Impact of Unplanned Treatment Gaps and Dose Rate Effect on Survival During Radiotherapy in Breast Cancer (BRIDGE study)

Ankita Pandey[1], Ganesh Kumar Patel[2], Shreya Singh[1]

[1]M.D. Radiation Oncology, [2]PhD. Medical Physics
Department of Radiotherapy and Radiation Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Abstract: Background: Radiotherapy is an integral part of management in breast cancer that can be delivered by external beam or brachytherapy. Interruptions during radiotherapy are frequent and sometimes inevitable that may cause loss in the efficacy of the radiation. To account for real dose delivered after treatment gaps biological equivalent dose is calculated. The proposed study intended to evaluate effect of BED taking into account overall treatment time and source activity in brachytherapy on the outcome in breast cancer patients.
Materials and methods: This retrospective study included 50 patients of breast cancer after BCS who received WBRT followed by lumpectomy cavity boost by brachytherapy (Arm-A, n=20) and 6 MV photon EBRT (Arm-B, n=30). The prescribed dose of EBRT was 40Gy in 15 fractions with 2.67Gy dose per fraction. Boost dose delivered in both arms were 14Gy in 4fractions with 3.5Gy dose per fraction. The modified equation of BED was used for calculation taking into account overall treatment time, repopulation effect of tumor cells and intracellular time repair factor in brachytherapy.
Results: Median follow up duration of the cohort was 56 months (range: 30-89). All patients completed RT within 7weeks. Median treatment gap in Arm-A was 12.5days compared to 0.50days in Arm-B. Taking into account the time factor, mean calculated BED for late reacting tissue and tumor control was 94.27Gy_3 and 81.54Gy_4 in Arm-A and 101.7Gy_3 and 88.40Gy_4 in Arm-B, respectively.Median overall survival and disease free survival was 35 months (range: 24-45) and 32 months (range: 22-41). Three year OS and DFS were 94% and 88% respectively.Four patients in arm A and 2 in arm B developed loco-regional recurrence.
Conclusion: Overall treatment time and dose rate of brachytherapy source equally carries importance during treatment delivery and predicting the outcome. With prolong gap and decay in source activity, chances of local recurrence increases. Appropriate measures should be taken to minimize treatment interruption.

Keywords: Breast cancer, Overall treatment time, treatment interruption, Biological equivalent dose

Introduction

Breast cancer is one of the most common cancers worldwide[1]. In the past decade, treatment approaches mainly focussing on improved outcome and decreasing the overall treatment time are established[2]. Radiotherapy is an integral part of the breast cancer treatment which includes external beam radiotherapy (EBRT)to the whole breast followed by tumor bed boost (TBB), which can be delivered by electron beam therapy, photon beam therapy or brachytherapy (BT). Brachytherapy has an edge over other modalities in delivering high dose to the local region without compromising dose constraints of nearby normal organs. Various fractionation schedules have been studied in the past which is feasible to the patients and provide good tumor control[3–6].

Interruptions during radiotherapy are frequent and sometimes inevitable that may cause loss in the efficacy of the radiation. Also, the effect of radiation delivered by external beam and brachytherapy differs due to different doses, timing and difference in daily source activity in case of brachytherapy. Radiobiological models have shown that breast tissue is late reacting and hence hypofractionated schemes have been studied that gave equivalent results as conventional RT in term of OS and DFS[7]. BED method has been used traditionally to evaluate the biological effectiveness of these schedules[8]. Interstitial brachytherapy with Ir-192 source is used to give additional dose to the tumor bed. This HDR source is installed in the initial strength of 10Curie. Due to short half life, it is required to change this source every 3-4 months. However, in resource deprived setup, where timely source replacement is challenging, source strength may fall down by factor of 2 or 3, and hence increasing the treatment duration. This situation does not arise when patient is treated by EBRT and tumor bed boost is given by the same.

Although role of BT has been extensively studied with various doses per fraction, the actual data on BED taking into account time gap between whole breast irradiation (WBI) and delivery of BT is lacking. Taking into account this

issue, we conducted retrospective BRIDGE (Breast cancer Radiotherapy and Impact of Dose rate and treatment Gap effect on outcome) study where we evaluated effect of combined BED from external beam whole breast irradiation and tumor bed boost by EBRT or BT by two different formulas, taking into account treatment interruptions and source activity or dose rate at the time of treatment.

