case Series

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Kilovoltage radiotherapy as a supportive treatment in locally advanced or metastatic breast cancer – a series of six case reports

Abstract

Kilovoltage (kV) radiotherapy, also called superficial radiotherapy (SXT) or orthovoltage radiotherapy (DXT), is a well-known and effective treatment option for non-melanoma skin cancer and some benign skin and musculoskeletal conditions. Given its surface dose delivery, its use in radiation oncology beyond superficial skin cancers is generally limited, but it has also been shown to be extremely useful for specific palliative applications. Here, we describe the characteristics of kilovoltage radiotherapy and report on six cases of locally advanced and/or metastatic breast cancer in which kilovoltage radiotherapy was used as the primary modality or as supportive treatment to linac-based radiotherapy to gain local tumor control and improve the patient's quality of life.

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Introduction

Breast cancer is the most common cancer in women in Europe with an estimated incidence of 523,000 cases in 2018, and it is the leading cause of death in women.[1] In Serbia, with a population of about seven million people, 6724 new cases of breast cancer were diagnosed in 2020.[2]

Radiation therapy (RT) is an important part of the multidisciplinary treatment of breast cancer together with surgery and adjuvant therapies. RT is commonly delivered postoperatively but can also be prescribed preoperatively/radically and for palliation. Regardless of the intention, RT in breast carcinoma is performed on linear accelerators using megavoltage x-ray energy. The procedure entails a planning CT scan, contouring of the PTV volumes and organs-at-risk and then treatment planning on a TPS, which is conducted by medical physicists. The prescribed dose to the whole breast volume is in the range of 50 Gy in 25 fractions (42.4 Gy/16 fx) with or without a 10 Gy boost for the postoperative approach.[3] Irradiation of the regional lymphatics depends on the patho-histological postoperative findings or on imaging findings in the case of non-operated patients. In addition, for a well-selected group of patients with early-stage breast cancer, accelerated partial breast irradiation can be applied.[4] For radical/preoperative treatment, the radiation dose ranges from 50 Gy to a maximum dose of 60 Gy, and in palliative settings it can vary from 8 Gy in one fraction to 50 Gy in 25 fractions.[5-6]

In daily practice, patients often present with inoperable breast tumors. Sometimes it is immediately difficult to correctly classify the patient into a particular setting or to define the total dose and fractionation regime. During RT, the treatment intention can often change from palliative to radical or vice versa depending on the patient's performance status or their loco-regional and systemic response to therapy. Patients with fungating tumors are a specific challenge, and the total dose and treatment regimen must be made based on the experience of the radiation oncologist and in accordance with the patient's general condition, age, extent of disease and currently applied systemic therapy.

Today, RT treatment is linac-based and is delivered with megavoltage x-rays/electrons in the 6 MV to 15 MV range. RT is highly recommended after breast-conserving surgery or following mastectomy in patients with positive lymph nodes to reduce the risk of disease recurrence.[7-8] Megavoltage x-rays are preferred to treat deep-seated tumors as they are attenuated less than lower energy photons and will penetrate further with a lower dose to the skin.[9] Conversely, there are machines that generate x-rays in the 60-300 kV energy range. Due to their fast attenuation, kV x-rays are typically used for superficial irradiation.[10] In selected patients presenting with bulky, locally advanced, or metastatic breast cancer, the immediate challenge is to gain local tumor control and relieve symptoms, such as bleeding, as quickly as possible. To avoid delay, particularly in frail or elderly patients unsuitable for systemic therapy, or in those who may refuse systemic treatment, we initiate treatment on a kilovoltage machine. Here we describe the treatment and outcomes of six cases treated with the Xstrahl 300 machine as single modality treatment or as supportive therapy to linac-based irradiation. All described patient cases were irradiated once per day for five days a week.

Case 1

Case 1 is a 65-year-old woman with stage T4bN2M0, ER and PR negative, HER2-positive invasive ductal breast carcinoma. Following biopsy, she was treated with a neoadjuvant approach with trastuzumab, pertuzumab and anthracyclines, followed by docetaxel and the same combination of monoclonal antibodies. After six months of systemic therapy, her disease was stable with no evidence of distant metastasis. Radiation therapy was started at 2.5 Gy per day in one direct field for seven fractions to a total dose of 17.5 Gy using an Xstrahl 300 kV machine. A round applicator measuring 10 centimeters (cm) in diameter was used without any stand-in factor correction. The treatment depth was calculated at 1.5 cm with a kV beam of 120 kV. Immediately following the five kV treatments, the patient then received 39 Gy to the whole breast in 13 fractions and 30 Gy in 10 fractions to the axilla, and supraclavicular regions on a linac. Four months post-RT, the patient underwent a radical mastectomy. Figure 1 shows significant tumor regression during the two months of hospitalization in the radiotherapy department.

