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Impact of loco-regional treatment including radiotherapy in patients presenting with metastatic breast cancer

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Original Article

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Abstract

Background: The impact of loco-regional treatment (LRT) with radiotherapy (RT) in patients presenting with metastatic breast cancer (MBC) has not been widely studied. The aim of this study was to review the treatment outcomes of LRT including RT in patients with MBC.
Materials and methods: Patients who presented with MBC were included in this retrospective study. Analysis was undertaken to determine the difference in local disease control, overall survival (OS) and progression-free survival (PFS) with systemic treatment alone, surgery alone, surgery plus RT and RT alone with long-rank test. Multivariate analysis was done, using the cox regression for factors affecting PFS and OS.
Results: From 2007 to 2014, data of 257 patients with MBC were collected. Totally, 185 patients received LRT and 72 did not. LRT was surgery plus RT, surgery only and RT only in 113, 47 and 25 patients, respectively. Cytotoxic chemotherapy and hormone therapy were received by 205 and 166 patients, respectively. Median follow-up was 36 months (6–120 months). PFS and OS at 3 years with and without LRT were 31% versus 6% ($p < 0{\cdot}001$) and 41% versus 17% ($p < 0{\cdot}001$), respectively. PFS at 3 years with surgery plus RT, RT alone and surgery was 40, 33 and 6%, respectively. OS at 3 years with surgery plus RT, RT alone and surgery was 50, 38 and 17%, respectively. Patients without LRT had worse PFS and OS, 6 and 17%, respectively. RT had significant impact on PFS and OS along with chemotherapy and hormone treatment.
Conclusion: In patients with MBC, improved local control, PFS and OS were achieved with loco-regional RT. Loco-regional RT along with chemotherapy and hormones were significant factors for PFS and OS irrespective of surgery.

Introduction

Breast cancer is the most common cancer among females in urban areas according to population-based cancer registries in India. Five percent of these patients present with distant metastases at diagnosis.[1] Traditionally, these patients were treated primarily with systemic therapy. Novel chemotherapy agents such as taxanes and trastuzumab have led to improved survival rates in these patients. Therefore, there is a need to address local disease in these patients. Loco-regional treatment (LRT) not only controls symptoms (ulceration and bleeding) but also improves local disease control and increases disease-free and progression-free survival (PFS) in patients with metastatic breast cancer (MBC).[2] In most of the published studies, LRT was in the form of surgery and only a few studies included radiotherapy (RT).[3–5] These studies showed improvement in both PFS and overall survival (OS) with LRT. Impact of exclusive RT as LRT was not a major end point in these studies. RT is a non-invasive procedure with negligible risk of complications as compared to surgery and it can be offered to patients who are unfit for surgery on outpatient basis. RT dose in the published studies ranged from 30 to 50 Gy delivered in 10–25 fractions mainly with photons.[3,4] RT may also lead to abscopal effect with a possibility to control the systemic disease in oligometastasis. RT also achieves palliation in inoperable fungated/ulcerated disease. Recently, few studies have been reported which has demonstrated benefit of RT as a LRT in patients presenting with MBC.[6–8] In this study, we analysed impact of loco-regional RT on PFS and OS as LRT in patients with MBC. We analysed each modality independently (systemic treatment alone, RT alone, surgery alone and surgery plus RT) to further strengthen the impact of RT on clinical outcomes.

Materials and Methods

Patients

This retrospective study included patients from 2007 to 2014, to allow for a good sample size and a long-term follow-up of up to 5 years, at the Department of Radiation Oncology at PGIMER, Chandigarh, India. Study was approved by departmental committee. Eligible patients included those

who presented with MBC and also who developed metastases within 2 months of surgery, no synchronous contralateral breast primary, limited visceral metastasis, patients with brain metastasis if expected survival was more than 6 months and not pregnant or nursing. Cytotoxic chemotherapy and hormonal therapy were given as per indication. Treatment and follow-up details were collected from patient's file. Staging was done according to AJCC 8th edition.[9] Patients were further divided into those who were treated with surgery alone, RT alone and surgery plus RT for comparison of outcomes.