Materials and methods

In this retrospective study, 50 patients of early stage breast cancer from 2017 to 2021 who underwent breast conserving surgery were recruited. Patients with lumpectomy and axillary lymph node dissection received WBI using 6MV photon followed by TBB by HDR interstitial brachytherapy (Arm A, n=20 patients) or 6MV photon (Arm B, n=30 patients). Lumpectomy cavity for boost delivery was determined by pre operative clinical and mammographic findings, changes on CT scan, seroma, USG breast findings and surgical clips. Standard accepted field limits were used for treatment delivery. Treatment technique used for WBI was 3DCRT/IMRT/VMAT. Patients who were randomized in EBRT photon boost arm, received boost to tumor bed by 3DCRT technique. Regional lymph nodes (SCF and axilla) were irradiated in node positive patients.

Radiotherapy dose

The dose delivered by external beam radiotherapy (EBRT) was 40Gy in 15 fractions, 2.66Gy daily fraction followed by TBB either by BT or external beam photon therapy. Boost dose delivered in both arms were 14Gy in 4fractions with 3.5Gy per fraction. In BT group, boost dose was delivered 6 hours apart, 2 fractions per day, completed in two days. In Arm B, dingle fraction was delivered daily, completed in four days.

Calculation of BED

To assess the clinical outcome, BED was calculated in both groups of patients, taking into account time gap between completions of WBRT and starting of boost treatment. This correction factor considers the repopulation effect of tumor cells due to time gap and intracellular time repair factor in BT. Using the LQ cell survival model, total BED for whole breast and boost volume was calculated. For this calculation, α/β for tumor control was taken as 4Gy. Biological comparison between standard conventional schedule and experimented schedule of current study was also assessed.

BED formula for patients treated by EBRT (equation 1)

$$\mathrm{BED} = \left[\mathrm{nd}\left(1 + \frac{\mathrm{d_{WBRT}}}{\frac{\alpha}{\beta}}\right)\right] + \left[\mathrm{nd}\left(1 + \frac{\mathrm{d_{boost}}}{\frac{\alpha}{\beta}}\right)\right] - \mathrm{K(T - T_k)}$$

BED formula for patients treated by brachytherapy (equation 2)

$$\mathrm{BED} = \left[\mathrm{nd}\left(1 + \frac{\mathrm{d_{WBRT}}}{\frac{\alpha}{\beta}}\right) + \mathrm{nd}\left(1 + \frac{\mathrm{gd_{boost}}}{\frac{\alpha}{\beta}}\right)\right] - \mathrm{K(T - T_k)}$$

Where,

BED = biological equivalent dose, n = no. of fractions, d = dose per fraction, d_{WBRT} = 2.66Gy, d_{boost} = 3.5 Gy, α/β = 4Gy (for tumor control), α/β = 3Gy (for late effect), k = 0.693/ αT_{pot}, α = 0.08, T_{pot} = 14 days, T = total treatment duration starting from day 1 of radiotherapy upto last day of radiation, T_k = kick off time (21 days), g is dose rate factor for intracellular repair of radiation lesions and is calculated as:

$$g = 2\,[\mu T - 1 + \exp(-\mu T)]/(\mu T)^2$$

In another calculation, g factor was not considered in BT and only OTT was used to calculate the BED and its impact with the outcome was assessed.

Statistical analysis

Statistical analysis was performed using student paired t- test to determine statistical difference between the BT and EBRT boost group. The p value of <0.05 were considered as significant

Overall survival was determined from the day to diagnosis to the date of death due to any cause. Disease free survival was assessed from the day of surgery to the date of appearance of disease locally or loco-regionally. Kaplan Meir graph was used to determine OS and DFS in both the groups.

Result

A total of 50 patients were included in this study. Median follow up duration was 56 months (range: 30-89). All patients had early stage breast cancer of stage I or II. Taxane based neoadjuvant chemotherapy were received by 15 patients. All patients of luminal A or B received either tamoxifen or anastrazole depending on menopausal status while her2neu positive patients received 17 cycles of transtuzumab in adjuvant setting.

