BRE008-12

Phase II Study of Postoperative, Cardiac-Sparing Proton Radiotherapy for Patients with Stage II/III, Loco-Regional, Non-Metastatic Breast Cancer Requiring Whole Breast or Chest Wall Irradiation with Lymph Node Irradiation

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PROTOCOL SIGNATURE PAGE

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Protocol Version March 31, 2014

I certify that I have read the protocol. I agree to conduct the protocol according to ethical principles stated in the Declaration of Helsinki, the applicable guidelines for good clinical practice, or the applicable laws and regulations, whichever provides the greatest protection of the individual. I will accept the monitor's oversight of the study.

_____ _____

Signature of the Site Principal Investigator Date

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Principal Investigator's Printed Name

_____

Name of Facility

_____

Location of Facility (City, State)

PLEASE COMPLETE AND SEND TO THE PROTON COLLABORATIVE GROUP OFFICE VIA EMAIL: HQ@PCGRESEARCH.ORG

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BRE008-12 Phase II Study of Postoperative, Cardiac-Sparing Proton Radiotherapy for Patients with Stage II/III, Loco-Regional, Non-Metastatic Breast Cancer Requiring Whole Breast or Chest Wall Irradiation with Lymph Node Irradiation

SCHEMA

R E G I S T E R	**PROTON RADIOTHERAPY** BREAST CONSERVING THERAPY: Whole breast and regional lymph nodes (axilla levels I-III, supraclavicular*): 45 - 50.4 Gy (RBE) in 25 - 28 fractions of 1.8 Gy (RBE) per fraction and Internal mammary node chain (IMC) for stage III patients*: 45 - 50.4 Gy (RBE) in 25 - 28 fractions of 1.8 Gy (RBE). + Lumpectomy tumor bed boost to a total cumulative dose of 61.2 - 66.6 Gy (RBE) in 1.8 Gy (RBE) per fraction In case of inclusion of internal mammary node chain (IMC), boost as follows: a) Clinically negative IMC: no boost beyond 45-50.4 Gy (RBE) b) Clinically positive IMC nodes with response to chemotherapy: boost to a total cumulative dose of 54 - 55.8 Gy (RBE) in 1.8 Gy (RBE) per fraction. c) Clinically positive IMC nodes with persisting positivity post-chemotherapy: boost to a total cumulative dose of 61.2 - 66.6 Gy (RBE) in 1.8 Gy (RBE) per fraction. MASTECTOMY: Chest wall and regional lymph nodes (axilla levels I-III, supraclavicular*): 45 -50.4 Gy (RBE) in 25 - 28 fractions of 1.8 Gy (RBE). and Internal mammary node chain (IMC), for stage III patients*: 45 - 50.4 Gy (RBE) in 25 - 28 fractions of 1.8 Gy (RBE). + Chest wall scar boost (optional): for a total cumulative dose of 61.2 Gy (RBE) in 1.8 Gy (RBE) per fraction. In case of inclusion of internal mammary node chain (IMC), boost as follows: a) Clinically negative IMC: no boost beyond 45 - 50.4 Gy (RBE) b) Clinically positive IMC nodes with response to chemotherapy: boost to a total cumulative dose of 54 - 55.8 Gy (RBE) in 1.8 Gy (RBE) per fraction. c) Clinically positive IMC nodes with persisting positivity post-chemotherapy: boost to a total cumulative dose of 61.2 - 66.6 Gy (RBE) in 1.8 Gy (RBE) per fraction REGIONAL LYMPH NODE MINIMUM DOSE REQUIREMENTS: Any undissected lymph node region (axilla, infraclavicular, supraclavicular and/or IMC node) – whether post-lumpectomy or post-mastectomy, should receive a minimum dose within the following ranges: a) 45.0 - 50.4 Gy (RBE) when clinical negative. b) 54.0 - 55.8 Gy (RBE) in clinically positive but responsive to chemotherapy c) 61.2 - 66.6 Gy (RBE) for persistently positive lymph node disease These are levels are meant to determine the minimum doses. The option to deliver a higher dose beyond these minimum ranges will be left to the discretion of the treating investigator as long as: 1) The total dose prescribed never exceeds 66.6 Gy (RBE) without individual case discussion with the study chair 2) Any organ at risk maximum dose constraint such as maximum dose to brachial plexus of 66 Gy (RBE) must be respected.

Required Sample Size: N/A

1.0 INTRODUCTION

Proton radiotherapy (PT) with its physical characteristics of improved dose distribution in tumor and reduced radiation dose to surrounding normal tissues has been successfully used worldwide for several decades. It is now an accepted treatment modality for tumors in difficult to treat locations, i.e. the skull base or along the spinal axis, as well as in pediatric patients, where minimizing normal tissue radiation exposure is of paramount importance. As PT is established for certain diseases, the next phase is to determine its role in more common malignancies. The Proton Collaborative Group is actively involved in clinical particle therapy and one main focus of clinical research is to determine the feasibility and the potential role of PT in the adjuvant radiotherapy of locoregionally advanced breast cancer. The proposed Phase II study is seeking to build clinical data as a continuation of the original dosimetric analysis published by Ares et al.[1] performed at Paul-Scherrer Institute (PSI). That comparison demonstrated a benefit form proton planning for patients with non-metastatic breast cancer requiring complex, loco-regional, postoperative radiotherapy.[1] The advantages of PT were improved target coverage compared to standard photon irradiation and reduced dose to heart, lungs and contralateral breast.

The study goal is to demonstrate a "meaningful benefit" of proton therapy for women with loco-regionally advanced breast cancer. The main clinical endpoints of this trial are the reduction of cardiac morbidity and mortality (coronary artery disease, myocardial infarction, cardiac insufficiency) and the reduction of contralateral, second breast cancer. Both adverse events are presently associated with external beam photon therapy. Both goals require longitudinal follow-up of minimum 5-10 years. Despite the logistical challenges of long term follow-up, the effort is needed in view of the compelling preclinical evidence of dose avoidance or even absence of radiation dose to heart and contralateral breast uniquely accomplishable by protons only.

Although conventional photon radiation therapy has been used successfully and in general safely for decades for the postoperative treatment of breast cancer, recent long-term outcomes data have raised concerns about a small, yet significant, increase in mortality from long-term cardiac toxicity, clinically relevant pulmonary disease and function loss, as well as an increased incidence of contralateral breast cancer and other secondary malignancies.

The present project aims at translating the outcomes of the previous preclinical treatment planning study into clinical practice by studying the technical feasibility and safety of postoperative adjuvant chest wall, breast, and regional lymph node PT. The study will target patients with breast cancer undergoing postoperative external beam radiotherapy to whole breast or chest who require irradiation to draining lymph nodes. The indication for proton therapy will be based on the standards of care and on the appropriateness of indication. The profile of indications will not be changed, merely photons will be replace by protons. The value of proton therapy will be multifactorial. For women who seek proton therapy despite the ability of photon plans to generate treatment plans without inclusion of the heart, the benefit of proton will be in the likelihood of reduced risk for induction of second malignancy by decreased irradiation to non-target and/or "unspecified" normal tissues in general, i.e. exposing fewer normal cells to potential DNA changes due to ionizing irradiation. Patients with left-sided Stage III breast cancer requiring loco-regional irradiation represent the patient subgroup at highest risk for developing late complication, i.e. women with breast cancer requiring complex loco-regional irradiation of primary site and draining lymphatics. This high-risk subgroup also includes women with lower stage disease (stage II), in whom conventional radiotherapy plans would result in significant radiation dose to the heart, for example patients with anatomic variations that place the heart close to the chest wall. To qualify for the trial, women must have undergone mastectomy or lumpectomy.

1.1 Clinical Background

Several meta-analyses have established that breast cancer (BCa) mortality can be reduced by loco or loco-regional radiotherapy (RT) in the treatment of both early and locally-advanced BCa. Trial overviews indicate that for every four local failures prevented, one fewer death from BCa can be expected. [2] However, a small, but identifiable excess of morbidity and mortality due to treatment related cardiovascular toxicity has been observed.[3,4,5, 6]Approximately 1% additional deaths due to causes other than BCa were observed in patients having received loco-regional RT. This excess mortality was mainly due to cardiac-vascular causes, and to a lesser extent to secondary malignancies. The overview from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [3] indicates that adjuvant RT after breast-conserving surgery results in statistically significant reductions in the 5-year risk of local recurrence (26% versus 7%), the 15-year breast cancer mortality risk (5.4% reduction), and overall mortality (5.3% reduction). The benefits of RT are similar for those patients treated after mastectomy, with reductions in local recurrence, breast cancer mortality, and overall mortality. Although the overview clearly shows the benefit of radiation, it also has confirmed the toxicities. Patients who were treated with radiation had increased risk of contralateral breast cancer, lung cancer, and mortality from cardiac disease (rate ratio = 1.27, $p<0.001$). There was, at least with some of the older radiotherapy regimens, a significant excess incidence of contralateral breast cancer (rate ratio 1.18, SE 0.06, 2p=0.002) and a significant excess of non-breast-cancer mortality in irradiated women (rate ratio 1.12, SE 0.04, 2p=0.001). Both late effects occurred during the first 5 years, but continued after year 15. The excess mortality was mainly from heart disease (rate ratio 1.27, SE 0.07, 2p=0.0001) and lung cancer (rate ratio 1.78, SE 0.22, 2p=0.0004).

A major deficit of the present literature is the de facto lack of incidence numbers and incidence rates of clinically symptomatic coronary artery disease (CAD) or cardiac disease in patients treated for Stage III breast cancer following radiotherapy. Large cohort studies only captured "mortality" as endpoint but not "morbidity". It is obvious, that the morbidity rate for CAD will be much higher than actual death from CAD. In addition, there are almost no data on larger patient cohorts regarding the patient population at highest risk of developing CAD, which is the population receiving highest dose of RT to heart and coronaries as is the case with the patient cohort of this study. By and large, RT for early stage breast cancer with its routine use of tangential fields will deliver less irradiation to the heart compared to the complex field arrangements required to cover the IMC lymph nodes appropriately.

The research group at University of Pennsylvania performed detailed reviews of the medical records of 961 stage I-II breast cancer patients treated from 1977 to 1995 at the University of Pennsylvania. All patients underwent conventional tangential beam radiation treatment (RT) using 6 MV to 15 MV photons, followed by a boost to the tumor bed to a median total tumor bed dose of 64Gy (range, 59.75 to 71.60 Gy).
Correa at al. reported that screening for cardiac stress tests and catheterizations performed after RT revealed 82 patients. [7] At diagnosis, patients with left-sided and right-sided breast cancer had the same estimated 10-year risk (both 7%) of developing coronary artery disease. At a median time of 12 years post-RT (range, 2 to 24 years), 46 patients with left sided and 36 patients with right-sided breast cancer had undergone cardiac stress testing. A statistically significant higher prevalence of stress test abnormalities was found among left (27 of 46; 59%) versus right-side irradiated patients (three of 36; 8%; *P* _ .001). Furthermore, 19 of 27 of left-sided abnormalities (70%) were in the left anterior descending artery territory. Thirteen left-side irradiated patients also

underwent cardiac catheterization revealing 12 of 13 with coronary stenosis (92%) and eight of 13 with coronary stenosis (62%) solely in the left anterior descending artery.