Figure 1 Tumor regression during kV and MV treatment.

Case 2

Case 2 is a 41-year-old woman with a history of depression. She was diagnosed with stage T4bN2M0, ER, PR, HER2-positive lobular breast carcinoma measuring 10 cm in diameter. She refused intravenous therapy, but accepted ovariectomy, an aromatase inhibitor and RT. Treatment was initiated on the Xstrahl 300 kV machine (Fig-2A) with 15 Gy in 6 fractions (2.5 Gy daily) and was then continued on the linac using a standard fractionation schedule of 2 Gy per day to a total of 50 Gy to the breast and 48 Gy to the axilla and supraclavicular regions. The effect of radiation therapy after four months is shown in Figure 2B. Two years post-radiotherapy, the patient remains on an aromatase inhibitor and is free of distant metastases. The treatment parameters for the kV treatment were as follows: one direct field, applicator diameter 10 cm, voltage 120 kV, calculated depth at 1.5 cm.

Figure 2A Position of Xstrahl 300 during the treatment.

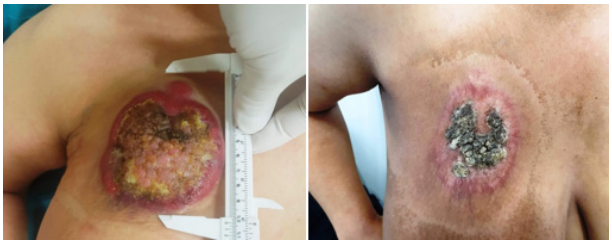

Figure 2B Effect of initial kV radiation therapy followed by standard breast linac-based treatment – at start and one month after complete RT treatment.

Case 3

Case 3 describes an 88 – year old patient with stage T4b N2 M0 ductal breast carcinoma measuring about six cm in diameter. Histopathology revealed a triple-negative tumor and therefore RT was considered the only treatment option given the patient's age and performance status. A linac-based hypofractionated regimen to the whole breast to a dose of 42.4 Gy in 2.6 Gy daily fractions was initiated followed by an orthovoltage kV boost to the tumor site of 15 Gy in 6 fractions (Figures 3 and 3A). The parameters for kV treatment were: one direct field, applicator 6x6cm, voltage 200kV, calculated depth at 2 cm.

Figure 3 & 3A Presentation after completion of the initial phase of linac-based treatment to a total of 42.4 Gy in 16 daily fractions (Figure 3) and four months after completion of radiation therapy, which included an additional kV boost of 15 Gy in 6 fractions on the Xstrahl 300 (Figure 3A).

Case 4

Case 4 is a middle-aged woman with stage IV triple-negative medullary breast carcinoma with metastasis to the bones and liver, and hypercalcemia. Oncological treatment was started with bisphosphonates and palliative irradiation of the thoracic vertebrae. After stabilization of blood parameters, the patient received first-line hormonal therapy (HT) and four cycles of anthracyclines, but did not achieve any systemic or a local response. As the tumor was fungating and bleeding, the medical board decided to irradiate the patient's breast tumor, concomitant with a second line of chemotherapy (paclitaxel) in an attempt to gain some local control. Because of her general condition, coupled with vertebral metastasic pain and the inability to achieve a supine position, the decision was made to irradiate only the breast tumor as quickly and as easily as possible for the purpose of ultimate palliation. We set up two "tangential" fields, a medial and a lateral, and the tumor was irradiated similar to the isocenter on the linac (Figure 4). Just one field was irradiated per day using a daily dose of 3 Gy (maximum surface dose 3.7 Gy) to a total dose of 45 Gy. We used a square 10 x 10 cm applicator, a voltage of 300 kV and a calculated depth of 3 cm. Figure 4A shows the successful result four months after treatment using the Xstrahl 300 machine.

Figure 4 Bulky tumor at the start of RT treatment and irradiation fields.

Figure 4A Initial presentation versus results four months after kV treatment only.

Case 5

Case 5 is a 70-year-old patient with hormone-positive, HER-2 negative lobular breast carcinoma with metastases to the bones and liver and a pleural effusion. Her vertebral metastases were already irradiated for palliative purposes. She also received chemotherapy, which stabilized her metastatic disease, but then she experienced local progression. Her treatment was switched to tamoxifen and the decision was made to irradiate the tumor in an attempt to stop its growth and prevent ulceration. She received only kV treatment with one direct field to a total dose of 39 Gy in 13 fractions at 3 Gy per day. Parameters for the kV treatment were as follows: one direct field, round applicator diameter 10 cm, voltage 80kV, calculated depth at 0.5cm. Figure 5 shows the response to kV treatment and tamoxifen.