Treatment

All patients received systemic therapy as chemotherapy or hormonal therapy. Chemotherapy regimens were FAC (5-FU, doxorubicin cyclophosphamide) or taxol based. Surgery was either total mastectomy with axillary clearance and wide local excision or breast-conserving surgery (BCS). All patients who received RT were planned on a two-dimensional (2D) simulator. Treatment was done with two standard opposing tangential fields. RT dose was 35 Gy in 15 fractions in 3 weeks in patients who underwent mastectomy and 40 Gy in 16 fractions to those with BCS. Patients who did not undergo surgery received RT dose of 30–40 Gy in 10–16 fractions in 2–3 weeks to the whole breast, prescribed at mid separation. Bolus was used in patients with skin ulceration because of the surface nature of the tumour and in those who underwent mastectomy. Supraclavicular fossa was treated with a single incident field. Dose was 30–40 Gy in 10–15 fractions with prescription at $D_{max.}$

Follow-up

Patients were examined clinically and radiologically after completion of treatment. RT acute skin toxicities were assessed using RTOG toxicity scale at 1 month of RT completion.[10] Follow-up was undertaken every 3 months during the 1st year, every 4 months in the 2nd year and then 6 months till 5 years. Clinical evaluation of primary and metastatic sites was done on every visit. Radiological evaluation was performed if there were symptoms of disease progression. Patients received second-line chemotherapy or hormonal therapy on disease progression.

Statistical analysis

Demographic and patient characteristics as well as adjuvant therapies received were compared between cohorts (LRT versus no LRT and different LRTs) using Fisher's exact tests. Kaplan–Meier PFS and OS curves were constructed and compared between the two cohorts using log-rank tests. Disease progression was defined as any progression, local or distant. PFS was calculated from the date of diagnosis to the date of disease progression. OS was calculated from the date of diagnosis till death or last follow-up. Clinical outcomes were also compared between subgroups of patients receiving LRT in the form of surgery, surgery plus RT, RT alone and no LRT. Multivariate analysis was done with Cox regression model for age, co-morbidity, tumour stage, nodal involvement, chemotherapy, surgery, RT, hormonal treatment and bone/visceral metastases. p Value $< 0{\cdot}05$ was considered as statistically significant. Statistical analysis was performed on SPSS software version 23.0.

Results

Patient and treatment characteristics

A total of 257 patients were included in the study. The mean age of the patients was 50 years (range 18–76 years). Mean tumour size was 8 cm (2–20 cm). Most patients (72%) had large (T3/T4) tumours and involved lymph nodes N2/N3 (48%). Sites of metastasis included bone (65%), lung (15%) and liver (9%). Eleven percent of patients had multiple sites of metastases. Eighty percent of patients received adjuvant chemotherapy, which included anthracyclins (48%) and anthracyclins plus taxanes (52%). Hormonal therapy was given to 65% of patients.

LRT was given to 185 patients. The cohort of patients who did not receive LRT was comprised of 72 patients. Table 1 summarises the characteristics between the two cohorts. Co-morbidity was comparable between the two groups. The use of LRT was not deterred by age or co-morbidity. Patients who received no LRT

Table 1. Patient characteristics

Characteristics	All patients ($n = 257$)	Loco-regional treatment ($n = 185$)	No loco-regional treatment ($n = 72$)	p-value Fisher's exact test
Mean age	50 years	51	49	1·000
Age (%)				
≤ 50 years	131 (51)	91 (49)	40 (56)	0·41
> 50 years	126 (49)	94 (51)	32 (44)	
T stage (%)				
T1/T2	72 (28)	66 (36)	6 (8)	<0·001
T3/T4	185 (72)	119 (64)	66 (92)	
N stage (%)				
N0/N1	133 (52)	110 (59)	23 (32)	<0·001
N2/N3	124 (48)	75 (41)	49 (68)	
Co-morbidity (%)				
Yes	87 (34)	64 (35)	23 (32)	0·77
No	170 (66)	121 (65)	49 (68)	
Site of metastasis (%)				
Bone	166 (65)	137 (74)	29 (40)	<0·001
Lung	39 (15)	21 (11)	18 (25)	
Liver	24 (9)	14 (8)	10 (14)	
Multiple	28 (11)	13 (7)	15 (21)	
Histology (%)				
IDC	238 (93)	171 (92)	67 (93)	1·000
ILC	12 (5)	9 (5)	3 (4)	
Other	7 (3)	5 (3)	2 (3)	
Chemotherapy (%)				
Yes	205 (80)	142 (77)	63 (88)	0·059
No	52 (20)	43 (23)	9 (12)	
Chemotherapy (%)				
FAC	93 (48)	65 (46)	28 (44)	0·88
Taxol-based	112 (52)	77 (54)	35 (56)	
Hormone therapy (%)				
Yes	166 (65)	123 (66)	43 (60)	0·313
No	91 (35)	62 (34%)	29 (20)	