Harris EE et al.[8] analyzing the identical patient cohort at Univ. Pennsylvania (961 stage I-II breast cancer patients treated from 1977 to 1995) reported on the incidence of late cardiac morbidity and mortality. At a median follow-up time of 12 years (range, 2-27 years) there was no difference in overall mortality from any cardiac cause. Death from any cardiac cause occurred in 2% of right-sided patients and 3.5% of left-sided patients. However, in the second decade after treatment, there was a higher rate of cardiac deaths in left-sided patients, with a cumulative risk of 6.4% (95% CI, 3.5% to 11.5%) for left-sided compared with 3.6% (95% CI, 1.8% to 7.2%) for right sided patients at 20 years. There were statistically higher rates of chest pain, coronary artery disease, and myocardial infarction diagnosed in left-sided patients.

There was no significant difference between right- and left-sided breast cancer patients in the development of CHF, palpitations, any arrhythmia, atrial fibrillation, any valvular disorder, or mitral valve prolapsed. However, there were significant differences in the development of chest pain, and in any diagnosis of coronary artery disease and MI, all of which were more likely to occur in left-sided patients. The 20-year actuarial freedom from coronary artery disease was 90% in right-sided patients and 75% in left-sided patients (*P* _ .001). The 20-year actuarial freedom from MI was95%in right-sided patient and 85% in left-sided patients (*P*_.002).

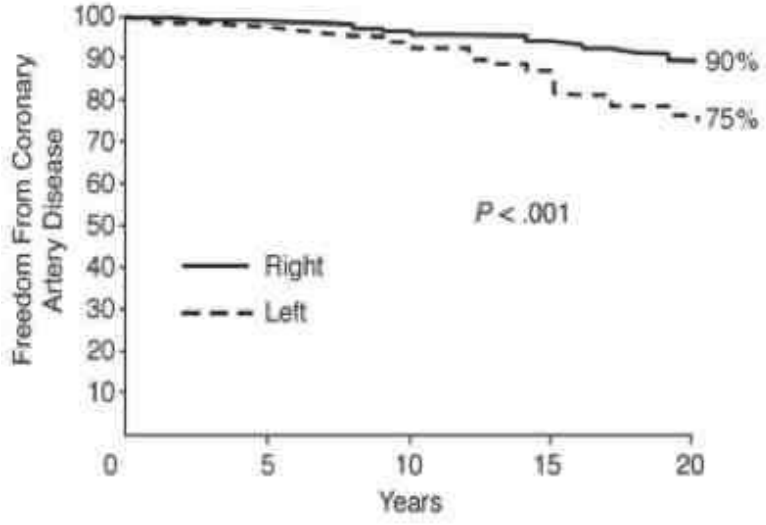


Fig.:1
Freedom from coronary artery disease in 961 Stage I-II breast cancer patients following conventional radiotherapy of breast and lymph nodes. Median follow-up time 12 years. A significantly higher rate of fatal and nonfatal diagnoses of coronary artery disease was seen in left-sided patients compared with right-sided patients using Kaplan-Meier analysis. From: Harris EE, Late Cardiac Mortality and Morbidity in Early-Stage Breast Cancer Patients after Breast-Conservation Treatment, *J Clin Oncol 24:4100-410, 2006.*

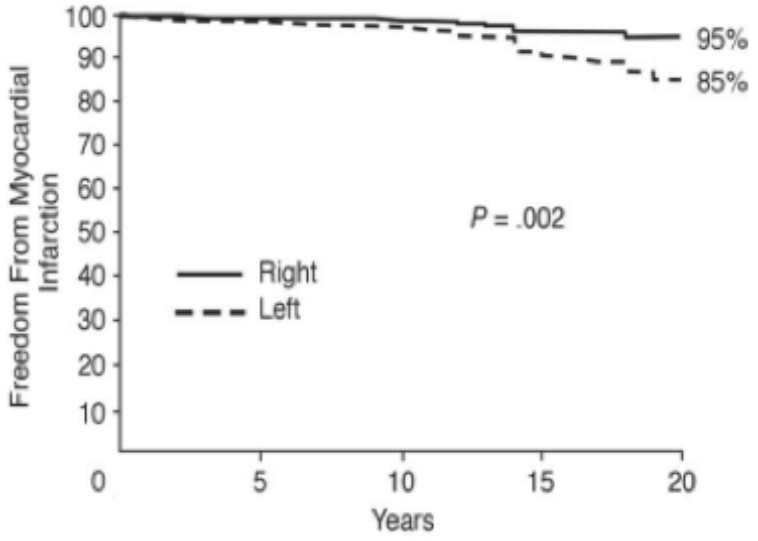


Fig.:2
Freedom from myocardial infarction in 961 Stage I-II breast cancer patients following conventional radiotherapy of breast and lymph nodes. Median follow-up time 12 years. A significantly higher rate of any diagnosis of myocardial infarction, fatal or nonfatal, was seen in left-sided compared with right-sided patients; however, deaths as a result of myocardial infarction were not significantly different between the two groups. From: Harris EE, Late Cardiac Mortality and Morbidity in Early-Stage Breast Cancer Patients After Breast-Conservation Treatment, *J Clin Oncol 24:4100-410, 2006.*

Internal mammary node (IMN) fields were used in 14% (n_68) of left-sided patients and 11% (n_54) of right-sided patients. The impact on morbidity of the use of IMN fields was examined. Coronary artery disease was significantly associated with the use of IMN fields: 7% without IMN compared with 18% with IMN (*P* _ .001). MIs were significantly more common after the use of an IMN field: 3% without IMN versus 9% with IMN (*P*_.01).

When the risk of cardiac morbidity was adjusted for baseline risk factors, hypertension demonstrated an interaction effect with laterality in patients who developed coronary artery disease. The hazard ratio (HR) for developing coronary artery disease was elevated for all patients with hypertension, and the highest HR was seen in left-sided patients with hypertension [11.4 (95% CI, 5.0 to 26.2)]. Overall, the presence of hypertension was associated with a higher risk of coronary artery disease in left-sided patients.

In summary, the data from Univ. of Pennsylvania established the evidence that there is a correlation of radiotherapy of the heart with increasing risk of developing pre-clinical coronary artery stenosis and clinically symptomatic coronary artery disease and ultimately myocardial infarction. It also established the influence of confounding risk factors. It can only be assumed that this risk is higher for our patient population of more advanced disease stage.
Radiation pneumonitis (RP) has been associated with increasing volume of irradiated lung and chemotherapy use. In a series from the Joint Center of Radiotherapy, RP was observed in 1.4% of patients treated with nodal RT.[9] Estimates for RP vary by RT technique, which largely reflects differences in the volume of irradiated lung.[10] Following careful RT treatment planning, subjective assessments from the Danish Breast Cancer Cooperative Group (DBCCG) 82b and 82c did not show an increase in the rates of

dyspnea and cough following RT compared with controls (level II evidence). [11] The risk of asymptomatic pulmonary fibrosis, as measured by serial chest radiographs, was, however, increased.

These findings indicate the potential clinical importance of dose sparing to organs at risk (OARs) in the treatment of BCa. Considering the high incidence of BCa and the high prospect of cure, any improvement in therapeutic treatment delivery resulting in reduction of late complications has to be considered worthwhile. Relative risks for late adverse events may well be higher for specifically defined subgroups of patients (see below) as our pre-clinical treatment comparison study between photon and proton RT has demonstrated.

The incidence of RT related toxicity can be reduced by refinements in radiation technique. Optimization of BCa radiotherapy can be categorized in three aspects: improvement of dose homogeneity within the target volume, maximum reduction of cardiopulmonary dose, and minimizing risks of second malignancy induction.

Introduction of three-dimensional, conformal RT (3D-CRT) using conventional megavoltage photon RT as postoperative local irradiation limited to the breast, following breast conserving surgery (BCS), or to the chest wall, after modified radical mastectomy (MRM) has significantly improved the precision of dose delivery and is routinely used with relatively low risks for late toxicity [12]. However, when loco-regional treatment requires extensive inclusion of lymph-node areas radiation doses to heart, lungs and contralateral breast can remain significant.

IMRT has been implemented in the clinic[13,14,15] for selected patients and more complex scenarios. In practice, IMRT in breast cancer uses multiple fields from various entrance angles and computer-determined multi-leaf subfields as a three dimensional dose compensator to improve target homogeneity. Although IMRT can indeed increase the intended dose delivery to the target, it unavoidably results in an increased volume of irradiated normal tissues. Similarly, Tomotherapy is an expansion of the IMRT approach by utilizing an arch-system of fields. This results in further improvements of high-dose conformality and dose target homogeneity. The consequence is a further enlargement of the irradiated normal tissue volume.

The incidence of metastatic internal mammary chain (IMC) node involvement ranges from 10% in axillary node-negative patients to 50% in patients with axillary node invasion.[16] Despite this incidence the need to irradiate this region remains controversial. Several reports indicate that nodal irradiation in selected patients not only reduces the risk of loco-regional recurrences but also the number of distant metastases and ultimately increases survival rates. [17,18,19] However, some reports have even indicated a detrimental effect on long term survival attributable to late RT related toxicity.[20] The EORTC (22922/10925) conducted a study comparing tangential field radiotherapy of the breast alone versus tangential field radiotherapy of the breast with additional inclusion of the IMC and medial supraclavicular (MSC) nodes using 3D-planning. This study has been completed and results are pending.

Although many radiation oncologists do not routinely include the IMC's unless they are overtly involved, the rationale is based primarily on avoidance of additional normal tissue damage by not extending the target volumes further medially (which would be required in order to include IMC's). Few practitioners in the field would argue against inclusion of

IMC's if this could be accomplished without added normal tissue dose. It is exactly for this very reason that we will conduct this pilot study emphasizing inclusion of IMC's in Stage III disease, i.e. to demonstrate that proton therapy will permit routine inclusion of IMC's "with impunity".

1.1.1 The influence of unusual thoracic anatomy on normal tissue dose distribution:

It is well known that certain anatomic abnormalities of the thoracic contour, chest wall, and position of internal organs can lead to an overall unfavorable dosimetry by use of external beam photon radiation therapy. Unusual, abnormal chest wall contours essentially lead to increased inclusion of thoracic organs (lung, heart) in the irradiated volume by use of photon RT. In analogy, if internal thoracic organs are positioned abnormally close to the anterior chest wall the same effects will lead to an unfavorable dose distribution. An unusual chest wall contour or an unusual position of internal organs may occur either as congenital abnormality or secondary due to posttraumatic scar formation, cachexia, or due to thoracic wall deformity following long-standing COPD.