Case 6

Case 6 describes an 89-year-old woman with bilateral lung pleural effusions, bone metastases and a tumor-amputated left breast at the time of presentation. Biopsy showed a skin infiltrating carcinoma with weak ER and PR receptors (both 5), and the patient was staged as T4b N2 M1. Oncology treatment was started with an aromatase inhibitor and the medical board decided to also irradiate the exulcerated tumor

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on the left chest wall with 42.4 Gy in 14 fractions. Parameters for the kV treatment were as follows: one direct field, applicator 10 cm x 10 cm, voltage 180 kV, calculated depth at 1 cm. Figure 6 shows tumor regression and re-epithelization one year after treatment.

Figure 5 Before and five months after kV radiotherapy on the Xstrahl 300.

Figure 6 Tumor-amputated breast before treatment and one year following kV treatment with concomitant use of an aromatase inhibitor.

Discussion

The availability of breast cancer screening has demonstrated a significant reduction in breast cancer mortality. A large Swedish study also showed that breast cancer screening is associated with a 25 % reduction in the rate of advanced breast cancers.[11] However, between 10 % and 30 % of new breast cancer cases are still locally advanced and approximately 2 % to 5 % of these will develop into fungating tumors.[12] In low- and middle-income countries, breast cancer is generally diagnosed at more advanced stages due to poor socioeconomic status and access to treatment. A single institution retrospective Indian study of 2,394 breast cancer patients revealed that 316 (29 %) had stage T4b cancer at diagnosis and 79 (3.3 %) had a fungating tumor.[13]

Advanced breast cancer, in our local experience, commonly presents as a fungating breast mass with symptoms of pain, a bulky tumor mass, bleeding, and malodorous discharge with subsequent infection.[12] Fungating tumors present an enormous challenge and have a significant impact on the patient's quality of life and social wellbeing.[13]

The management of fungating breast lesions is not particularly well-researched. A 2020 paper by Rupert and Fehl provides care recommendations, but international guidelines are lacking. Treatment is usually multimodality with surgery, systemic therapy, and radiation therapy all possible options in the general quest for local and systemic control.[12] Appropriate wound care, nutrition, pain relief and an understanding of the microbiome are also an important part of management. For these reasons, a multidisciplinary approach is needed for optimal care.[14]

Radiation therapy is a well-known and effective palliative treatment for fungating breast tumors. The benefits of radiation therapy include pain resolution, bleeding cessation, wound improvement, and a high rate of local control.[15] However, there is no consensus on the radiation dose, treatment technique or timing of this intervention.[13,15]

Current guidelines for palliative RT for symptomatic breast tumors suggest several RT fractionation regimes based on the patient's prognosis and performance status and these include a single fraction of 8 Gy, 20 Gy in five fractions through to 30/39 Gy in 10/13 fractions, and 50 Gy in 25 fractions.[13,6] Common palliative doses in this setting such as 20 Gy in 5 fractions or 30 Gy in 10 fractions would seem reasonable.[6,18] Quackenbush and colleagues suggested that 30-35 Gy in five fractions provides a higher biologic effective dose (BED), absence of additional side effects and greater patient convenience.[15] In a single case report, Gao reported a dramatic response to radiation therapy in a patient with a 15 cm x 10 cm fungating tumor who received an initial treatment of 36.4 Gy in 13 fractions via 6-10 MV tangential photons with a 0.5 cm bolus followed by a 15 Gy boost in five fractions using 15 MeV electron beams with a 0.5 cm bolus. No significant toxicity was apparent despite a cumulative dose of approximately 55 Gy equivalent dose in 2 Gy fractions (EQD2).[13] In a small case series, Vempati and colleagues observed that six of nine patients who received 30 Gy or more reported a clinical response, but that no benefit was reported in the four patients who received less than 30 Gy.[16] While these results may loosely suggest a dose-response relationship, Chia and colleagues found no difference between a higher and lower mean BED in terms of duration of palliation or survival in a retrospective review of 35 patients with fungating breast cancer; however, we can expect a local response rate up to 90 % and a median local progression-free survival of 10 months, regardless of histology.[17]

Our series of six patients provides further evidence on the significant role of orthovoltage radiation therapy alone or as an adjunct to linac-based treatment for patients with fungating locally advanced or metastatic breast cancer. Patients were carefully selected, and while this methodology may be unconventional and lacks high-level evidence, our institutional experience found that it enabled treatment to be started immediately and was effective at rapidly relieving discharge or bleeding.