Abbreviations: T1T2, tumour stage; N, nodes; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma; FAC, 5-Fluorouracil, adriamycin, cyclophosphamide.

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Table 2. Baseline patient characteristics according to loco-regional treatment

Characteristics	Surgery ($n = 47$)	RT ($n = 25$)	Surgery + RT ($n = 113$)	p-value Fisher's exact test
Mean age	50 years	49 years	50 years	1·00
Age (%)				
≤ 50 years	23 (49)	11 (44)	57 (50)	0·87
> 50 years	24 (51)	14 (56)	56 (50)	
T stage (%)				
T1/T2	16 (34)	0 (0)	51 (45)	<0·001
T3/T4	31 (66)	25 (100)	62 (55)	
N stage (%)				
N0	10 (21)	11 (44)	20 (18)	0·023
N1–3	37 (79)	14 (56)	93 (82)	
Co-morbidity (%)				
Yes	13 (28)	7 (28)	43 (38)	0·40
No	34 (72)	18 (72)	70 (62)	
Site of metastasis (%)				
Bone	19 (40)	17 (68)	80 (71)	0·001
Visceral	28 (60)	8 (32)	33 (29)	
Histology (%)				
IDC	41 (87)	22 (88)	103 (91)	0·73
Other	6 (13)	3 (12)	10 (9)	
Chemotherapy (%)				
Yes	43 (91)	19 (76)	80 (71)	0·013
No	4 (9)	6 (24)	33 (29)	
Hormone therapy (%)				0·027
Yes	24 (51)	19 (76)	81 (72)	
No	23 (49)	6 (24)	32 (28)	

Abbreviations: T1T2, tumour stage; N, nodes; IDC, infiltrating ductal carcinoma.