RT schedule was 40Gy in 15 fractions for whole breast irradiation either by 3DCRT or IMRT followed by tumor bed boost by interstitial brachytherapy (n=20) or by 6MV photon beam external beam therapy (n=30). All patients received RT within 6 months of the surgery. Radiotherapy was completed within within 7 weeks in current study (table1). Patients in EBRT boost arm completed treatment earlier than the brachytherapy boost arm patients (p=0.006). Gap between WBRT and boost was also less in EBRT group patients. Significant difference in treatment gap was observed in BT boost group with a median of 12.5 days compared to 0.50 days in EBRT boost group (p=0.006).

BED value with and without g factor

Without taking into account time factor and g factor, BED of the cohort was 105.89 Gy_3 (late effect) and 92.92 Gy_4 (tumor control) as shown in table 2. However, with time factor and decay factor in consideration as shown in equation 1 and 2, mean BED was reduced to 97.97$Gy_3$for late effect and 85$Gy_4$for tumor effect in BT patients.As there was minimal treatment gap in arm B patients, this did not affect the BED in this subgroup.

BED was also calculated without taking into account g factor for brachytherapy patients. Graph was plotted to depict fall in BED with OTT and the relation between the calculated BED with and without g factor. It was observed that below 40days of OTT, g factor had more effect on decreasing BED compared to time factor. However, as treatment gap was increased beyond 40 days, the effect of g factor on sloping down the graph was less compared to increasing OTT where drastic drop in BED value was seen (Graph 1). In subgroup analysis, it was observed that increasing g value was significantly associated with disease recurrence and mortality (p= 0.006) as shown in graph 2.

Survival analysis

There was no significant difference in OS and DFS in both the groups (Graph 3 and 4). Median overall survival and disease free survival was 35 months (range: 24-45) and 32 months (range: 22-41). Three year OS and DFS of the cohort were 94% and 88% respectively. Four patients in arm A and two in arm B developed loco-regional recurrence. Two patients in arm A died due to metastasis after 2 years of treatment completion. In arm B, 1 patient died due to pneumonitis. With the increasing BED, trend of improve survival in terms of OS and DFS was observed (Graph 5).

Discussion

Treatment of Early stage breast cancer has now been widely accepted as breast conserving surgery followed by radiotherapy to whole breast and lumpectomy cavity. TBB has been proven to improve the local control. Standard radiotherapy schedule has now been replaced by hypofractionated regimen in order to reduce the OTT[7]. This reduction in treatment time is feasible for both patients and hospital administration. Also, several studies have reported that increasing treatment time is associated with increase in local recurrence[9–11].

OTT is an important factor that determines probability of recurrence of disease. OTT is mainly important in fast proliferating tumors like head and neck cancers where repopulation occurs 4 +/- 1 week of starting of radiotherapy[12]. The role of overall treatment time in slowly growing tumors like breast and prostate cancer has also been studied. It is not clear that repopulation factor is required in cancers other than squamous cell carcinomas[13]. Dubray et al., in 1971 analysed 398 breast cancer patients treated by external beam radiotherapy followed by interstitial brachytherapy and concluded that if there is a long time interval between external beam RT and brachytherapy , then there is probability of increasing recurrence[9].In our study, patients planned for brachytherapy faced longer treatment duration due to more gap between WBRT and starting of brachytherapy procedure. This can be explained by the fact that brachytherapy is done under general anesthesia, for which pre anesthetic checkup is mandatory. Additional investigations are required for the same which requires time after completion of first phase of treatment. Financial arrangement for brachytherapy procedure and arrangements for hospital stay by the patients also delayed the starting of procedure.

According to Clarke et al., higher risk of recurrence in breast cancer patients were reported if time duration between initial biopsy and radiation therapy was more than 7 weeks, though it was marginally significant[10]. In the retrospective study by Van Limbergen et al., local control in breast cancer patients were significantly lower when total treatment time was more than 75 days[11].

Fourquet et al., compared tumor bed boost technique by Ir-192 implant of median dose rate of 0.64 Gy^{-1} versus cobalt-60 EBRT[14]. This study was later analysed by Guerrero et al., to determine TCP by the two modalities. They found that local control with Ir-192 implant was superior to Co-60 boost therapy due to the fact that total treatment time was less in former. But in this study, they have not considered any treatment gap between WBRT and delivery of boost[15].

