

Accelerated hypofractionated Whole Breast Irradiation with Concurrent TB Boost: Toxicity & cosmesisSara Hassan Shams El Din¹, Shaimaa Lasheen¹, Mohamed Hassan¹, Farouk Hagag¹, Rania Moussa²¹NEMROCK Center- Kaser Al-AINI- Faculty of Medicine- Cairo University, Department of Clinical Oncology, Cairo, Egypt.²NEMROCK Center- Kaser Al-AINI- Faculty of Medicine- Cairo University, Department Of Medical Physics, Cairo, Egypt.Sara.hassan.shams85@gmail.com

Abstract: Background: Conventional fractionated radiation therapy over 4-5 weeks with sequential boost is the standard of care for postoperative RT treatment for patients with early stage breast cancer who undergo breast conservative surgery (BCS). However, the use of an accelerated RT course can be used in departments with high patients flow to reduce waiting list and machine loads as well as to improve patient compliance. **Patients and Methods:** This is a prospective phase II study conducted at Kasr El-aini Center of Clinical Oncology and Nuclear Medicine (NEMROCK). Patients who underwent breast conservative surgery were recruited according to inclusion and exclusion criteria. Recruited patients were planned using 3D conformal technique to receive a hypofractionated radiation schedule using 40 Gy/2.67 Gy per fraction over 3 weeks to the whole breast with Concurrent boost 8.0 Gy/0.5 Gy per fraction over 3 weeks. All patients was evaluated for acute toxicity and cosmetic outcome. **Results:** During the period from June 2014 to January 2017, a total of 63 patients with a median age of 51 years were included. Regarding acute skin toxicity, only 20% of patients developed GII skin toxicity, while 68% of patients developed G0-I skin toxicity, none of the patients developed GIII or more skin toxicity. The overall cosmetic assessment was excellent in 80.95 % of patients and good in 19% of patients. **Conclusions:** Hypofractionated radiotherapy in three weeks to the whole breast with a concomitant boost in patients undergoing breast conserving surgery (BCS), allows acceptable outcomes in terms of acute toxicity and early cosmetic results and is a good approach for our department NEMROK due to the reduction of 15 days when compared to standard RT treatment of breast cancer. long- term follow up data are needed to assess late toxicity, cosmesis, and clinical outcomes.

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Key words: Altered fractionation - Concomitant boost - Breast conserving therapy - Tumor bed.

1. Introduction

Breast conserving surgery and post lumpectomy radiotherapy are standard alternatives to mastectomy for eligible patients with early stage breast cancer (1). Post lumpectomy radiotherapy has been shown to improve local control and breast cancer mortality in patients treated with breast-conserving surgery (BCS) for invasive breast cancer (2,3,4).

In the **Early Breast Cancer Trialists' Collaborative Group (EBCTCG)** meta-analysis of individual patient data for 10,801 women in 17 randomized trials of radiotherapy versus no radiotherapy after breast-conserving surgery, 8,337 with pathologically confirmed node-negative (pN0) or node-positive (pN+) disease, who received BCS, the EBCTCG showed that RT reduced five-year local recurrence rate (LRR) rates any first recurrence by approximately 50% and continued to show improved long-term survival (5).

Four prospective randomized clinical trials have shown promising results with hypofractionated schedules for WBI in each of these studies, the goal

was to deliver a hypofractionated dose schedule that is biologically equivalent to the standard fractionation breast dose of 50 Gy in 25 fractions of 2 Gy. With 5-10 year follow-up of these studies, there has been similarity in breast local control and cosmetic outcomes between the hypofractionated and standard fractionated arm. As a result, hypofractionated WBI have been adapted as a standard of care options for post operative RT to WBI (6,7,8,9,10).

The linear-quadratic concept is the most commonly used radiobiologic model to predict the differential response of the acute and the late reacting tissues to radiotherapy. The α/β ratio (the dose at which cell killing by the linear [α] and quadratic [β] components are equal) is an essential part of this concept and reflects the inherent radiation sensitivity of the relevant tissue. Acute reacting tissues, such as skin epidermis, develop a reaction to radiation within 1 to 3 weeks of treatment. They generally have a high α/β ratio (range, 10-30 or more). Although sensitive to the total dose of radiation, they are much less sensitive to the fraction size. In contrast, late reacting tissues,

such as soft-tissue and neurologic structures, do not show reactions to radiation until several years after treatment. They have a lower α/β ratio in the range of 1 to 5 and are much more sensitive to dose per fraction (11).