The scenario is best exemplified using the most common abnormality of a chest contour, called "pectus excavatum" -the Latin term meaning "hollowed chest". It is the most common congenital deformity of the anterior wall of the chest in which several ribs and the sternum grow abnormally. This produces a caved-in or sunken appearance of the chest. This is also referred to as "sunken chest" or "funnel chest". The dent in the sternum of the chest results in general in an increased dose to anterior lung tissue and -in case of left sided breast cancer – of heart in an attempt to include the most medial portion of breast tissue or internal mammary lymph nodes in the classic approach of opposing tangential fields. The classic tangential field approach typically also results in an increased dose to the contralateral breast. [21] Several methods to potentially improve this suboptimal situation have been published, including change of patient positioning, but mostly by use of intensity modulated radiotherapy (IMRT). [22,23,19] IMRT was found feasible in treating breast cancer patients with pectus excavatum, and decreased the ipsilateral lung volume receiving high dose radiation. However, it was noted that this came at the expense of an increasing volume of surrounding normal tissues, receiving low dose irradiation. The potential advantages of helical tomotherapy (HT) in treatment planning and delivery has been compared with conformal as well as intensity modulated photon therapy modalities. [24] The report by Uhl, M et al. was the first to evaluate the potential benefit of tomotherapy comparing to three-dimensional conformal radiotherapy in a group of 10 patients with pectus excavatum; there was improved uniformity and conformity with reduction of high dose to organs at risk however, with significantly larger volume of low dose to the lungs and contralateral breast. Thus, comparison plans between helical tomotherapy and protons will also be performed.[25,26,27]

The preclinical treatment planning comparison by Ares et al.[1] has demonstrated the benefits of proton therapy over conventional photon irradiation in patients with regular, i.e. favorable anatomic contour of the anterior thoracic wall (see below). In patients with abnormal chest wall contour, as is the case in pectus excavatum, the dose volume histograms of normal tissues are invariably worse for conventional photon RT, i.e. resulting in a higher tissue radiation dose exposure in these patients. However, the favorable features of proton therapy will remain essentially unchanged. Therefore, it can be concluded that proton therapy will be even more suitable for these patients with abnormal, and thereby "unfavorable", chest wall contour.

This study will permit accrual of patients with unfavorable anatomy only in the context of eligibility criteria, i.e. for patients requiring external beam radiotherapy to chest wall or

whole breast. This study will have the added benefit of demonstrating and documenting in treatment comparisons between photons and protons the advantages as well as feasibility of proton therapy in women with unfavorable anatomy.

1.2 Supporting Data for Proton Radiotherapy

Proton therapy is in routine clinical operation at all PCG member institutions. For example, it was introduced into clinical practice at the Procure Oklahoma City Proton Therapy Center having treated more than 600 patients with over 70 different primary malignancy sites. As of early 2012 PCG has 3 prospective clinical trials open for accrual. Proton therapy is routinely applied for pediatric malignancies, including infants. PCG has been conducting a proton registry since June of 2009 which collects prospective data on all enrolled patients. Thus far no unexpected acute or late toxicities have been reported. The patient population in the registry includes patients with thoracic, paraspinal tumors or chest wall sarcomas where routinely parts of the hemi-thorax / thoracic wall have to be included in the treatment volume. Extra-cranial PT also includes large retroperitoneal sarcomas or large pelvic tumors.

Hence, the medical teams at PCG participating proton centers are experienced in the treatment of large target volumes and various malignancies of the thoracic, abdominal and pelvic region. In summary, we believe we are well prepared to conduct this study and we do not foresee that the quality of technical challenges are more complex compared to our previous clinical projects of introducing new indications.

Publications on proton therapy for breast cancer are rather limited. Preclinical studies have focused on treatment planning comparisons, and only 2 clinical studies have been conducted. The preclinical therapy comparisons [1,28,29,30]indicated the potential of protons for normal tissue sparing in a systematic manner. Highly conformal dose distributions can be achieved with protons. PT results characteristically in homogeneous dose distribution in the target area, followed by a steep fall-off to zero-dose distally to the target. In a frequently quoted review on the practical and theoretical indications of proton therapy encompassing the spectrum of current radiation therapy indications Björk-Eriksson et al. [31] included breast cancer. No clinical data have thus far been published on the topic of postoperative PT for loco-regional breast cancer, which is the topic of proposed study. The only clinical data available are 2 pilot studies, conducted by the groups at Massachusetts General Hospital and Loma Linda University Medical Center on PT as replacement of external beam photon therapy or brachytherapy in the treatment of partial breast irradiation [32,27]). Partial breast irradiation is currently undergoing a worldwide evaluation as alternative to whole breast irradiation for early stage, favorable disease. The MGH study involved 20 patients with a median follow-up of 12 months, and demonstrated the principal feasibility of proton therapy. The authors reported some early but not late skin toxicities, which they explained by insufficient treatment technique, which was subsequently changed. In contrast, David Bush for the Loma Linda Group did not observe significant acute or long-term skin toxicity in a cohort of 50 patients participating in a Phase II study of partial breast proton irradiation. Patients received 40 Gy(RBE) in 10 fractions over 2 weeks, and data analysis was based on a median follow-up of 48 months. Only mild dermatitis was observed as acute toxicity. [33] Proton and conformal x-ray plans were compared using dose-volume histogram analysis to determine volumes of normal breast tissue and skin treated with each technique. Protons therapy provided substantial normal tissue protection compared with the use of conformal x-rays when used for partial breast treatment. [31]

The preclinical treatment modality comparison project conducted at Paul Scherrer Institute (PSI) and reported by Ares et al. demonstrated advantages of PT versus photon-based 3D-CRT or IMRT for left-sided breast cancer patients by comparing treatment plans for different and increasingly complex target volumes.[1] The goal of the study was to identify a selected subgroup of patients who would benefit most from proton-radiotherapy. This treatment plan comparison was performed on planning-CT scans of 20 consecutive left sided BCa patients who previously underwent either breast conserving surgery (BCS, 10 patients) or modified radical mastectomy (MRM, 10 patients). For each scan three progressively more complex different treatment-scenarios were defined and named "planning target volume (PTV) 1, 2 and 3. These 3 scenarios were deliberately chosen to reflect most frequent indications in clinical practice in the postoperative treatment of breast cancer: PTV1 = Whole breast (WB) / Chest wall (CW) only, PTV2 = WB/CW + Medial Supraclavicular (MSC) + Lateral Supraclavicular (LSC) + Axillary III (AxIII) nodes, PTV 3 = WB / CW + MSC + LSC + AxIII + Internal mammary chain (IMC) nodes. For each patient three 3D-CRT (photons), three IMRT (photons) and three IMPT (protons) plans were calculated. The results of this study confirmed that for irradiation of the WB or CW-only, standard 3D-CRT photon radiotherapy provided excellent target coverage. Although IMRT and IMPT increased target dose homogeneity, the differences in normal tissue radiation exposure between 3D-CRT and PT for a standard-risk patient were relatively minor. For PTV2-scenarios the level of low dose that relative volumes of the left lung, the right lung, the heart and the contralateral breast received, was significantly reduced using proton plans compared with photon plan.

For PTV3-scenario none of the 3D-CRT plans were able to meet the stringent criteria for target dose coverage due to target complexity. All 3D photon plans would have required significant compromises of target coverage in order to meet lung tolerance constraints – this is a finding well known in clinical practice. The specific cause was the difficulty of obtaining correct PTV coverage of the IMC lymph nodes with the standard combination of photon and electron beams to treat this region. In practice 3D-CRT plans for PTV3-scenarios routinely compromise target coverage in order to remain within the ipsilateral lung dose constraints. PTV coverage was improved with IMRT-and proton-plans. However, analogues to the PTV2-scenario, PTV coverage by IMRT came at the cost of the "bath" of low-dose irradiation at the level of the left-lung, the right lung, the heart and the contralateral breast. This was markedly reduced or even eliminated by use of protons. In summary considering the endpoints of a) dose distribution, b) target coverage, c) minimizing dose to left-lung, heart and contralateral breast, as well as d) minimizing the low-dose volume of all irradiated tissues (= "dose-bath") the benefits of PT became more obvious with increasing target complexity, i.e. increasing from PTV1 to PTV2 and to PTV3. Benefits were directly pointing towards the potential of reducing late toxicity, specifically pulmonary and cardiac toxicity and risk of secondary neoplasm in general and contralateral breast cancer in particular.

We conducted at the ProCure Proton Therapy Center in Chicago a treatment planning comparison between proton therapy and IMRT photon therapy for the scenarios of Stage III breast cancer with internal mammary nodal irradiation following mastectomy, i.e. irradiation of the chest wall plus LN, as well as following lumpectomy, i.e. irradiation of the breast plus LN. The proton plan used the planning system and delivery equipment, as used in routine practice.

The comparison depicted below assumed a dose prescription for both plans using the specifications of "95 % isodose to cover 95 % of PTV". We subsequently subtracted the proton-plan with its dose distribution from the IMRT photon plan to depict the dose distribution and amount of excess irradiation delivered to normal tissues by IMRT photon RT compared to protons. This radiation dose does not contribute to tumor control, since both plans accomplished target coverage.