In the present study we have considered potential doubling time of breast cancer as 14 days, according to the recommendations by Hall et al[16]. In another study by Haustersman et al., the author found median T_{pot} of 15 days (Range 4-74). T_{pot} is the cell cycle time divided by the proportion of the cell actually in the cycle and is the inverse of the cell birth rate[17].

It has been hypothesized that approximately 0.6Gy per days wasted in compensating tumor cell proliferation in breast cancer after whole breast irradiation. Median follow up data of 10 years based on UK START trial suggests that OTT is significantly associated with loco-regional recurrence (LRR). Knowledge of tumor cell kinetics is of utmost importance before commenting on effects of treatment time. In breast cancer, high thymidine labeling index is considered to be of worse prognosis compared to low index. Also, proportion of cell in S phase carry poor prognosis. Even though breast tumor is considered as slowly proliferating, growth rate may show wide range of variation due to tumor heterogeneity which may consists of both slowly and rapidly proliferating tissue[18]. Cell kinetics is considered as important prognostic marker in breast cancer. Hence, OTT and BED should be considered in breast cancer treatment also[19].

Interstitial brachytherapy is an effective modality to accelerate tumor bed dose without compromising OARs constraints and hence, measures should be taken to reduce the time gap between the WBRT and brachytherapy. Measures like lumpectomy cavity delineation before starting of WBRT by appropriate imaging and preoperative clinical findings, conducting pre anesthetic checkup during last week of EBRT and proper counseling of brachytherapy patients regarding hospital stay and financial arrangements should be taken to minimize treatment gap.

The major advantage of EBRT photon boost is that the entire treatment is planned before starting of radiotherapy in same CT simulated images and treatment of both the phases (WBRT and tumor bed boost) can be continued without any interruptions. This adds to higher BED than brachytherapy when repopulation effect is considered.

Conclusion

The present study is the first study conducted in our institution in which we have emphasized on realizing the importance of difference in time gap between WBRT and tumor bed boost in patients treated either by EBRT photon or brachytherapy. Measures like preEBRT planning, patient counseling and effective lumpectomy cavity delineation should be taken to minimize the gap and complete treatment in prescribed duration. Like in rapidly proliferating tumors, repopulation factor in calculating BED should be considered in breast cancer also. This will provide an exact picture of local control and late effects. Dose rate of brachytherapy source also carries equal importance during treatment delivery. With prolong gap and decay in source activity, chances of local recurrence increases.

Conflict of interest: none

Financial support: none

References

1. Sung H, Ferlay J, Siegel RL, et al (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 71:209–249. https://doi.org/10.3322/caac.21660

2. Girinsky T, Rey A, Roche B, et al (1993) Overall treatment time in advanced cervical carcinomas: A critical parameter in treatment outcome. Int J Radiat Oncol 27:1051–1056.

https://doi.org/10.1016/0360-3016(93)90522-W

3. Vicini FA, Horwitz EM, Lacerna MD, et al (1997) Long-term outcome with interstitial brachytherapy in the management of patients with early-stage breast cancer treated with breast-conserving therapy. Int J Radiat Oncol Biol Phys 37:845–52. https://doi.org/10.1016/s0360-3016(96)00606-2

4. Baglan KL, Martinez AA, Frazier RC, et al (2001) The use of high-dose-rate brachytherapy alone after lumpectomy in patients with early-stage breast cancer treated with breast-conserving therapy. Int J Radiat Oncol Biol Phys 50:1003–11. https://doi.org/10.1016/s0360-3016(01)01547-4

5. Ulutin HC, Ash D, Dodwell D (2003) Brachytherapy boost to the tumour bed in high risk patients after limited surgery for breast cancer. Clin Oncol (R Coll Radiol) 15:156–9. https://doi.org/10.1053/clon.2002.0187

6. Bartelink H, Maingon P, Poortmans P, et al (2015) Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol 16:47–56. https://doi.org/10.1016/S1470-2045(14)71156-8

7. START Trialists' Group, Bentzen SM, Agrawal RK, et al (2008) The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet (London, England) 371:1098–107. https://doi.org/10.1016/S0140-6736(08)60348-7

8. Fowler JF (2010) 21 Years of biologically effective dose. Br J Radiol 83:554–568. https://doi.org/10.1259/bjr/31372149