A pilot study was designed by Yarnold et al to test the sensitivity of breast tissue to modest increases in fraction size and to determine an estimate of the α/β ratio for late effects in the breast. Based on differences between the fractionation schedules in change to breast appearance and toxicity over time, α/β ratios were determined. The α/β for late change in breast appearance was 3.6 Gy (95% confidence interval [CI], 1.8-5.4) and the α/β ratio for breast induration was 3.1 Gy (95% CI, 1.8-4.4 Gy). A subsequent analysis estimated the α/β ratio for tumor recurrence to be 4 Gy (95% CI, 1.0-7.8 Gy) (12).

Proposed accelerated hypofractionated radiation schedule using 3D conformal technique appears preliminarily to be a feasible technique that has the advantage of shortening the treatment course and increasing the dose per fraction which results in the delivery of a potentially more effective biological dose to the breast and tumor bed without significantly increasing doses to risk organs.

2. Patients & Methods

This study was conducted at Kasr Al-Aini Center of Clinical Oncology & Nuclear Medicine (NEMROCK) during the period between June 2014 to January 2017. A total of 63 patients were recruited according to the inclusion & exclusion criteria.

Inclusion criteria included histologically proven diagnosis of breast adenocarcinoma, conservative breast surgery, negative surgical margins, pathological stage pT1-T3 pN0 according to the American Joint Committee-Union International Contrlele Cancer staging system (7th edition AJCC-TNM) and no evidence of distant metastases at diagnosis.

Exclusion criteria included positive resection margins, contraindication to breast conservative surgery e.g. locally advanced disease (T4, N3 breast cancer), metastatic disease, prior radiation to the thoracic region. pregnancy, and double primary disease.

Patient Positioning, Immobilization & CT Scanning: Patients were positioned with breast boards elevated at 10 degrees with both hands grasping the middle column. A treatment planning CT scan in the treatment position was required to define the clinical target volumes (CTV) and planning target volumes (PTV). Radio-opaque markers (guide-wire) were placed on external landmarks at the acquisition of the CT scan to facilitate contouring of target volumes. A CT scan image thickness of ≤ 0.5 cm was done.

External skin localizing marks i.e., permanent tattoos, were used for daily localization and set-up accuracy.

Targets volumes and Organs at Risk (OAR)
Contouring; Breast CTV was delineated following the consensus guidelines from **The RTOG Breast Cancer Atlas for Radiation Therapy Planning**. **Lumpectomy CTV** was identified by the wires localized over the lumpectomy scar and by the pre-operative mammography, also by the seroma in CT cuts, and by the surgical clips if present. Tumor cavity size & depth from the skin was known through the pathological report of surgery. In general, the pectoralis and/or serratus anterior muscles were excluded from the lumpectomy CTV unless indicated by the patient's pathological report. **Lumpectomy PTV** was generated by adding 5mm 3D symmetrical expansion around the lumpectomy CTV. **Contouring Of Organs at Risk (OAR); Ipsilateral lung** was contoured using auto-segmentation with manual verification. **Contralateral lung** was contoured using auto-segmentation with manual verification. **Heart** was contoured on all cases- not just left sided breast cancer cases. The heart was contoured beginning just inferior to the level in which the pulmonary trunk branches into the left and right pulmonary arteries (PA). The heart was contoured on every contiguous slice thereafter to its inferior most extent near the diaphragm and the pericardium was excluded. **Contralateral breast** was contoured to include the apparent CT glandular breast tissue visualized by CT including the overlying skin and excluding the pectoralis muscles, serratus anterior muscles, ribs, bony thorax and lung/heart.

Radiobiological equivalent dose was calculated according to the linear quadratic model (11).

Treatment Planning; Doses coverage of the target volumes and dosimetric constraine regarding (OAR) were compatible per our hypofractionated protocol.

Plan acceptance was done by reviewing whole breast plan and boost plan separately, then a plan summation was evaluated. Finally, the isocenter and the dose normalization point for the breast and the boost plan were identical (when possible). Beam-eye view was revised for each plan to ensure proper coverage of the CTV with maximum sparing of the risk organs. Isodose lines on axial CT cuts were revised to evaluate dose homogeneity and adequate CTV coverage.