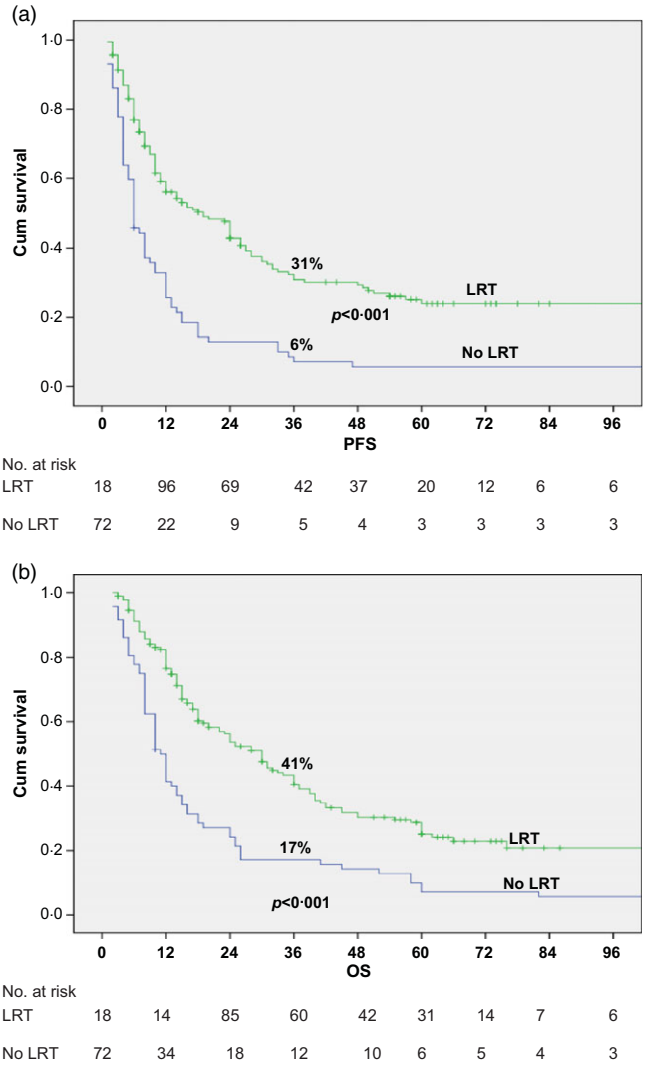

Figure 1. (a) 3 years PFS with and without loco-regional treatment. (b) 3 years OS with and without loco-regional treatment.

had significantly larger tumours (92%) and greater nodal involvement (68%). More patients in the LRT group had bone metastasis, 74% as compared to 40% without LRT ($p < 0·001$). More patients in the no LRT cohort received adjuvant chemotherapy (88%) compared with patients in the LRT cohort (77%), although the distribution of chemotherapy regimens was not significant ($p = 0·059$). Majority of patients received taxane-based chemotherapy in both the arms. The use of hormone therapy was similar between the cohorts.

The cohort of patients who received LRT was comprised of 47 patients who received surgery alone, 25 patients who received RT alone and 113 patients who received surgery plus RT; total 185 patients. Baseline characteristics of the patients in different LRT groups are shown in Table 2. Majority of patients in the surgery arm had nodal (79%) and visceral disease (60%). Majority of them also received chemotherapy (91%) and hormones in 51%. In RT only arm, all patients had advanced tumour stage (T3/T4).

Clinical outcomes

Median follow-up was 36 months (6–120 months). RTOG acute skin radiation toxicity grade ≥2 was observed in 11 (8%) patients. Patients receiving LRT had significantly better local control (87%). Local recurrence occurred in 24 (13%) patients after LRT. Distant progression was similar with and without LRT, 96 (52%) and 41 (56%), respectively. PFS and OS were better in women who received LRT. PFS and OS at 3 years with and without LRT were 31% versus 6% ($p < 0·001$) and 41% versus 17% ($p < 0·001$), respectively (Figures 1a and 1b). PFS at 3 years with surgery plus RT, RT alone and surgery alone was 40, 33 and 6%, respectively (Figure 2a). OS at 3 years with surgery plus RT, RT alone and surgery alone was 50, 38 and 17%, respectively. Patients without LRT had worse PFS and OS, 6% and 17%, respectively (Figure 2b).

Patients who had not undergone surgery also benefitted with local RT. PFS in these patients was 34 and 5% with and without RT ($p < 0·001$), respectively (Figure 3a). OS at 3 years in patients who were not operated was 45 and 13% with and without RT ($p < 0·001$), respectively (Figure 3b).

The benefit of RT was evident and irrespective of tumour, nodal stage and surgery. On a multivariate analysis, RT had significant impact on PFS [hazard ratio (HR) 1·4, 95% CI 1·2–2·4; $p < 0·001$)] and OS (HR 0·5, 95% CI 0·4–0·8; $p = 0·002$) along with chemotherapy and hormones (Table 3). Patients with bone metastasis had significant better PFS (HR 1·8, 95% CI 1·3–2·5;