9. Dubray B, Mazeron JJ, Simon JM, et al (1992) Time factors in breast carcinoma: influence of delay between external irradiation and brachytherapy. Radiother Oncol 25:267–72. https://doi.org/10.1016/0167-8140(92)90246-q

10. Clarke DH, G. Lê M, Sarrazin D, et al (1985) Analysis of local-regional relapses in patients with early breast cancers treated by excision and radiotherapy: experience of the Institut Gustave-Roussy. Int J Radiat Oncol Biol Phys 11:137–145. https://doi.org/10.1016/0360-3016(85)90372-4

11. Van Limbergen E, Van der Schueren E, Van den Bogaert W, Van Wing J (1990) Local control of operable breast cancer after radiotherapy alone. Eur J Cancer Clin Oncol 26:674–679. https://doi.org/10.1016/0277-5379(90)90115-A

12. Withers HR, Taylor JM, Maciejewski B (1988) The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 27:131–46.

https://doi.org/10.3109/02841868809090333

13. Jones B, Dale RG, Deehan C, et al (2001) The Role of Biologically Effective Dose (BED) in Clinical Oncology. Clin Oncol 13:71–81. https://doi.org/10.1007/s001740170083

14. Fourquet A, Campana F, Mosseri V, et al (1995) Iridium-192 versus cobalt-60 boost in 3-7 cm breast cancer treated by irradiation alone: final results of a randomized trial. Radiother Oncol 34:114–20. https://doi.org/10.1016/0167-8140(94)01492-l

15. Guerrero M, Li XA (2003) Analysis of a large number of clinical studies for breast cancer radiotherapy: Estimation of radiobiological parameters for treatment planning. Phys Med Biol 48:3307–3326. https://doi.org/10.1088/0031-9155/48/20/004

16. Eric J. Hall A, Giaccia. J (2019) Radiobiology for the radiologist, 8th ed. Wolters Kluwer,

17. Haustermans K, Fowler J, Geboes K, et al (1998) Relationship between potential doubling time (T(POT)), labeling index and duration of DNA synthesis in 60 esophageal and 35 breast tumors: Is it worthwhile to measure T(POT)? Radiother Oncol 46:157–167. https://doi.org/10.1016/S0167-8140(97)00164-3

18. JOHNSON HA, BOND VP A method of labeling tissues with tritiated thymidine in vitro and its use in comparing rates of cell proliferation in duct epithelium, fibroadenoma, and carcinoma of human breast. Cancer 14:639–43. https://doi.org/10.1002/1097-0142(199005/06)14:3<639::aid-cncr2820140327>3.0.co;2-c

19. Silvestrini R, Daidone MG, Gasparini G (1985) Cell kinetics as a prognostic marker in node-negative breast cancer. Cancer 56:1982–7. https://doi.org/10.1002/1097-0142(19851015)56:8<1982::aid-cncr2820560816>3.0.co;2-i