Simulation to localize treatment portals isocenter on each patient's skin using its definition in relation to the C.T reference point from the treatment planning system data, by means of distances in X,Y & Z directions. The isocenter of the treatment portal was verified by comparing simulator images with the

corresponding DRRs obtained from planning computed tomography (CT) scan.

Treatment Verification: by Electronic portal image (EPI) of the set up and for the tangential fields were taken before the first treatment session and were matched with digitally reconstructed radiographs (DRRs) obtained from planning computed tomography (CT) scan. Differences of 0-4.9 mm were considered acceptable while ≥ 5 mm. were not accepted. & in that case patients were re-simulated. Plan verification with Electronic portal imaging device (EPID) was done once weekly to verify setup reproducibility.

Follow-up and Cosmetic Evaluation for all patients were evaluated on a weekly basis during the whole treatment course to assess acute toxicity. Late toxicity was scored starting from 6 months after the

end of the treatment course. The maximal detected toxicity was scored according to **The RTOG/EORTC Common Terminology Criteria for Radiation Morbidity Scoring Schema, version 3.0** (14).

Ethical considerations:

The research protocol was presented and accepted by the research ethics committee and the scientific research committee of the department of clinical oncology, Faculty of Medicine, Cairo University.

Statistical analysis:

All data were evaluated statistically by the statistical package for the social sciences (SPSS) version 16.

3. Result

Table 1: Clinical features of patients:

Age (years):	
-median	51
-mean+/-SD	50.85% +/-8.98
-range	(22-65 years)
Menopausal status:	
-pre-menopausal	32 (50.79%)
-post-menopausal	31 (49.21%)
Side:	
-right	29 (46.03%)
-left	34 (53.97%)
Site:	
-UOQ	30 (47.62%)
-UIQ	19 (30.16%)
-LOQ	6 (9.52%)
-LIQ	4(6.35%)
Retroareolar	4(6.35%)
Family history:	
- Negative	49 (77.78%)
- Positive	14 (22.22%)
EF%:	
-mean+/-SD	63% +/- .055
- range	53-77

(**UOQ:** Upper outer quadrant, **UIQ:** Upper inner quadrant, **LOQ:** lower outer quadrant, **LIQ:** lower inner quadrant), **EF:** Ejection fraction.

Patients Characteristics:

A. Clinical features:

Including median age was 51, menopausal status, side and site of disease, family history, EF%. These data are shown in **Table 1**.

B. Pathological features:

Including the pathological type, grade, T stage of the tumor, ER, PR and Her-2-neu status, KI 67, biological subtypes as shown in **Table 2**.

C. Adjuvant systemic therapy:

For the current study (65.08%) of the patients received adjuvant chemotherapy while (34.92%) of the patients didn't received adjuvant chemotherapy as shown in **Figure (1)**, and as regard the adjuvant

hormonal therapy (82.54%) of the patients received adjuvant hormonal therapy as shown in **Figure (2)**

D. Baseline body measures:

For the current study Mean +/-SD for **tangential separation (cm)** was 16.12+/-2.5. Other body measurements eg breast volume and width, boost volume are shown in **Table 3**.

Toxicity Result

All patients were evaluated on a weekly basis during the whole treatment course to assess acute toxicity. Late toxicity was scored starting from 6 months after the end of the treatment course. The maximal detected toxicity was scored according to **The Common Terminology Criteria for Adverse**

Events, version 3.0, using the RTOG/EORTC toxicity.

In our study; (68.25%) of the patients had G1 acute skin toxicity, (20.63%) of the patients had G2 acute skin toxicity, and no patients had G3 nor G4 acute skin toxicity as shown in **Figure (3)**. There were no reported acute cardiac nor pulmonary toxicity.

As regard late skin toxicity (71.43%) of the patients had G0 late skin toxicity, and (28.57%) of the patients had G1 late skin toxicity no patients had G3 nor G4 late skin toxicity as shown in **Figure (4)**. There were no reported cardiac nor pulmonary late toxicity, however longer follow up is needed to evaluate late toxicity.