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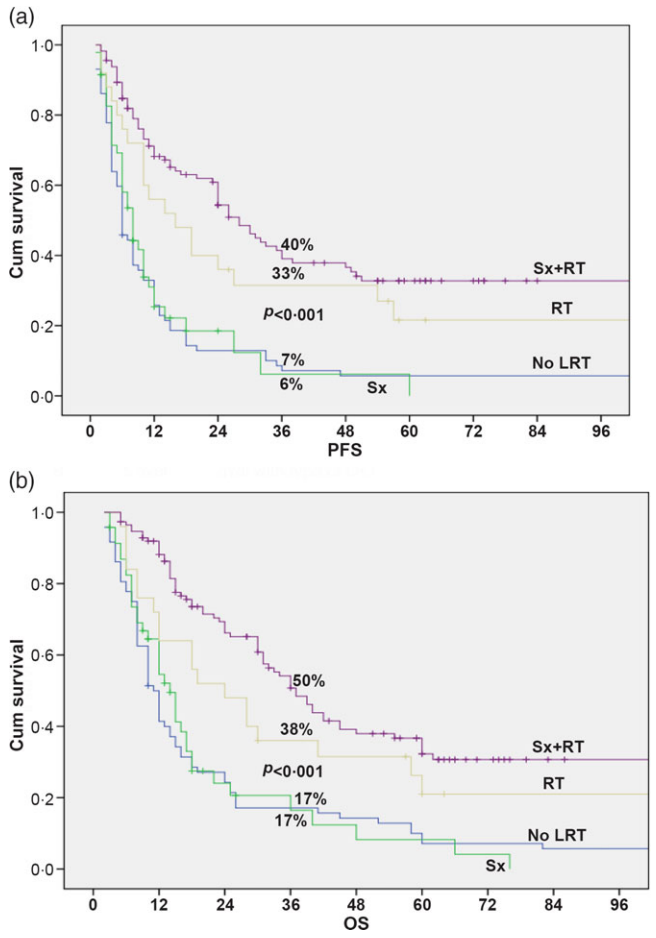

Figure 2. (a) 3 years PFS with type of loco-regional treatment. (b) 3 years OS with type of loco-regional treatment.

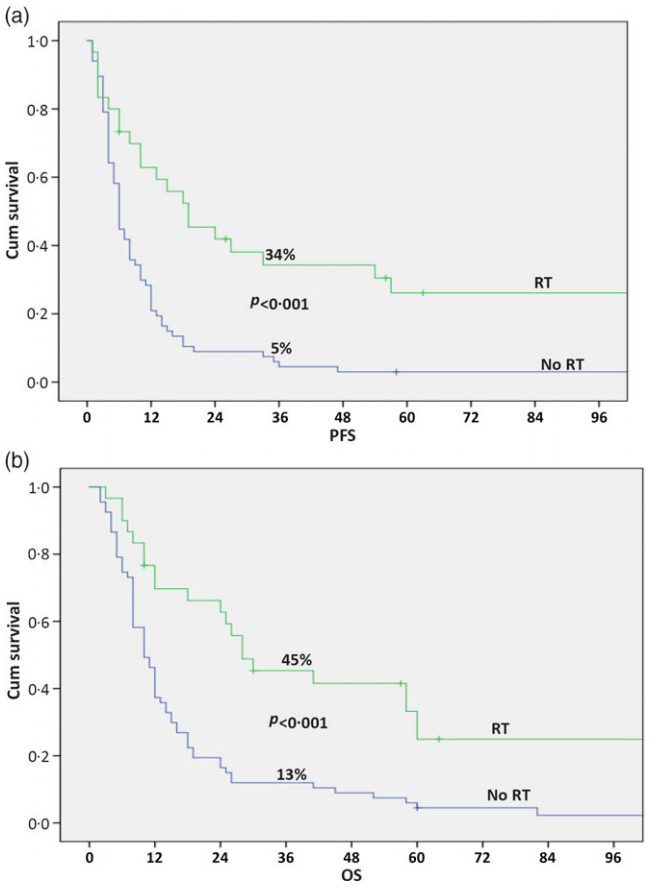

Figure 3. (a) 3 years PFS with RT in patients with no surgery. (b) 3 years OS with RT in patients with no surgery.

$p < 0{\cdot}001$) and OS (HR 0·5, 95% CI 0·4–0·7; $p < 0{\cdot}001$) with LRT than those with visceral metastases.

Discussion

In this retrospective study, we examined the impact of LRT in patients presenting with MBC. It was seen that LRT with RT after systemic therapy improved PFS and OS in these patients. Improvement in PFS and OS with RT was irrespective of surgery, tumour and nodal stage. Patients with bone metastases had better PFS and OS with LRT as compared to those with visceral metastases.

Guidelines for the use of LRT in MBC are lacking. Addressing primary breast disease may improve outcome and quality of life in these patients. Survival advantage in patients receiving LRT over patients receiving chemotherapy only remains controversial. Despite such controversy, LRT is commonly practiced.[3–5,11] The use of LRT ranges from 37 to 61% in patients presenting with metastatic disease.[3] In the present study, 42% patients received LRT as per data from our institute.