Table 1: Patient and treatment characteristics

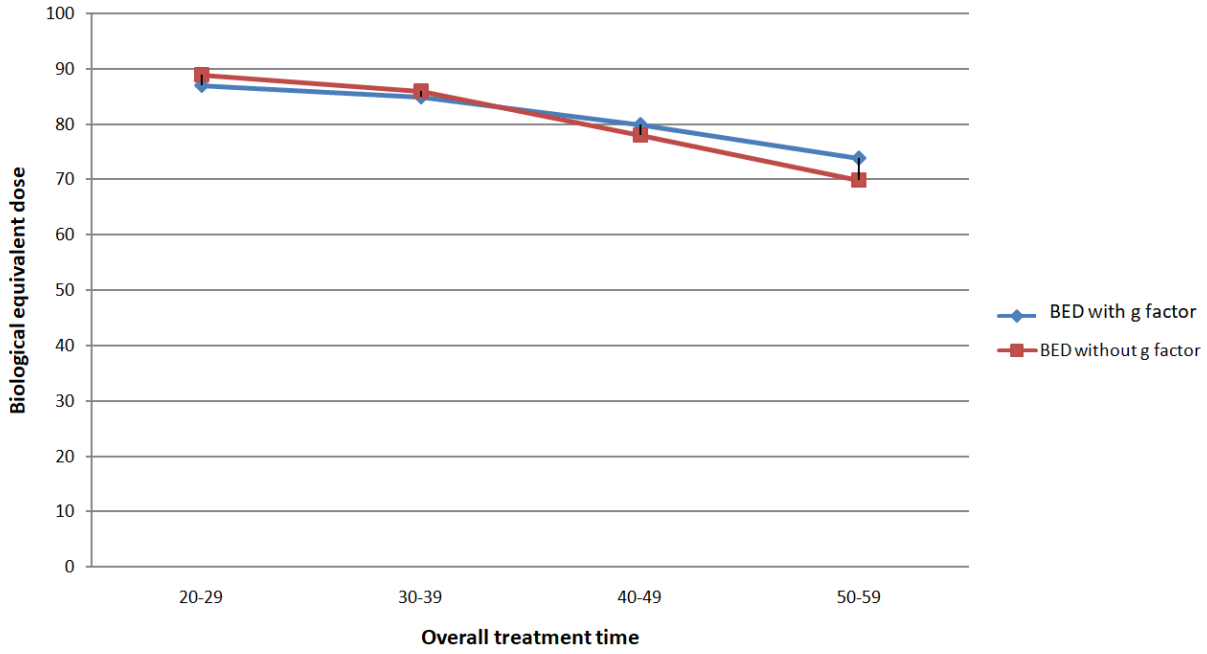
Parameters	Brachytherapy boost arm (20 patients)	Photon boost arm (30 patients)	p value
Age Mean (SD) Median Range	 42.87 ± 9.16 41 **28-67**	 50.20 ± 13.07 50 30-70	 0.38
Clinical stage Stage 1 Stage 2 Stage 3	 4 14 2	 6 20 4	 1.000
Pathological stage Stage 1 Stage 2 Stage 3	 6 10 4	 8 18 4	 0.481

WBRT technique 3DCRT IMRT VMAT	 16 4 0	 17 10 3	 0.660
Treatment duration Less than 4 weeks 5-6 weeks More than 6 weeks	 2 12 6	 14 16 0	 **0.006**
Treatment gap (days) Mean Median Range	 15.2 12.5 4-31	 1.6 0.50 0-7	 **0.006**
BED_3 for late effect Mean Median Range	 94.27 95.17 84.82 -99.57	 101.66 101.73 100.51- 102.95	 **0.020**
BED_4 for tumor control Mean Median Range	 81.54 82.35 71.97 – 86.89	 88.40 88.52 87.28 – 89.76	 **0.024**

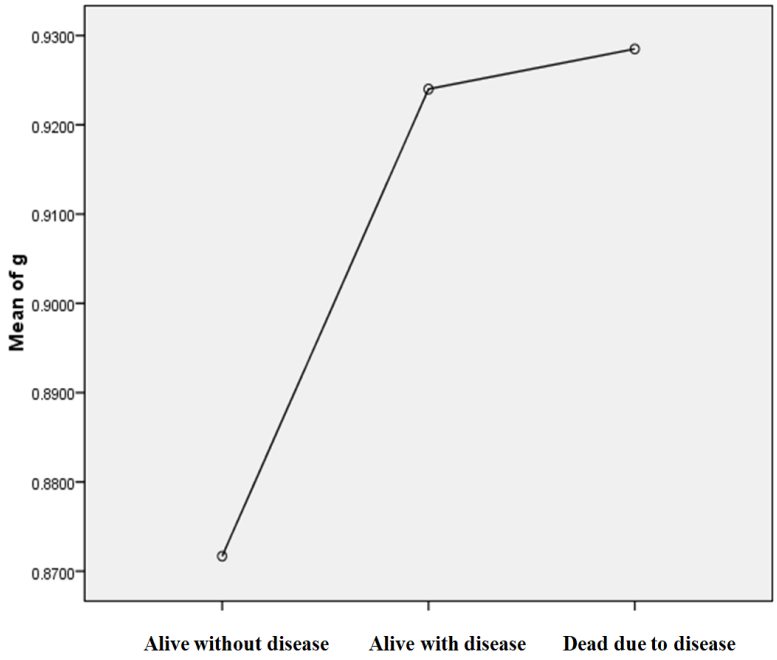
Table 2: Comparison of BED between standard conventional schedule and current study