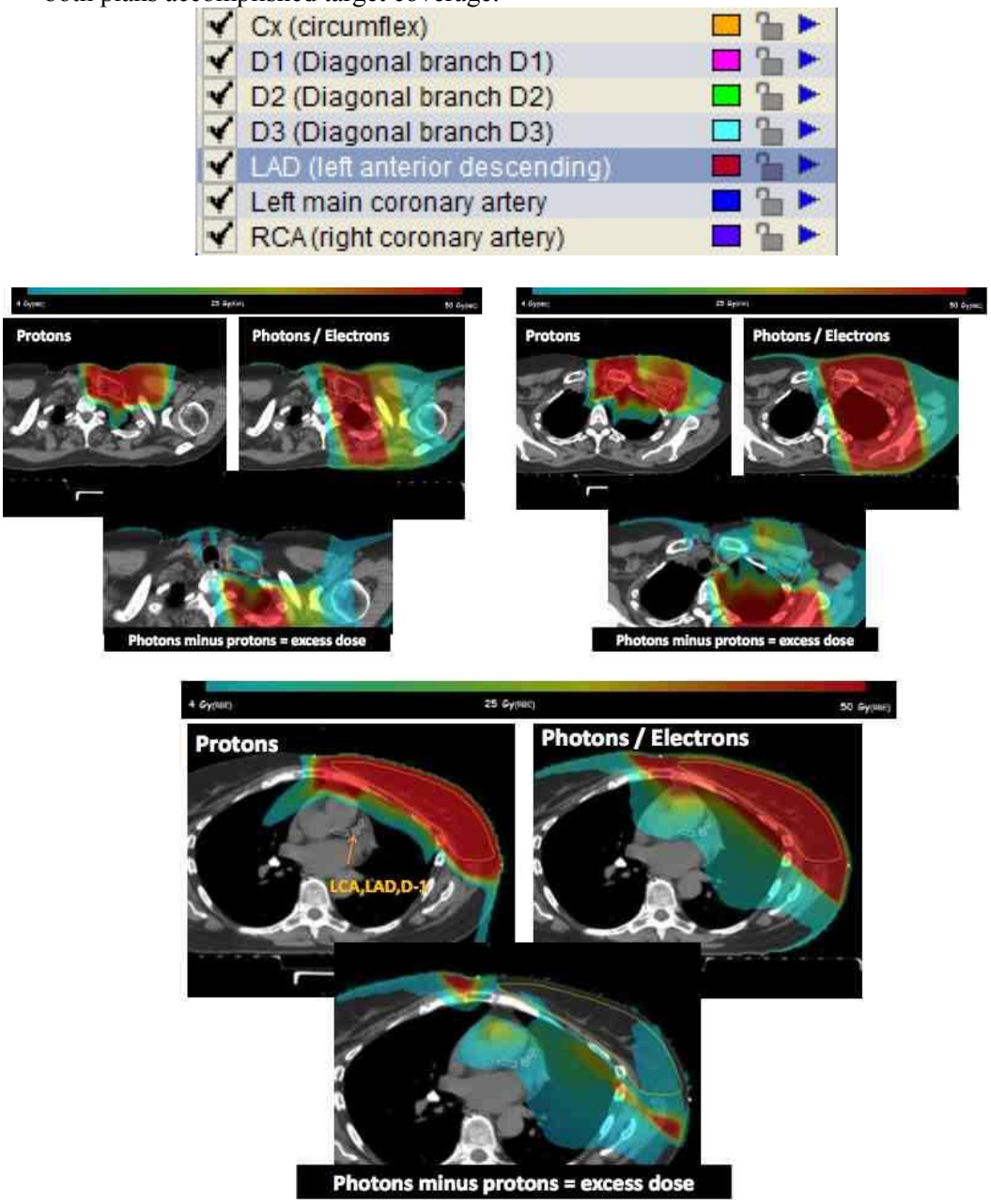


Fig.: 3A

Stage III breast cancer treatment comparison plans between protons and IMRT-based photons / electrons. Representative axial slices from supraclavicular LN overage superiorly to mid-level breast including IMC's inferiorly. Treatment prescriptions based on 50.4 Gy (RBE) total dose with 95% isodose coverage of 95% of PTV. Proton plans were subtracted from photon/electron plans to reveal the excess dose delivered by use of photons/electrons compared to protons to normal tissues. Color-dose scale range from 4 Gy to 54 Gy. LCA = left coronary artery, LAD=left ascending artery, D-1= first diagonal branch off the LAD.

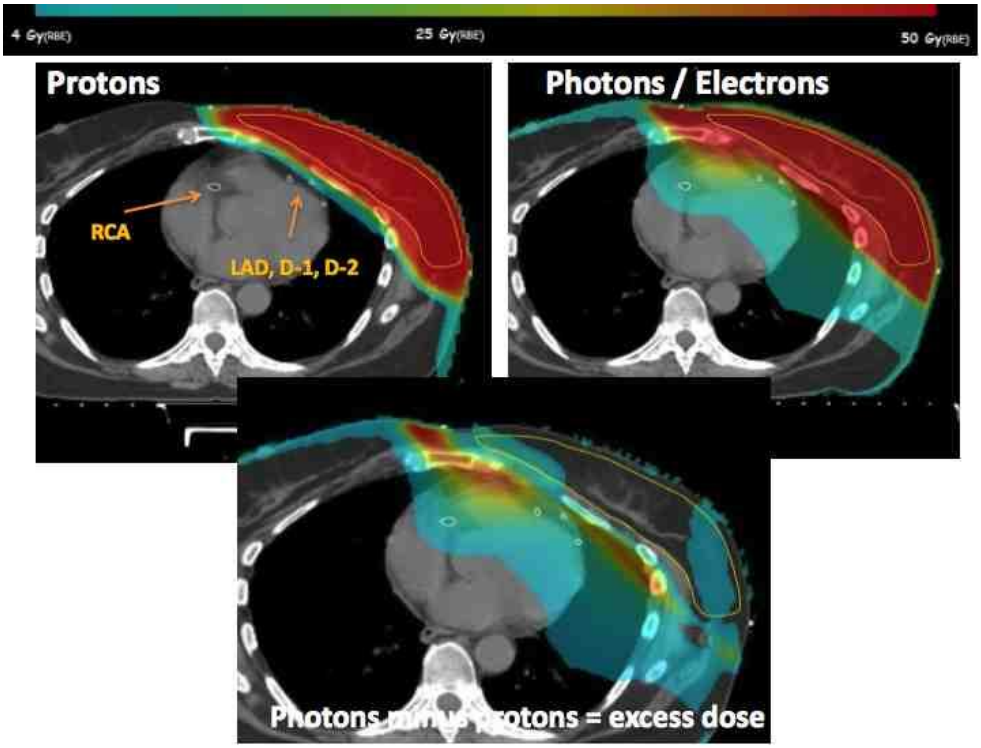


Fig.: 3B

Stage III breast cancer treatment comparison plans between protons and IMRT-based photons/electrons,. Representative axial slices at inferior breast and mid-heart level. Treatment prescriptions based on 50.4 Gy (RBE) total dose with 95% isodose coverage of 95% of PTV. Proton plans were subtracted from photon/electron plans to reveal the excess dose delivered by use of photons/electrons compared to protons to normal tissues. Color-dose scale ranging from 4 Gy to 54 Gy. RCA= right coronary artery, LCA = left coronary artery, LAD=left ascending artery, D-1 and D-2= first and second diagonal branch off the LAD.

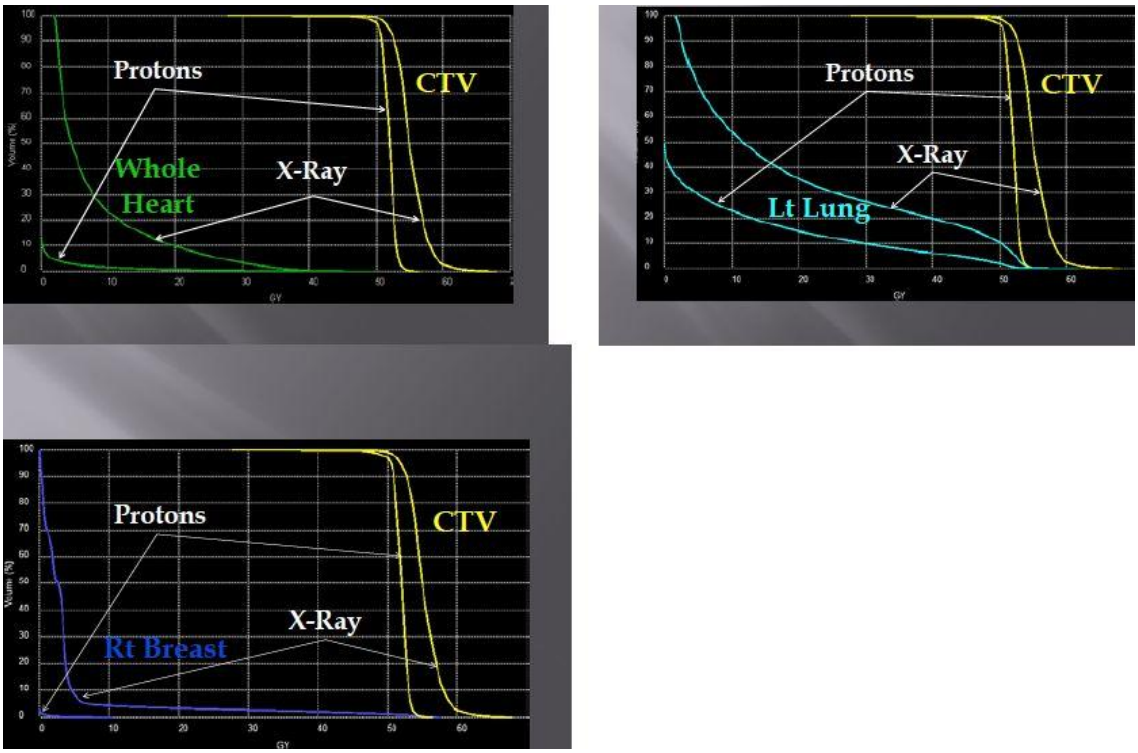


Fig.: 4
Stage III breast cancer treatment comparison plans between protons and IMRT-based photons/electrons. Dose-Volume Histograms (DVH's) of the entire heart, ipsilateral lung and contralateral breast. Treatment prescriptions based on 50.4 Gy (RBE) total dose with 95% isodose coverage of 95% of PTV.

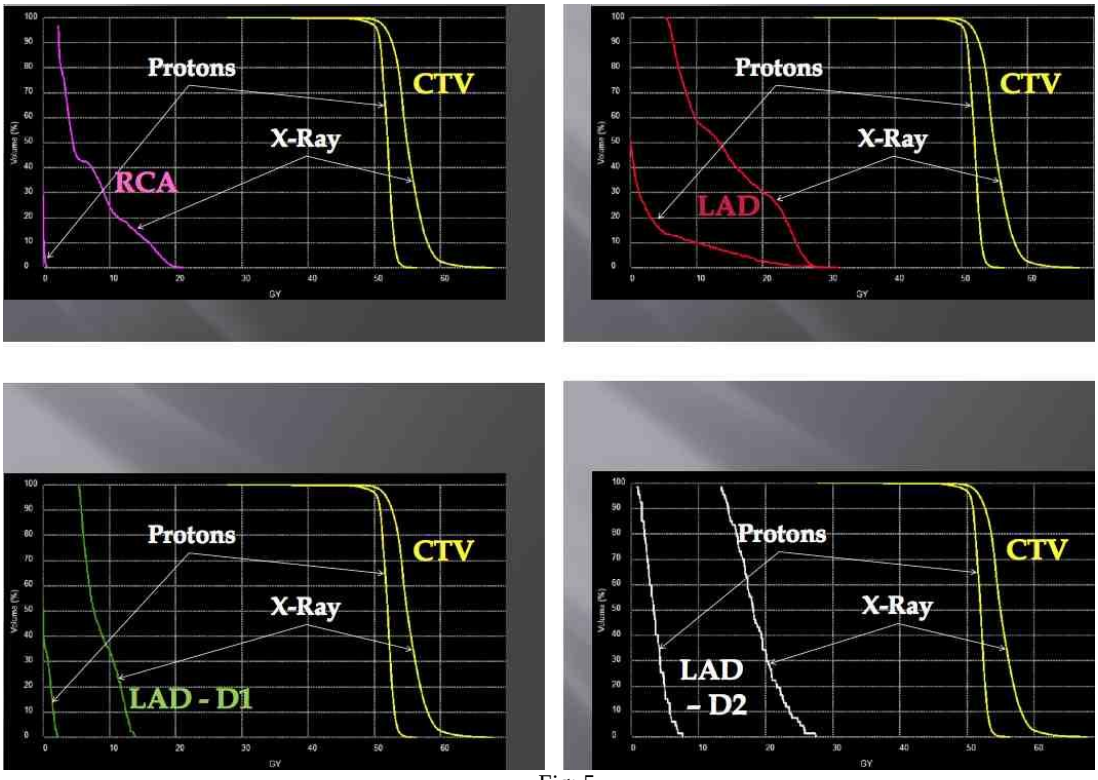


Fig: 5

Stage III breast cancer treatment comparison plans between protons and IMRT-based photons/electrons. Dose-Volume Histograms (DVH's) of the entire heart, ipsilateral lung and contralateral breast. Treatment prescriptions based on 50.4 Gy (RBE) total dose with 95% isodose coverage of 95% of PTV. RCA= right coronary artery, LCA = left coronary artery, LAD=left ascending artery, D-1 and D-2= first and second diagonal branch off the LAD

The following table quantifies the comparison proton and photon/electron treatment plans. We deliberately applied the strict normal tissue constraints as outlined in RTOG protocol 1005. Note should be taken that RTOB 1005 is not intended to treat axillary and supraclavicular nodes, hence the protocol guidelines are relatively strict when compared to our study proposal of treating Stage III patients. Yet, even within those strict normal tissue criteria the proton plan was able to meet all normal tissue constraints. In contrast, the photon/electron plan failed to 6/8 normal tissue constraints.