Cosmetic result:

Patient reported cosmetic scores according to Harverd criteria as following: Excellent cosmesis:

defined as designating little or no change, it was reported by 51 (80.95%) of the patients. Good cosmesis: defined as minimal but noticeable change was reported by 12 (19.05%) patients as shown in **Figure (5)**.

Similarly, physician reported cosmetic scores according to objective score as following excellent cosmesis was noted in (80.95%) of the patients, good cosmesis was noted in (19.05%) patients as shown in **Figure (6)**.

Clinical results: Local control and disease free survival:

In our study, A total of 63 patients were recruited and followed for a median period of 24 months ranged from 18 to 32 months. No local recurrences or distant metastasis were reported during the follow up period.

Table2: Pathological features of the tumor:

Pathological types:	
IDC	54 (85.71%)
ILC	4 (6.35%)
Medullary carcinoma	3 (4.76)
Mixed IDC/ILC	2 (4.76)
Tumor grade:	
G1	2 (3.17%)
G2	56 (88.89%)
G3	5 (7.94%)
T stage:	
T1	24 (38.10%)
T2	37 (58.73%)
T3	2 (3.17%)
Maximum diameter:	
Median	2.6
Mean+/-SD	2.27+/-1.11
Range	0.8-6 cm
Surgical management of axillary LNs:	
-ALND:	59 (94%)
Median	17
Mean+/-SD	2.7+/-1.1
Range	8-31
-SLNB	4 (6%)
ER status:	
ER positive	51(80.95%)
ER negative	12 (19.05%)
PR status:	
PR positive	51 (80.95%)
PR negative	12(19.05%)
Her2neu amplification:	
Negative	52 (82.54%)
Positive	11 (17.46%)
KI 67:	
Low i.e. ≤ 14	35 (55.56%)
High i.e. > 14	28 (44.44%)

(ALD) axillary lymph node dissection – (SLNB) sentinel lymph node biopsy- IDC: Invasive duct carcinoma, ILC: Invasive lobular carcinoma, ER: Estrogen receptor, PR: Progesterone receptor.

Table 3: Body measures of patients:

Parameter	Value
Tangential separation (cm): -Mean +/-SD -Range	16.12+/-2.5 11-24.5
Breast width (cm): -Mean +/-SD -Range	5.3+/-2.0 2-13
Breast volume (cm³): -Mean +/-SD -Range	929+/-471 268-2673
Boost volume (cm³): -Mean +/-SD -Range	42.2+/-23.6 3.5-122
CLB volume (cm³): -mean +/-SD -Range	1004.7+/-367.7 330-1895
Heart volume (cm³): -mean +/-SD -Range	588.9 +/-144.6 385-1152
Ipsilateral lung volume (cm³): -mean +/-SD -Range	1217.2+/-242.3 832-2000

CLB: Contra-lateral breast, SD: Standard deviation.

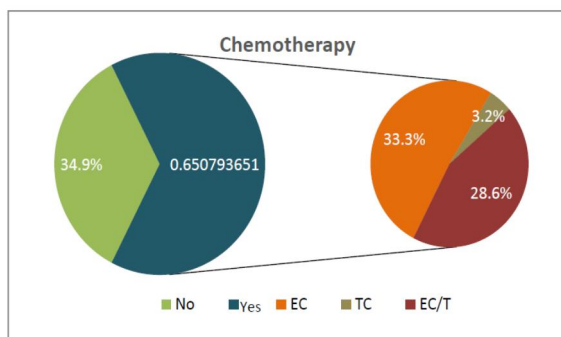


Figure (1): Shows that (65.01%) of the patients received adjuvant chemotherapy therapy and (34.92%) of the patients didn't receive adjuvant chemotherapy.

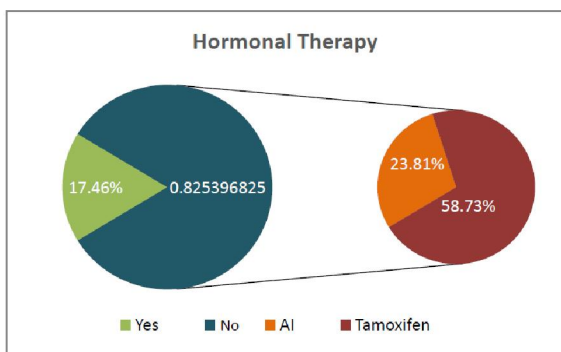


Figure (2): shows that (82.54%) of the patients received adjuvant hormonal therapy and (17.94%) of the patients didn't receive adjuvant hormonal therapy.