Adjuvant WBRT dose	Adjuvant tumor bed boost dose	BED late effect $\alpha/\beta = 3Gy^{-1}$	BED tumor control $\alpha/\beta = 4Gy^{-1}$	BED late effect $\alpha/\beta = 3Gy^{-1}$ (including time factor and g factor)	BED tumor control $\alpha/\beta = 4Gy^{-1}$ (including time factor and g factor)
50Gy/25# (conventional schedule)	10Gy/5#	100	90	-----	-----
40Gy/15# (START B trial)	10Gy/5#	92.33	81.67	-----	-----
40Gy/15# (current study)	14Gy/4#	105.89	92.92	Mean = 97.97 Median = 100.40 Range = 84.82 – 102.95	Mean = 85.00 Median = 87.08 Range = 71.97 – 89.76

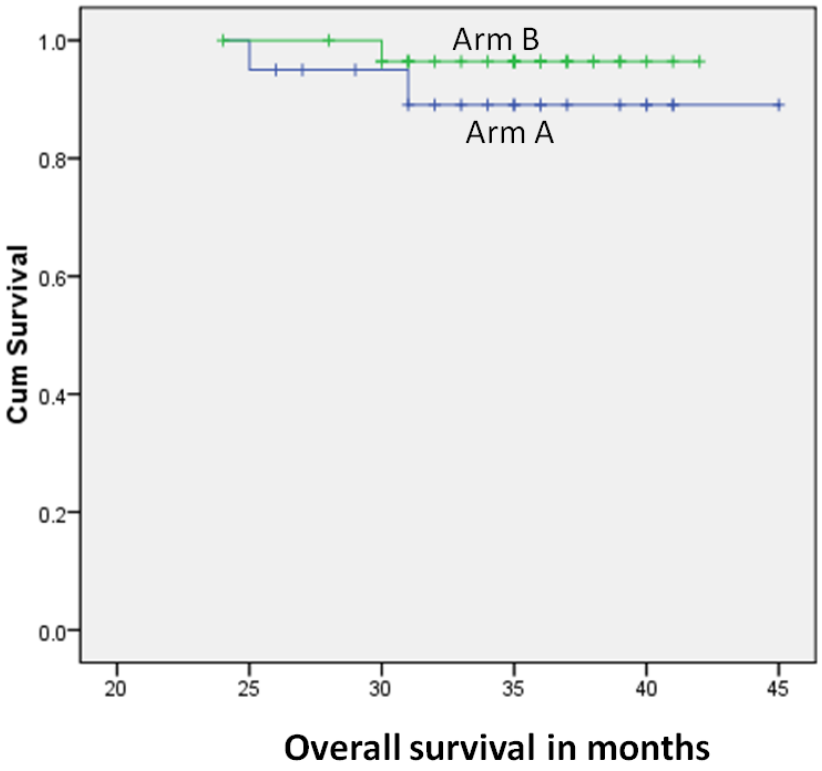
Graph 1: Showing effect of OTT and g factor on BED