RTOG 1005 Guidelines	Proton Plan	Photon/Electron Matching Plan
PTV Minus Skin: V95% (95%) Preferred, V90% (90%) Acceptable	N/A	V95% = 98%
CTV Minus Skin: V95% (95%) Preferred, V90% (90%) Acceptable	V95% = 99%	V95% =100%
Contralateral Breast: < V5% : 1.86Gy Preferred, < V5% : 3.1Gy Acceptable	0 Gy(RBE)	7 Gy
Ipsilateral Lung V(20Gy): <15% Preferred, <20% Acceptable	15%	36%
Ipsilateral Lung V(10Gy): <35% Preferred, <40% Acceptable	23%	54%
Ipsilateral Lung V(5Gy): <50% Preferred, <55% Acceptable	29%	72%
Contralateral Lung V(5Gy): <10% Preferred, <15% Acceptable	4%	4%
Heart D(5%): <20Gy Preferred, <25Gy Acceptable	2 Gy(RBE)	27 Gy
Heart V(10Gy): <30% Preferred, <35% Acceptable	2%	23%
Heart Mean Dose: <4Gy Preferred, <5Gy Acceptable	0.6 Gy(RBE)	8 Gy

Table: 1
Tabulated DVH parameters comparing a proton treatment plan for patient with Stage III breast cancer with the corresponding IMRT plan using a combined photon/electron technique. Dose and volume parameters for each normal tissue were applied as specified in RTOG protocol 1005 Guidelines. Green= meeting dose constraints; red = higher than dose constraints.

In clinical photon practice, it is a well-known fact that in the majority of patients, strict adherence to the specification of 95% isodose to cover 95% of the PTV results in unacceptable high dose to normal organs. Therefore, in clinical practice and in major multi-institutional trials it is customary to permit a dose specification of "90% isodose to cover 90% of the planning volume".
Hence, we conducted a second planning comparison, in which the proton specifications of "95% dose to 95% PTV" were maintained, yet the specifications for the IMRT photon plan deliberately relaxed to "90% dose to 90% PTV". This comparison revealed a slightly more advantageous dose distribution for photons, but not qualitatively different separation between protons and photons.

Our comparison plans revealed the following data and confirmed the published PSI planning comparison:
1) Proton Therapy in comparison to IMRT photon irradiation consistently meets the desired target / dose specifications of "95% dose to 95% PTV" without the need to compromise.
2) Proton Therapy in comparison to IMRT photon irradiation results consistently in reduced irradiation of lung parenchyma, in markedly reduced irradiation of heart and in essentially absent dose to contralateral breast.
3) Proton Therapy in comparison to IMRT photon irradiation reduces markedly the dose to coronary arteries (for details see section 1.2).
4) Proton Therapy in comparison to IMRT photon irradiation significantly reduces the irradiated volume of normal tissue in general exposed to unnecessary radiation dose.

1.3 Toxicity Risk after Postoperative RT in Breast Cancer

1.3.1 Heart Irradiation and Late Cardiovascular Toxicity

Multiple long-term studies have demonstrated the benefits of radiotherapy for loco-regionally advanced breast cancer. However, the majority of long-term studies with literally thousands of women enrolled revealed a small, but significant, increased risk of cardiac morbidity and mortality, appearing approximately 5 to 10 years after irradiation. A significant number of women die from cardiovascular disease caused by the inadvertent application of radiation during irradiation of chest wall, breast and draining lymphatics using photons.

1.3.1.1 Pathophysiology of Radiation-induced Cardiovascular Disease

Radiation induced heart disease may be described as a result of damage to the microvasculature and macrovasculature. [34] The damage of a microvasculature component begins with injury of endothelial cells with various heart structures. Capillary swelling and progressive obstruction of the vessel lumen result in ischemia, which in turn leads to the replacement of cardiac tissue by fibrosis. [35] Endothelial damage leads to an acute inflammatory reaction (due to acute swelling of the endothelial cells). The morphological alterations of the first phase, about 6 hours after exposure, include acute inflammation of small/medium size arteries and neutrophilic infiltrate involving all layers of the heart. The activation of the coagulation mechanism leads to fibrin deposition. These early effects are followed, in the late phase, by fibroblastic proliferation and enhanced atherosclerosis. Eventually, the decreased patency of capillaries results in ischemia and subsequent myocardial cell death. The pathology and mechanism of coronary artery damage in irradiated patients appear to be similar to those of coronary disease in the general population. [36,37,38.39,

There are four distinct patterns of radiation-induced arterial damage, each characterized by different pathology and time frames. Early arterial wall necrosis causing arterial rupture is a rare, but potentially fatal, complication. Mural thrombosis, occurring in the irradiated segment, usually present within 5 years. Fibrotic occlusion of the irradiated artery typically becomes symptomatic within 10 years, whereas pericardial fibrosis and accelerated atherosclerosis may become symptomatic as late as > 20 years after radiotherapy.[40]

1.3.1.2 Clinical Studies Documenting Radiation-induced Cardiovascular Toxicity

In general, large population –based studies have unveiled an increase of cardiovascular death risk in patients irradiated for cancer of the left breast. [41] Onset of cardiovascular disease occurs after 5-10 years. Thus, studies with sufficiently long follow up time are required and it is not surprising that reports with shorter follow have failed to demonstrate cardiac events.

Studies published in the 80's first demonstrated that postoperative radiotherapy lowered the risk of cancer mortality, but mortality from cardiac toxicity had increased. The largest meta-analysis exploring the impact of RT on breast cancer mortality and on mortality from other causes was conducted by the Early Breast Cancer Trialists Collaborative Group. [3] The analysis was based on 19,582 women enrolled in 40 randomized trials begun before 1990. With 178,000 woman-years of follow-up, the annual mortality rate from breast cancer was reduced by 13.2%, but the annual mortality rate from other causes was increased by 21.1%. The increased non-breast mortality was primarily due to an excess number of deaths from vascular causes. Most of the non-breast cancer deaths occurred in trials where both breast/chest wall and regional lymph nodes were radiated; only 7% were in trials in which RT was limited to the breast.

Rutqvist et. al.[42] (analyzed the cardiovascular mortality in a group of 960 patients in the Denmark enrolled on a three-arm randomized trial of preoperative RT, postoperative RT or surgery alone. In preoperative cases, the breast and IMC nodes were treated with tangential fields to 45Gy. In postoperative cases, the chest wall and IMC nodes were treated with an oblique electron field with energies ranging from 7.5-15 MeV. With a mean follow-up of 16 years, there was no difference in cardiovascular mortality in the irradiated patients and controls. However, when analyzed according to estimated dose of radiation to the myocardium, the subset of patients who received the highest dose (patients treated with tangential cobalt fields for left-sided tumors) were found to have a significantly increased risk of death caused by ischemic heart disease compared to the surgical controls (relative hazard (RH) 3.2; $p < 0.5$).

Clinical evidence based on Tumor Registry data analysis includes 2 large studies showing heightened risk of cardiovascular morbidity and mortality following RT for localized breast cancer. The methodology and rationale was similar in both studies where the risk of fatal myocardial infarction following irradiation for left-sided breast cancer was compared to the risk of fatal MI following right-sided disease. In the first, using data from the Surveillance, Epidemiology and End-Results (SEER) registries in the United States, Paszat et al.[43] identified a cohort of 206,523 women diagnosed with non-metastatic invasive breast cancer between 1973 and 1992. The relative risk of fatal MI comparing left versus right-sided was 1.17 (95% CI, 1.01 to 1.36). Subgroup analysis showed age and time interval from adjuvant RT to be important factors. The RR for a fatal MI among left-sided cases was increased for those less than 60 years of age (RR 1.98; 95% CI, 1.31 to 2.97), versus right sided cases, but not for those > 60

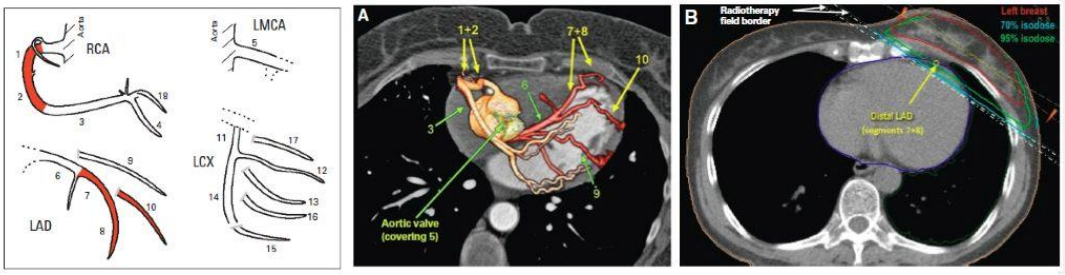
years of age. Among women less than 60 years of age who were treated with radiation, the RR was significantly greater for left-sided compared to right-sided cases in the cohort of survivors from 10-15 years after the diagnosis, but not within the 0 - 5 or 5 - 10 year conditional survival cohorts (RR, 5.28 v 2.01 v 1.53).

The second tumor registry study was conducted in Sweden.[44] Cause-specific mortality was analyzed according to laterality among 54,617 breast cancer patients from the registry between 1970 to 1985. With a median follow-up of 9 years, the number of deaths due to MI was significantly higher among patients with left-sided disease compared to right-sided (RR, 1.09; 95% CI, 1.02-1.17). Similar to the SEER data, the RR (left v right-sided tumors) appeared to increase over time. The RR was 1.06 in the first 5 years after diagnosis, but increased significantly to 1.13 during years 5 to 10 and 1.20 during years 10 to 15 (p= 0.22).