Loco-regional control was achieved in 87% patients in our study which is comparable to that reported by other studies.[2–4] Nguyen et al. observed that patients with LRT had better OS than those without LRT, irrespective of type of LRT.[4] In another study, LRT was an independent prognostic factor for OS.[12] OS with LRT in our study is comparable to 43·7% at 3 years reported by Le Scodan et al.[12] As observed in the present study, Bourgier et al. also in their study did not find any differences in PFS and OS with surgery plus RT or RT alone.[13] In a study by Chia et al., they grouped patients into four cohorts according to periods of availability of new systemic therapies and showed significant improvement in OS with taxanes and trastuzumab therapy.[14] In the present study also majority of patients 107 (52%) received anthracyclin and taxane-based chemotherapy. Trastuzumab was not received because of economic reasons, which may be one of the reasons for lower PFS and OS observed in our study. Another reason could be larger tumour size at presentation, mean tumour size was 8 cm (range 2–20 cm) in our patients.

Retrospective studies with surgery as LRT modality have reported improved survival in patients with MBC.[5,11,15] These studies emphasised to achieve a negative margin after surgery.[5,11] Role of RT combined with surgery or alone has been studied in few retrospective studies. Outcomes with RT alone or in combination with surgery were comparable to surgery only. It was also observed that in patients not fit for surgery, RT alone gives similar outcomes.[3,4] In one of the study, it was observed that OS was associated with local control irrespective of surgery.[16] In our study also significant improvement in OS and PFS was seen in patient receiving LRT whether operated or not (Figure 1). Outcomes were comparable with surgery plus RT or RT alone (Figures 2a and 2b). Exclusive surgery was not better than RT, but it should be interpreted with caution as many patients in the surgery only group had nodal and visceral disease (Table 2). In RT group, all patients had T3/T4 disease and 56% had nodal involvement but still they

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Table 3. Multivariate Cox regression analysis for progression-free and overall survival

Factors	Progression-free survival			Overall survival		
	HR	95% CI	Sig.	HR	95% CI	Sig.
Age (<50 versus ≥50 years)	0·958	0·716–1·281	0·772	1·000	0·749–1·335	0·999
Tumour stage (T1T2 versus T3T4)	0·844	0·590–1·208	0·354	0·785	0·549–1·121	0·183
Nodes (negative versus positive)	0·727	0·490–1·079	0·113	1·278	0·865–1·889	0·219
Metastases (Bone versus bone)	1·879	1·363–2·590	<0·001	0·561	0·408–0·770	<0·001
CCT (yes versus no)	0·367	0·226–0·597	<0·001	0·339	0·208–0·552	<0·001
Surgery (yes versus no)	1·320	0·961–1·813	0·087	1·274	0·925–1·754	0·139
RT (yes versus no)	1·746	1·241–2·456	<0·001	0·575	0·407–0·811	0·002
Hormones (yes versus no)	1·772	1·300–2·416	<0·001	1·545	1·139–2·095	0·005

Abbreviations: HR, hazard ratio; CI, confidence interval; T1T2, tumour stage; N, nodes; CCT, combination chemotherapy; RT, radiotherapy.

were benefitted. Surgery alone may not improve outcomes in MBC patients with high burden of disease, so a combination of surgery and RT may be better. Local RT may control the primary tumour and metastases by abscopal effect, but it has been under-studied. RT was well tolerated in the present study as only 11 (8%) patients had grade ≥2 skin toxicity. Grade 3 skin toxicity occurred in only 4 (3%) patients.

In a study by Nguyen et al., they observed that patients with bone metastases, younger age group, limited metastatic sites, ER positive and clear margin carry good prognosis after LRT.[4] In our study, patients were benefitted with RT irrespective of surgery, tumour and nodal stage. In a French study also LRT was associated with 35% reduction in hazard of death [HR = 0·65, 95% CI (0·55, 0·76); $p < 0·001$].[6] Rapiti et al. in their study also observed that surgery with negative margins was more beneficial in patients with bone metastases than metastases in other sites.[11] In the present study also LRT was more effective in patients with bone metastases (Table 3). In our study, patients who underwent mastectomy, 63 (50%), had T4 and N2/3 disease. Hence, advanced stage patients may also benefit from LRT. On a multivariate analysis, RT, chemotherapy, hormonal treatment and bone metastasis were significant factors affecting PFS and OS (Table 3).