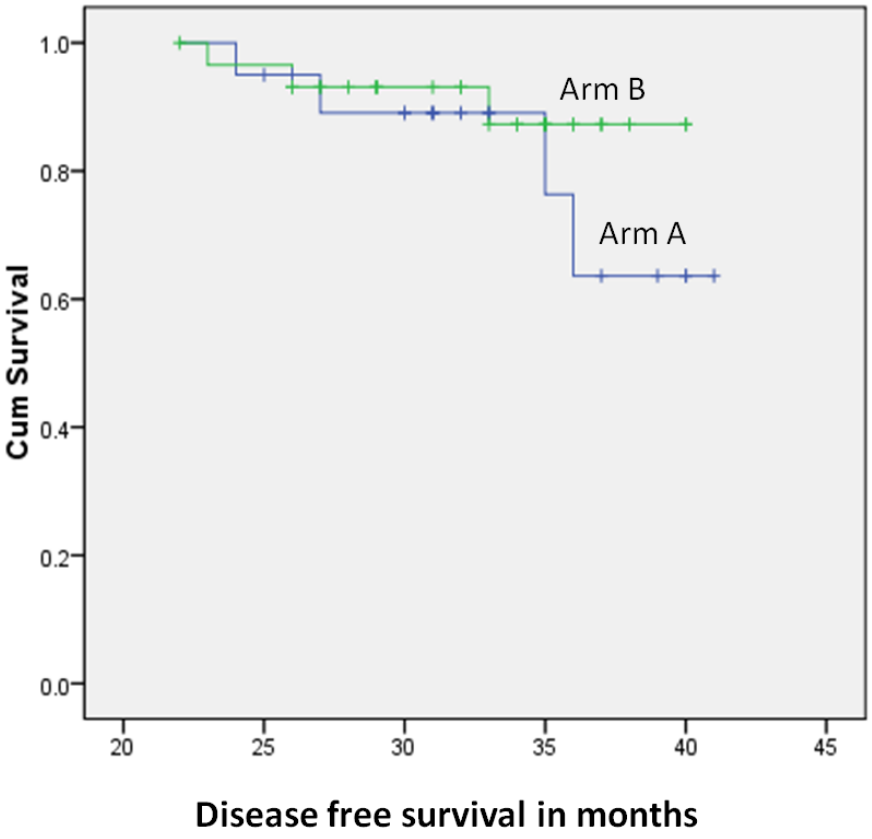
Graph 2: Correlation of g value and the disease status



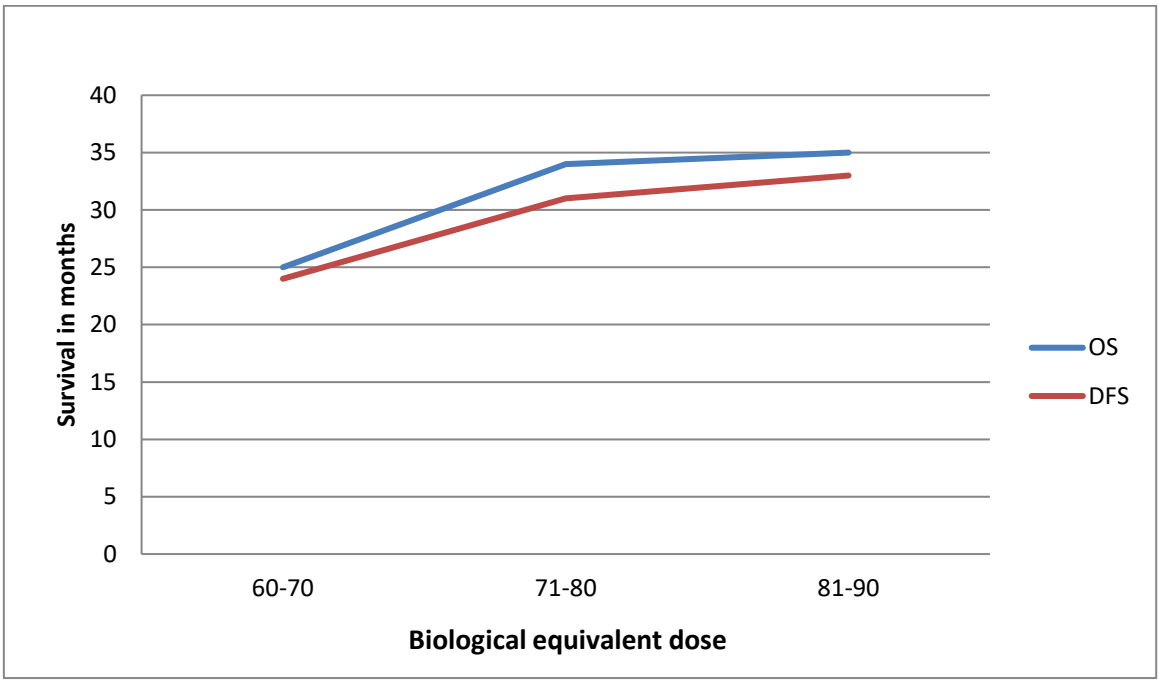
Graph 3: Kaplan-Meier graph showing overall survival in arm A and B



Graph 4: Kaplan-Meier graph showing disease free survival in arm A and B



Graph 5: Showing effect of increased BED on OS and DFS


40
35
30
25
20
15
10
5
0
Survival in months
60-70
71-80
81-90
Biological equivalent dose
OS
DFS