Other predisposing factors such as pre-existing cardiac disease have also been shown to be a risk factor for increase mortality post adjuvant left-sided breast radiotherapy. Gutt R et al [45] evaluated cardiac morbidity and mortality after breast conservation treatment with contemporary radiation techniques in patients with early-stage cancer and pre-existing cardiac disease. Medical records were reviewed for 41 patients with history of myocardial infarction, congestive heart failure (CHF) and/or coronary artery disease before radiotherapy. Patients were stratified for right versus left-sided breast cancer. The left-sided group experienced a higher incidence of cardiac deaths (right side 2 of 26 (9%); left side 4 of 15 (27%); HR, 4.2; p=0.08) 10 years after treatment.

1.3.1.3 Clinical Evidence and Treatment of Radiation-induced Coronary Artery Disease

A recent Swedish study for the first time correlated degree of coronary artery stenosis with radiation dose.[46] 199 women with breast cancer and adjuvant radiotherapy, who were subsequently diagnosed with coronary artery disease, were identified and cross-linked to the breast cancer registry during the same time period.[45] A detailed analysis was performed reviewing degrees of stenosis within 18 anatomic sub-segments of the major coronary arteries. These findings were correlated with the likely radiation dose received.



(Figures from Nilsson et al. (JCO, 2012). Coronary angiogram (left figure) superimposed on CT of heart illustrating anatomy of coronary arteries. Right coronary artery (RCA – orange), left circumflex and left anterior descending arteries (LMCA and LAD – red). Numbered arrows indicate segments. Middle figure with red segments indicate hotspots of RT according to irradiation dose assuming tangential-field irradiation (right figure)

The most commonly affected vessel was the left anterior descendent coronary artery, usually encompassed by the highest dose volume, both in post-mastectomy and breast preserving treatment settings. The anterior portion of the heart and in particular the left anterior descending coronary artery situated at the extremity of the cardiac silhouette, was a site associated with a high risk of myocardial infarction if exposed to

the target dose, often included in the treatment volume of tangential fields. The odds ratio was 7.22 for left-sided breast cancer patients developing high grade stenosis in the high-dose; anterior coronary artery segments compared to right-sided BC patients. For the first time, the authors were able to establish a direct link between radiation and radiation dose and location of coronary stenosis.

Treatment usually includes typical vascular surgery procedures, such as bypass grafting, angioplasty with stent placement, vascular anastomosis or endarterectomy. However, the surgical management of radiation induced arterial disease is considered high risk: dissection is usually more difficult, lesions tend to be more extensive and the rate of infection and postoperative lymphorrhea is relatively high. [47, 48,49]

The research group at University of Pennsylvania performed detailed reviews of the medical records of 961 stage I-II breast cancer patients treated from 1977 to 1995 at the University of Pennsylvania. All patients underwent conventional tangential beam radiation treatment (RT) using 6 MV to 15 MV photons, followed by a boost to the tumor bed to a median total tumor bed dose of 64Gy (range, 59.75 to 71.60 Gy).

Correa at al. reported that screening for cardiac stress tests and catheterizations performed after RT revealed 82 patients. [50] At diagnosis, patients with left-sided and right-sided breast cancer had the same estimated 10-year risk (both 7%) of developing coronary artery disease. At a median time of 12 years post-RT (range, 2 to 24 years), 46 patients with left sided and 36 patients with right-sided breast cancer had undergone cardiac stress testing. A statistically significant higher prevalence of stress test abnormalities was found among left (27 of 46; 59%) versus right-side irradiated patients (three of 36; 8%; *P* _ .001). Furthermore, 19 of 27 of left-sided abnormalities (70%) were in the left anterior descending artery territory. Thirteen left-side irradiated patients also underwent cardiac catheterization revealing 12 of 13 with coronary stenosis (92%) and eight of 13 with coronary stenosis (62%) solely in the left anterior descending artery. Fig 6 depicts multiple stenosis of coronary arteries.

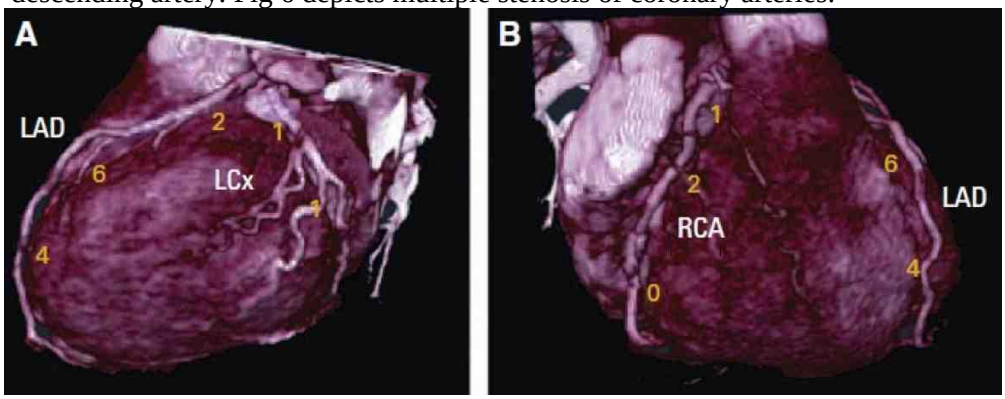


Fig: 6
3D-reconstruction of catheterization results of the heart of a patient with early stage breast cancer following radiotherapy. Multiple stenosis of several coronary arteries. From: Correa, C, Harris EE et al. J Clin Oncol 25:3031-3037, 2007. (A) Lateral and (B) medial views of left-side irradiated patient's catheterization findings. Counts in locations of coronary stenoses: proximal left circumflex (LCx), n _ 1; distal LCx, n _ 1; proximal left anterior descending (LAD), n _=2; mid LAD, n = 6; distal LAD, n _=4; proximal right coronary artery (RCA), n _=1; mid RCA, n _=2; distal RCA, n = 0.

The authors concluded that patients treated with left-sided radiation as a component of breast conservation have an increased risk of late, radiation-associated coronary damage.

Harris EE et al.[51] analyzing the identical patient cohort at Univ. Pennsylvania (961 stage I-II breast cancer patients treated from 1977 to 1995) reported on the incidence of late cardiac morbidity and mortality. At a median follow-up time of 12 years (range, 2-27 years) there was no difference in overall mortality from any cardiac cause. Death from any cardiac cause occurred in 2% of right-sided patients and 3.5% of left-sided patients. However, in the second decade after treatment, there was a higher rate of cardiac deaths in left-sided patients, with a cumulative risk of 6.4% (95% CI, 3.5% to 11.5%) for left-sided compared with 3.6% (95% CI, 1.8% to 7.2%) for right sided patients at 20 years. There were statistically higher rates of chest pain, coronary artery disease, and myocardial infarction diagnosed in left-sided patients.

There was no significant difference between right- and left-sided breast cancer patients in the development of CHF, palpitations, any arrhythmia, atrial fibrillation, any valvular disorder, or mitral valve prolapsed. However, there were significant differences in the development of chest pain, and in any diagnosis of coronary artery disease and MI, all of which were more likely to occur in left-sided patients. The 20-year actuarial freedom from coronary artery disease was 90% in right-sided patients and 75% in left-sided patients (*P* _ .001;). The20-year actuarial freedom fromMIwas95%in right-sided patient and 85% in left-sided patients (*P*_.002;).

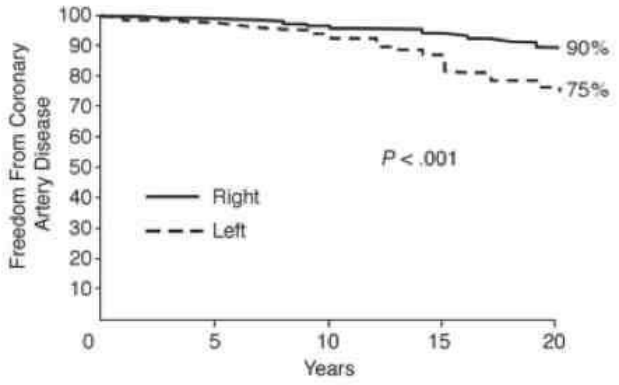


Fig.: 7
Freedom from coronary artery disease in 961 Stage I-II breast cancer patients following conventional radiotherapy of breast and lymph nodes. Median follow-up time 12 years. A significantly higher rate of fatal and nonfatal diagnoses of coronary artery disease was seen in left-sided patients compared with right-sided patients using Kaplan-Meier analysis. From: Harris EE, Late Cardiac Mortality and Morbidity in Early-Stage Breast Cancer Patients After Breast-Conservation Treatment, *J Clin Oncol 24:4100-410, 2006.*

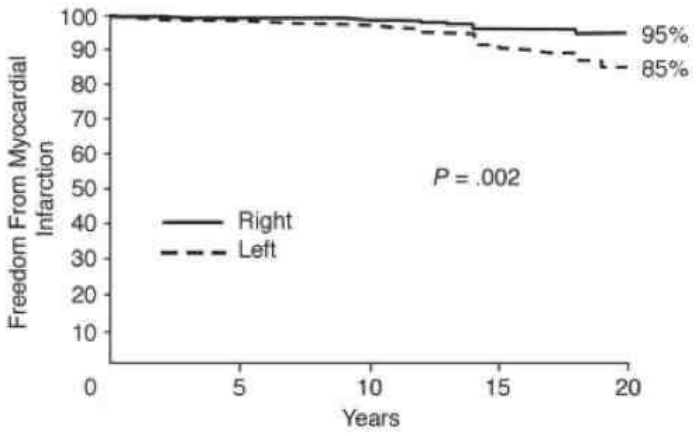


Fig: 8
Freedom from myocardial infarction in 961 Stage I-II breast cancer patients following conventional radiotherapy of breast and lymph nodes. Median follow-up time 12 years. A significantly higher rate of any diagnosis of myocardial infarction, fatal or nonfatal, was seen in left-sided compared with right-sided patients; however, deaths as a result of myocardial infarction were not significantly different between the two groups. From: Harris EE, Late Cardiac Mortality and Morbidity in Early-Stage Breast Cancer Patients After Breast-Conservation Treatment, *J Clin Oncol 24:4100-410, 2006.*

Internal mammary node (IMN) fields were used in 14% (n_68) of left-sided patients and 11% (n_54) of right-sided patients. The impact on morbidity of the use of IMN fields was examined. Coronary artery disease was significantly associated with the use of IMN fields: 7% without IMN compared with 18% with IMN (*P* _ .001). MIs were significantly more common after the use of an IMN field: 3%without IMN versus 9% with IMN (*P*_.01).

When the risk of cardiac morbidity was adjusted for baseline risk factors, hypertension demonstrated an interaction effect with laterality in patients who developed coronary artery disease. The hazard ratio (HR) for developing coronary artery disease was elevated for all patients with hypertension, and the highest HR was seen in left-sided patients with hypertension [11.4 (95% CI, 5.0 to 26.2)]. Overall, the presence of hypertension was associated with a higher risk of coronary artery disease in left-sided patients.