Cases 1-3 received a combination of kV and MV. We usually reserve this approach for patients with bulky/ulcerating tumors without distant metastases who are in good overall condition. We initiate treatment on our Xstrahl 300 machine, capable of delivering superficial and orthovoltage radiation therapy, and give six or seven fractions at 2.5 Gy per day. We then continue treatment on the linac with a dose of 50 Gy in 25 fractions or use a hypofractionated schedule of 45 Gy given in 15 fractions at 3 Gy per day. We also irradiate the regional lymphatics with 48 Gy in 24 fractions or 30 Gy in 10 fractions, if using a hypofractionated schedule, and this is reasonable only in patients with a longer expected survival, e.g., in young to middle-aged women without co-morbidities in whom a good response to overall therapy is expected. The goal is to apply a total dose of 70-75 Gy (BED) to the tumor itself, which is equal or slightly higher than other documented case reports.[13,15,17] Of course, one must account for limitations to the organs-at-risk as there is no accurate insight with kV into the actual dose received, especially to the heart. Therefore, we recommended checking; at least approximately, what volume of heart is in the irradiation field on a conventional simulator before treatment. All our patients tolerated radiation extremely well, experiencing only a mild skin reaction and no other side effects. Patients were followed up for a relatively short period of time (up to two years) during which time there was no evidence of local disease progression. However, some patients developed systemic disease (metastases) and were referred to medical oncologists for further treatment which did not involve local reirradiation.

Cases 5 and 6 are patients with initial multi-metastatic disease who received definitive radiation therapy on the Xstrahl 300. It was believed that both these frail patients would be unable to maintain

a suitable position on the linac. Therefore, this approach was aimed at providing optimal patient comfort during treatment delivery to maximize compliance and outcome with minimal toxicity. It proved to be an effective treatment for pain, discomfort, ulceration, bleeding, and malodour.

Kilovoltage radiation therapy has several advantages. As it is a kilovoltage energy, the treatment room does not require as much radiation protection and footprint space as a linac. The treatment room has similar lead protection in the walls as an ordinary x-ray machine and the size of the treatment room is similar to the size of the x-ray cabinet. Our Xstrahl 300 also has a small moveable treatment head, so treating the patient in an ordinary hospital bed rather than on a dedicated treatment couch is possible and affords greater patient comfort. Fields of different shapes are easily trimmed by cutting 1-2 mm from the thick lead sheet. In general, kV radiation therapy offers easy planning, individual tailoring, and the ability to start treatment more rapidly, which we found highly beneficial among our selected patients. Orthovoltage radiation therapy also delivers 100 % of the prescribed dose to the skin's surface, as opposed to 6 MV, in which the D_{max} is to a depth of 1.5 cm without a bolus, which cannot be applied properly to bulky lesions.[18] Many applicators used with our Xstrahl 300 machine allow a large surface area to be treated easily: round applicators can treat up to the 10 cm in diameter and square applicators up to 20 cm x 20 cm. Furthermore, orthovoltage radiation therapy has a rapid dose fall-off on a lower voltage and exhibits a different radiobiological effect on tumor cells compared with megavoltage radiation therapy.[19]

One of the disadvantages of kV treatment compared to megavoltage is that homogeneity cannot be guaranteed over large areas, and this limits the treatment field to about eight cm in diameter, which was sufficient for the patients in our series. Planning is imprecise for undulating lesions or for more than one field. Given that no CT planning scan is required, there also is no record of where the dose has fallen at depth in tissue, so it is impossible to know with any accuracy the absorbed dose to organs-at-risk.[20] Finally, at least in our institution, a radiation oncologist needs to be present during nearly every treatment session.

Conclusion

Fungating breast tumors bring additional treatment challenges and there are no guidelines on their optimal management. Where the initial goal of treatment is to rapidly stop bleeding and discharge and to gain local control, our institutional experience is that kV treatment can be used alone or as an adjunct to linac-based treatment. Kilovoltage treatment has the advantages of easy planning, a rapid time to treatment start and easy patient positioning, particularly in frail patients who may be unable to maintain a suitable position on the linac. It also deposits 100 % dose delivery to the skin's surface. More research is needed to define optimal radiation doses and regimens.

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None.

Conflicts of interest

Authors declate that there is no conflicts of interest.

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