There are no randomised trials of LRT with RT in patients with MBC. Three randomised control trials were carried out to see impact of LRT in the form of surgery. First, Badwe et al. randomly assigned 350 patients with MBC following six cycles of chemotherapy to mastectomy, complete axillary dissection, plus RT, versus no LRT, and found that the non-surgical group had no worse survival than those who underwent mastectomy (19·2% versus 20·5%).[17] Local PFS was better with surgery plus RT (HR = 0·16), but distant PFS was worse in this group (HR = 1·42; $p = 0.01$). In our study also local control (87%) was better with RT but these patients had worse distant progression (60%).

Second, the Turkish Federation of Breast Cancer Society (MF 0701) compared survival of patients receiving chemotherapy only with patients receiving surgical treatment followed by adjuvant chemotherapy. There was no OS difference between the two groups at 36 months. However, at 40 months LRT group had better OS as compared to ST.[18] Our results are also comparable to Turkish study. Third, ECOG-E2108 phase III is a multicentre study aiming to recruit 880 patients. The primary objective of this study is to compare early surgery of intact primary disease with local palliative therapy only, in patients with stage IV breast cancer, whose disease does not progress during initial optimal systemic therapy and whether it will result in prolonged survival. Results of this study are awaited.[19] Another trial which may help to through more light on role of LRT in MBC is POSYTIVE trial expected by mid-2021.[20] So far, the randomised trials have shown that surgery has no OS benefit and inconsistent results on PFS, still this debate remains unresolved. None of these trials have included exclusive RT as LRT.

RT dose delivered was 30–50 Gy in 10–25 fractions delivered over 2–5 weeks with conventional or hypofractionated schedules with or without boost.[9,10] We treated all our patients with hypofractionated RT. In a study by Mauro et al., they reported that RT dose was an independent prognostic factor for local PFS and OS along with Karnofsky Performance Status, number of metastatic sites and hormonal therapy, and number of previous chemotherapy lines.[19] In a recent study, Pons-Tostivint et al. observed that loco-regional RT was significantly associated with better OS in de novo MBC, similar to surgery plus RT, compared with no RT.[20]

Limitations of the present study are its retrospective nature, so there could be selection bias on patients for LRT and many undocumented confounding factors, by virtue of it. RT was delivered by 2D technique. It is a single institutional study, and very few patients could afford targeted systemic therapy. In the present study, LRT was also used in patients with poor risk factors (advanced tumour, nodal and visceral disease) as compared to other studies where it has been mostly used in patients with good prognostic factors. RT efficacy and doses used were not studied. Although retrospective, but all three LRTs improved PFS and OS over no LRT. We used multivariate analysis which also supported that RT was associated with improved PFS and OS. These observations make a strong case for local RT after systemic therapy as an option for LRT in patients with MBC. RT is non-invasive, non-mutilating and an OPD procedure without risks of surgical complications (infection, haematoma and lymphedema) and sometimes surgery for advanced disease may end in incomplete resection or delay local RT. Patients unfit for surgery can also be offered RT. RT also helps to control pain, fungation, bleeding and ulceration. All these possibilities should be discussed with the patient before making a clinical decision about LRT.

After this study, we will offer RT as a LRT in patients who have controlled systemic disease, bone only or oligometastatic disease and patients needing palliation for the fungation, ulceration, bleeding and pain as an alternate to surgery. Future studies should focus

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on the RT dose, fraction, boost need and benefit of local RT along with irradiation of oligometastatic disease. We also need to understand the complexity of RT and abscopal effect in MBC.

Conclusion

LRT improved PFS and OS in patients with MBC. Benefit of RT was irrespective of tumour, nodal stage and surgery. Loco-regional RT along with chemotherapy and hormones were significant factors for PFS and OS irrespective surgery. These observations make a strong case for RT as an option of LRT in patients with MBC. So RT should be offered as a choice of LRT in these patients.

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