1.3.1.4 Present Status of Conventional Photon-based Radiotherapy re. Dose to Cardiovascular Structures

The Journal of Clinical Oncology published an editorial on the issue of radiation induced heart disease in women treated for breast cancer. 52 The authors acknowledged"… mounting evidence that RT can cause Coronary Artery Disease…". According to the authors: "…Radiation oncologists should exploit available tools/techniques that reduce doses to cardiovascular structures; however, for many patients with breast cancer… the RT beams will necessarily traverse the heart." Indeed, at present and in the foreseeable future, no photon-based technology (Tomotherapy, IMRT, "Truebeam," etc.) can accomplish simultaneously comformal target coverage and normal tissue sparing.

1.3.1.5 Clinical Imaging and Laboratory Indicators as Early Surrogates to Predict Clinically Symptomatic Cardiovascular Disease Following Radiotherapy

Several authors have examined the surrogate end point of radiologic changes in myocardial perfusion after RT. The group at Duke University [53,54] reported the results

on 114 patients enrolled in a prospective study involving pre-RT and serial post-RT single-photon-emission-computed-tomography (SPECT) scans to assess changes in regional cardiac perfusion. The rates of transient chest pain (within 0-14 months after RT) were significantly higher in patients with new perfusion defects. The incidence of perfusion defects was correlated with the volume of left ventricle (LV) in the RT-field (25% when 1% to 5% of the LV within the tangent fields vs. 55% when > 5% of the LV within the field). Perfusion defects persisted 3 to 5 years after RT. The clinical significance of these perfusion defects is presently unknown, but potentially correlated with abnormalities in wall motion, declines in ejection fraction, and episodes of chest pain. [55]Aside from transient, early chest pain, these and other studies have not been able to consistently correlate SPECT imaging with symptomatic cardiac disease.

Early damage to the myocardium and vasculature may be detected on myocardial perfusion imaging (MPI) by means of perfusion scintigraphy. [56] A number of studies have investigated MPI in breast cancer patients. A worrying percentage of new perfusion defects (27-50%) on MPI can be demonstrated as early as 6-13 months after radiotherapy. Preliminary data suggest that these defects tend to persist at 3-5 years of follow-up; additionally new defects may occur in a significant percentage of patients with normal MPI at 6-24 months after irradiation. [57] Demonstrated defects tend to follow the pattern of radiotherapy fields and localize in the anterior/apical regions of the heart.[47,58,59] Particularly worrying is the fact that the defects are also seen in patients treated with "modern" techniques believed to be safe. A significant incidence of perfusion defects occurs in patients receiving high doses to as little as 5-10% of the left ventricle (i.e. 2.5-5% of the heart). These exposures are barely seen on dose-volume histograms. [48, 52] Despite these excellent studies, the clinical relevance of these findings remain at present unclear.

1.3.1.6 Synergistic negative effects of cardiotoxic systemic therapy – specifically Herceptin and Anthracyclines - and conventional radiotherapy

Women with loco-regionally advanced breast cancer require combined modality therapy including systemic therapy and radiotherapy. Present chemotherapy frequently includes anthracyclines (doxorubicin = Adriamycin) known for their cardiotoxic profile, and trastuzumab (= Herceptin), for patient who have tumors that overexpress the oncogene HER2. Trastuzumab is the generic name for the antibody RhuMAbHER2.

In a phase II clinical trial 222 women whose tumors overexpressed p185HER2 with previously treated metastatic breast cancer received Herceptin. An overall response rate of 15% was reported. However, cardiac dysfunction occurred in 7% of patients, and in 5%, the cardiac dysfunction was regarded as severe [i.e., New York Heart Association (NYHA) classification III-IV]. Cardiac dysfunction included cardiomegaly, left-sided heart failure, congestive heart failure, and cardiomyopathy.

Results of several large Phase III trials evaluating the role of trastuzumab incorporated into standard anthracycline-based adjuvant chemotherapy regimens have demonstrated to improve disease-free survival (DFS) and overall survival (OS) in early-stage HER2-positive breast cancer. However, the benefits were achieved with a significant increase in congestive heart failure (CHF) ranging from 1.9-4.1%.

Recently, the NSABP = National Surgical Adjuvant Breast and Bowel Project) conducted a randomized trial offered to women with HER2-positive and node positive breast cancer (NSABP B31, patient accrual 2/2000- 2/2005). This trial is of particular

relevance for our present study, since many patients eligible for our proposed study would have been potential NSABP B31 participants.

Patients were randomized to receive chemotherapy alone consisting of four cycles of doxorubicin and cyclophosphamide (AC) followed by paclitaxel or to receive chemotherapy plus weekly trastuzumab. . The 3-year cumulative incidence of protocol-defined cardiac events (congestive heart failure with NYHA Class III/IV symptoms or definite or probable cardiac death) was 4.1% in the experimental arm vs. 0.8% in the control arm. Trastuzumab had to be discontinued before completion of 1 year of therapy in 15.5% of patients due to asymptomatic or symptomatic cardiac dysfunction. The 5-year cumulative incidence of protocol-defined cardiac events was 3.8% in the trastuzumab arm.

The North Central Cancer Treatment Group (NCCTG) N9831 trial compared three regimens: AC followed by weekly paclitaxel (Arm A); AC followed by paclitaxel followed by trastuzumab (Arm B); or AC followed by paclitaxel plus trastuzumab followed by trastuzumab alone (Arm C) (G5). NCCTG N9831 employed the same definition of a cardiac event as B-31. Reported 3-yearcumulative incidence rates of cardiac events were 0.3% for Arm A (n=664), 2.8% for Arm B (n=710), and 3.3% for Arm C (n=570).

The Herceptin Adjuvant (HERA) trial reported results comparing one year of trastuzumab treatment (n=1703) with observation alone (n=1698) after standard neoadjuvant or adjuvant chemotherapy. The reported incidence of severe CHF was very low but slightly increased in the trastuzumab arm (0.60 vs. 0.00) the incidence of symptomatic CHF was also higher in the trastuzumab arm (2.15 vs. 0.12).

The risk of cardiac dysfunction by Herceptin appears to be independent of responses to antitumor therapy. The nature of the cardiac dysfunction observed in these studies was similar to that seen in anthracycline-induced cardiomyopathy. The mechanism underlying the cardiac toxicity seen in the Herceptin trials is presently not known. In the HER2 knockout mouse model, deletion of HER2 has been shown to result in abnormal development of the cardiac trabeculae. HER2 and HER3 receptors have been found to be expressed by neonatal and adult ventricular myocytes in a rat model. However, there are currently no human data available to explain the cardiac effects seen with Herceptin. The long-term cardiac effects of Herceptin are also largely unknown. It is unknown whether Herceptin cardiotoxicity might follow an insidious pattern and show years of latency before causing cardiomyopathy.

Concerns of synergistic negative impacts of cardiotoxic systemic therapy and conventional radiotherapy are high among breast cancer specialists – specifically since the advent of Herceptin. Study designs and clinical decision processes are influenced by those concerns. For example, NSABP B31 trial stated specifically:
".. the possibility that there may be long-term cardiotoxic effects from Herceptin administration compounds the concern that radiation therapy to the chest may have a long-term cardiotoxic effect, particularly for women with left-sided breast lesions. Because of these concerns, irradiation of any internal mammary nodes will be prohibited in this trial…" and "This trial allows post-lumpectomy regional irradiation and post-mastectomy locoregional irradiation but prohibits the irradiation of internal mammary nodes because of the concern for possible additional cardiac toxicity from the combination of Herceptin and radiation therapy Investigators are requested to discuss

cardiac toxicity concerns with their radiation oncologist to ensure careful planning of the ports for left-sided lesions."

To paraphrase the recommendations of the NSABP committee of breast cancer specialists: It was recognized that patients at high risk for IMC involvement would likely benefit from irradiation of the IMC nodal chain. However, the potential local control benefits of irradiation needed to be balanced against the potentially synergistic damaging effects of radiation dose to the heart delivered by conventional irradiation in conjunction with cardiotoxic systemic therapy.

It is the intention of the present study to evaluate on a large patient cohort the capabilities of proton therapy to significantly reduce radiation dose to the heart in general, and eliminate irradiation dose to specific structures of the heart entirely. The advantage of dose sparing will be quantified comparing actually delivered proton treatment plans with state-of-the-art photon or combined photon / electron external beam modalities (3D RT, IMRT, Tomotherapy).

Patients participating in this study will benefit already at present from optimal application of all combined therapy modalities, without having to reduce one option out of concerns of toxicity.

1.3.1.7 Summary: Role of Proton Therapy as "Cardiovascular Protectant" in the Multi-Modality, Combined Therapy Approach for Women with Breast Cancer

- The increased risk of cardiovascular toxicity by conventional photon radiotherapy is a real and tangible threat to women surviving breast cancer.
- The real frequency of coronary artery events and risks of cardiac damage are in general probably underestimated and stage-specific assessments are largely unknown. Even large-scale, prospective clinical trials have not focused on acquisition of cardiac morbidity data and only report mortality data. The incidence of clinically symptomatic cardiac morbidity remains largely unknown. The inclusion of patients with Stage III disease represents the patient subgroup of this proposed study at highest risk for developing cardiovascular toxicity due to the complexity of required loco-regional irradiation.
- The risk of radiation-related cardiac damage gains additional significance due to the widespread use of combined-modality therapy involving systemic, cardiotoxic agents, such as anthracyclines, paclitaxel and trastuzumab.
- Other predisposing factors such as pre-existing cardiac disease, microvascular disease (diabetes) and some unfavorable anatomic conditions may contribute to an increased risk: a more anterior position of the heart in the mediastinum or macrosomic breasts where a substantial portion of the heart is unavoidably included in photon-based treatment fields.
- Due to their physical properties, only protons are in the unique position to achieve both, excellent target coverage and normal tissue sparing. This has been demonstrated by Ares et al. for the PSI-group in a preclinical treatment planning comparison between state-of-the-art photons and proton therapy. Protons resulted in both, essentially absence of radiation dose delivered to the contralateral breast and a minimal deposition of radiation to the heart. [1]

Hence, we hypothesize that proton irradiation is in the unique position to drastically reduce or possibly eliminate the excess risk of heart disease and contralateral breast cancer incidence attributable to irradiation.

1.3.1.8 Cardiac morbidity prevention – Contouring of coronary arteries

Radiotherapy can damage any anatomic cardiac structure, including valves, myocardium, and coronary arteries (*vide supra*). The predominant pathophysiology of cardiac morbidity and mortality in breast cancer patients undergoing radiotherapy is the induction of coronary artery stenosis causing symptomatic coronary artery disease (CAD), i.e. angina, progressing possibly to myocardial infarction and in some patient's cardiac death.

This study defines the coronary arteries as "organs at risk (OAR's). Every reasonable attempt will be made to obtain a diagnostic coronary artery CT scan to enable individual contouring of coronary arteries following fusion with the planning CT scan. It is the intention to have individual coronary contouring as an integral part of the treatment planning process. However, at present coronary artery CT scan is not routine part of breast cancer radiotherapy. Hence, in cases where no coronary artery CT scan can be obtained, coronary arteries will be contoured based on a standard planning CT scan. Variations in the normal anatomy of LAD and diagonal branches are infrequent, and it is therefore reasonable to contour the distal portions using a standard model. Proximal branches of coronary arteries are well visualized on non-contrast treatment planning CT scans.