Rtog acute skin toxicity

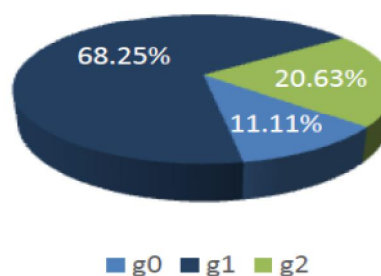


Figure (3): shows that (68.25%) of the patients had G1 acute skin toxicity, (20.63%) of the patients had G2 acute skin toxicity.

Rtoge late skin toxicity

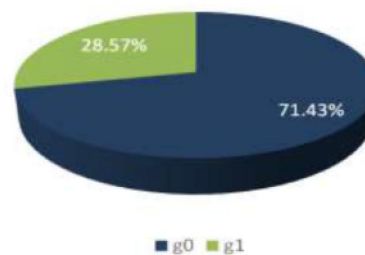


Figure (4): shows that (28.57%) of the patients had G1 late skin toxicity no patients had G3 nor G4 late skin toxicity.

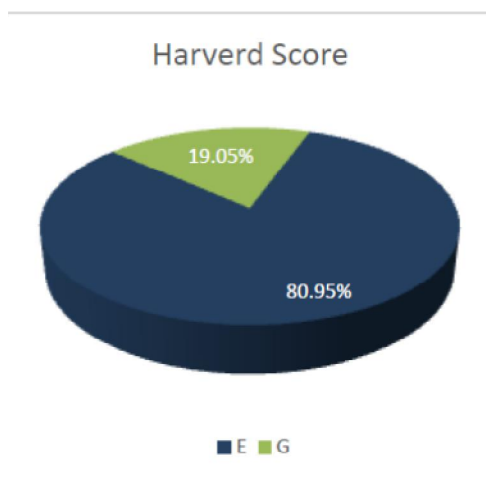


Figure (5): Shows excellent cosmesis in (80.95%) of patients and good cosmesis in (19.05%) of patients.

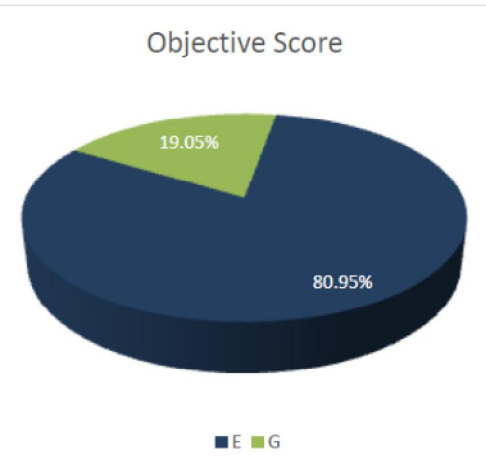


Figure (6): Shows excellent cosmesis in (80.95%) of patients and good cosmesis in (19.05%) of patients.

4. Discussion

In our department around sixty breast cancer patients receive postoperative radiation monthly, there are many potential benefits in delivering postoperative radiotherapy in a shorter period of time. The advantages include greater convenience for patients and therefore higher compliance, broad applicability to nearly all patients following lumpectomy, decreased treatment costs, and increased utilization of existing RT resources. Therefore, between July 2010 and December 2012 a study of conventional fractionation with concomitant boost versus sequential boost in breast conservative therapy for early stage breast cancer was conducted in our department to shorten the radiotherapy course from six weeks to five weeks.

Then, between June 2014 to January 2017, we conducted this study to evaluate a hypofractionated

radiation schedule using 40 Gy/2.67 Gy per fraction over 3 weeks to the whole breast with Concurrent boost 8.0 Gy/0.5 Gy per fraction over 3 weeks. The results of 63 patients were reported at a median follow-up period of 24 months ranged from 18 to 32 months.

Regarding, the clinical features; the median age was 51 years also about 50.78% of our patients were premenopausal. This is in contrast to international figures e.g. the SEER data document the median age at diagnosis for cancer of the breast to be 61 years of age. One explanation for this difference comes from Egyptian data of breast cancer epidemiology, where the data of the Gharbia cancer registry identified 3673 breast cancer patients having a median age of 50.1, while NCI of Egypt point to a median age of 46 years at presentation (15,16,17). Data from NEMROCK registry in the last ten years confirm a younger age of breast cancer patients at presentation, with median age 49 years.

Regarding the pathological features; in this study more than 85% of the tumours were IDC which is not far from the SEER data reporting IDC in 80%-90% of the breast cancer. And more than 83% of the patients had hormone receptor positive breast cancer, which is not far from the SEER reporting hormone-receptor positive breast cancer to represent approximately 75% of invasive breast cancers. As for Her-2-neu expression, about 17.49 % of the patients had over-expression of Her-2-neu by IHC, these figures are consistent with international figures, e.g. in the U.S. HER2 gene amplification was reported to be present in 15%-30% of invasive breast cancers. As for TNBC, about 9.52% of the patients were TNBC these is consistent with data reported that TNBC represents 10%-20% of invasive breast cancers (18,19,20).

The acute toxicity profile of our schedule was generally tolerable. The maximum acute skin toxicity by the end of treatment was grade 1 in 43 patients (68.25%), and grade 2 in 13 patients (20.63%). There was no grade 3 or higher skin toxicity. Late skin toxicity was grade 1 in (28.57%) of the patient. There were no late grade 2 or higher toxicity. Our data are not far different from those reported by **Valero Albarrán et al.**; where out of the 50 patients in their trial acute toxicity was confined to the skin and Grade 0-1 skin toxicity was present in 66% of patients. Grade 2 skin toxicity was reported in 28% of patients. No grade >3 skin toxicity was observed. The study conducted by **Chadha, et al**; the results of 105 patients were reported at a median follow-up of 24 months. There was no acute grade 3 or 4 toxicity There were no reported late toxicities. As for acute and late heart and lung toxicities, none were reported; however longer follow up is needed to further evaluate late toxicities among our patients.

In our study; post-treatment patient-reported and physician-reported cosmetic scores were excellent cosmesis in (80.95 %) of patients and good cosmesis in (19.05%) of patients. This data was not far different from those reported by the cited studies as by **Valero Albarrán et al.**; Cosmetic assessment was good-excellent in the 100% of patients, and also by **Chadha, et al**; there was no significant negative effect reported on cosmesis (21,22).

Regarding the use of accelerated hypofractionation in young patients 13% of our patient population were under 40 years, in these patients we didn't notice any increase in toxicities nor deterioration in the cosmetic outcome. In the **Canadian study** that delivered RT dose to the WB 42.5 Gy / 16 fraction, among the 25% of women who were under 50 years of age, the hypofractionated treatment was as efficacious as conventional fractionation. The **START-B** delivered hypofractionated radiotherapy (40 Gy in 15 fractions) for both breast conserving surgery and mastectomy regardless of age at diagnoses (6,7,8,9,10).

Regarding the use of accelerated hypofractionation in large breast volume we defined large breast as breast volume >1500 cm³ calculated at CT planning, as it couldn't be defined by cup size (our patients could not report it). In our study, 10% of patient population had large breast volume and we didn't notice any deterioration regarding toxicity nor cosmetic outcome in those patients. This is compatible with data reported by the group of **Corbin et al** who compared the acute toxicity observed in 93 large breasted women with early stage disease treated with hypofractionated whole breast radiotherapy (42.56 Gy in 16 fractions of 2.66 Gy or conventionally whole breast fractionated radiotherapy. No differences were observed in acute toxicity related to fraction size (23).

Conclusion and Recommendation

Radiotherapy, when indicated, is typically given after surgery and chemotherapy and usually represents the final component of a physically and emotionally demanding period of multimodality treatment that can stretch over a period of up to half a year or longer.

1. The accelerated hypofractionated with concomitant boost radiation technique is proposed for standard use in breast-conserving RT, because such short course of radiation therapy has obvious advantages in terms of patient convenience and cost.

2. Longer follow-up is needed to assess the impact of accelerated hypofractionated radiation therapy on local recurrence and disease free survival in early breast cancer.

3. Larger well-planned prospective randomized trials are needed to validate the optimal fractionation schedule and technique to be used.

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