The heart has three main coronary arteries: The left main or left coronary artery (LCA), which branches immediately after origin into the left anterior descending (LAD) artery as well as the circumflex coronary artery (Cx). A third branch is the right coronary artery (RCA) (see normal coronary artery anatomy, appendix IV). Nilsson et al. (ref) recently demonstrated the relevance of various coronary arteries and their respective segments as it relates to radiotherapy of patients with breast cancer. The anatomic areas closest to the target volume and therefore at highest risk of significant radiation dose are the anterior portions of the heart (closest to chest wall and IMC nodes) as well as the anterolateral portions of the heart including the apex of the heart in case of left-sided breast cancer. Corresponding coronary arteries are the RCA and LCA with LAD. The circumflex artery, providing blood supply to the posterior portions of the heart is relatively distant and thus not at specifically increased risk for high dose exposure.

The RCA shall be contoured from its origins to its distal end. The segments at highest risk of radiation damage are the proximal segments of the RCA. LCA as well as LAD shall be contoured including the 2 diagonal branches (D1, D2) of the LAD which provide blood supply to the lateral portions of the left ventricle, i.e., the anterolateral heart. At highest risks are the distal segments of LAD including apex of the heart and the second diagonal branch. (For details see Appendix IV).

1.3.2 Lung Irradiation and Late Toxicity

The majority of studies correlating lung toxicity with irradiated volume and dose have been performed in patients treated for primary intra-thoracic malignancies. Equivalent studies are presently not available for breast cancer patients and extrapolation of those data for breast cancer patients has its obvious limitations. However, all available data point towards the importance of reducing the lung dose, including at low dose levels (for example the volume receiving 5 Gy =V5), in patients treated with radiotherapy for breast cancer:

a) Mean lung dose and relative volume of lung receiving 20 Gy (V20) have been established as factors predicting radiation pneumonitis.[60] Graham et al. evaluated the risk for pneumonitis on 99 patients with inoperable lung cancer treated with 3D-CRT. The

actuarial risk of developing > Grade 2 pneumonitis was 14% at 6 months, 17% at 12 months, and 20% at 24 months after treatment. Multivariate analysis revealed that the percent of the total lung volume exceeding 20 Gy (V20) was statistically significant and the single independent predictor of pneumonitis. [61]
b) Even lung tissue receiving radiation dose as low as 5 Gy can develop clinically relevant damage. Wang [62] observed in 223 patients with lung cancer treated with concurrent chemo-radiotherapy that the relative lung V5 was the most significant factor associated with treatment-related pneumonitis (1-year actuarial incidence of Grade 3 pneumonitis 3% for V5 <42% compared to 38% incidence for V5 >42%, p=0. 001).[63] Five Gray corresponds to approximately 10% of the dose typically prescribed in postoperative breast cancer radiotherapy. This relatively low dose can produce acutely severe, but reversible Grade 3 pneumonitis. However, it may also translate into late symptomatic toxicity, especially when patients receive additional drugs with potential pulmonary toxicity.

1.3.3 Risk of Contralateral Breast Cancer and other Second Malignancy

The risks of radiation induced second malignant neoplasms (SMN) in breast cancer patients is generally divided in the risks of induction of contralateral breast malignancy and thoracic malignancies in general (mainly lung cancer).

The overview from the EBCTCG [3] documented the incidence of second cancers and of mortality from causes other than breast cancer in all trials that tested RT and all trials of surgery only vs. surgery plus radiotherapy (mastectomy vs. lumpectomy plus RT). There was an excess cancer incidence among women allocated to RT that mainly involved contralateral breast cancer (p=0.002) and lung cancer (p=0.0007); excess mortality from causes other than breast cancer mainly involved heart disease (2p=0.0001) and lung cancer (2p=0.0004). The averaged effects of radiotherapy regimens on contralateral breast cancer and on mortality from causes other than breast cancer on 15-year outcome were not large (9.3% vs. 7.5% for contralateral breast cancer, 15.9% vs. 14.6% for non-breast-cancer mortality), but varied substantially from one regimen to another. The excess of contralateral breast cancer with radiotherapy appeared mainly during the period 5–14 years and was significant even among women aged > 50 years. When the excess mortality from causes other than breast cancer was subdivided by time, the proportional excess again appeared to be less during the first 5 years than in subsequent years, but it was separately significant for the periods 5–14 years and 15 years or more.

Researchers at Yale analyzed the incidence of SMN in a cohort of patients who received surgery plus radiotherapy or surgery alone: 1,029 breast cancer patients who underwent lumpectomy plus radiotherapy; and 1,387 patients who underwent mastectomy only. [64] Median follow up time was 14.6 years (radiotherapy) and 16 years (no radiotherapy), respectively. For younger women (under the age of 45) who received radiotherapy, the 15-year risk of developing a secondary contra-lateral breast malignancies was 10%. Developing a secondary malignancy reduced the overall survival of patient in this study from 69% to 55% (p=0.05). The risk of developing a secondary contra-lateral breast cancer is believed to increase over time especially after 15 years and continuous. Hence, the issue of secondary malignancy risk is of particular importance in the younger patient group with an extended life expectancy thus a longer “exposure” to the statistical risk of second malignancy formation.

It appears that the risk of contralateral SMN is closely associated with breast tissue dose. A linear dose relationship is maintained at lower radiation doses, and there exists no low-dose threshold below which there is no excess risk.[65]

In addition to the EBCTG report [3], several studies independently corroborate the evidence that radiotherapy for breast cancer increases the risk of lung cancer of the ipsilateral lung. [47, 66, 67, 68] The risk of lung cancer is substantially increased in irradiated patients who smoked, compared with patients who never smoked. [69]

In summary, irradiation of the contralateral-breast as "collateral" to the irradiation of the ipsilateral, affected breast as well as the amount of dose to lung tissue remains a concern in photon-based radiotherapy.

In the planning comparison study by Ares et al., PT significantly reduced the dose to the contralateral breast and ipsilateral and contralateral lung compared to photons, which is expected to result in a reduced risk of radiation-induced, contralateral breast cancer and lung cancer.

The potential of proton therapy to reduce the risk of second malignant neoplasm has been investigated in several research projects by the group at PSI. [70, 71] Dose reduction by protons in direct treatment planning comparisons between protons and photons not only affected specific organs and normal tissues. Protons in general and consistently reduced the total amount of normal tissues exposed to irradiation, i.e. the integral volume of normal tissue exposure. All publications from the PSI group as well as other particle centers suggest a reduced risk of SMN induction by protons. The first clinical evidence was published by the Massachusetts General Hospital Group. It revealed an approximately 50% risk reduction by use of protons. In a matched pair analysis of patients treated with protons at MGH, compared to patients treated with photons the long-term risk of second malignant neoplasm in 503 proton patients followed for a median time of 107 months was 6.4% compared to 12.8% for photon patients ($p < 0.0001$). [72]

1.4 Dose Rationale

Dose prescription parameters [73] and treatment specifications will be identical to present day, standard photon radiotherapy concepts. Therefore, no difference in tumor control is expected. The only parameter changed in these patients' treatment is the exchange of photons with protons.

2.0 OBJECTIVES

The purpose of this study is to make heart-sparing and contralateral breast-sparing proton therapy available to patients with breast cancer at increased risk of developing cardiac morbidity, including coronary artery disease, and to evaluate outcomes prospectively and long-term. In addition, it is available to any patient with Stage II/III breast cancer seeking to minimize unnecessary irradiation to normal tissues. Objectives are to demonstrate that proton radiotherapy is a safe and feasible alternative to conventional photon-based radiotherapy judged by the incidence and severity of acute and long term side effects. For example, proton therapy is expected to reduce the cardiac morbidity and mortality by photon therapy from 15 and 10 percent, respectively at 15 years significantly. In addition, this study is designed to demonstrate that proton therapy can in clinical practice predictably and consistently eliminate irradiation of contralateral breast and significantly reduce irradiation of heart, coronary arteries, and lung parenchyma.

2.1 Primary

To determine the rates of acute and long term adverse events of postoperative proton radiotherapy for complex loco-regional irradiation in women with loco-regionally advanced breast cancer. This study specifically includes longitudinal follow up to assess the incidence of cardiac mortality and second malignant neoplasms at 5, 10 and 15 years following proton therapy.

2.2 Exploratory Objectives

2.2.1 To compare dosimetrically the dose volume histogram parameters of the PT plans of the initial 20 patients enrolled with photon IMRT and/orTomotherapy plans to evaluate the potential benefits of protons.

2.2.2 To determine dose distribution of proton therapy to coronary arteries, heart, ipsilateral and contralateral lung, and contralateral breast.

2.2.3 To determine the incidence of clinically symptomatic coronary artery disease, cardiac morbidity and mortality in general and incidence of secondary malignancy, including contralateral breast cancer.

2.2.4 To evaluate quality of life results.

2.2.5 Document local and regional control, metastatic status and disease-specific and overall survival.

3.0 PATIENT SELECTION

This study will be open to all patients who qualify at approved institutions. Patients who are enrolled on other protocols may still be enrolled concurrently on this protocol if the other protocol allows for proton radiotherapy. The study strongly encourages the start of adjuvant proton therapy within a time interval of $\leq$ 12 weeks from the last surgery for breast cancer (including re-excision of margins) or last adjuvant chemotherapy cycle. However, a longer time interval is permitted at the discretion of treating investigator.

3.1 Conditions for Eligibility

3.1.1 Must sign study-specific, IRB approved informed consent form prior to study entry. Note consent by legally authorized representative is not allowed for this trial.

3.1.2 Must be > = 18 years of age.

3.1.3 Must have a life expectancy of at least 10 years based on age and co-morbidities but excluding diagnosis of breast cancer.

3.1.4 Must have pathology proven breast cancer. Pathology must be invasive ductal or lobular carcinoma of the breast.

3.1.5 Must meet stage II - III group criteria per AJCC Staging manual 7th edition (see appendix II).

3.1.6 Must have had surgical treatment of the breast – either mastectomy or breast preserving surgey, such as lumpectomy. Re-excision of surgical margins is permitted.

3.1.7 Note: Multicentric breast cancer and Paget's disease of the nipple are permitted.

3.2 Conditions for Ineligibility

3.2.1 Weight over 410 pounds.

3.2.2 Non-epithelial breast malignancies such as sarcoma or lymphoma.

3.2.3 Surgical margins that cannot be microscopically assessed or are positive at pathologic evaluation. (If surgical margins are rendered free of disease by re-excision, the patient is eligible).

3.2.4 Breast size exceeding the technical limitation of daily set-up reproducibility. This may be center-specific and will be assessed at the discretion of the treating center.

3.2.5 Women with post-surgical temporary breast expanders will require individual assessment. Depending on the manufacturing product and other treatment planning-specific details the patient may be eligible or may be deemed ineligible, as determined by treating investigator.

3.2.6 Prior history of breast cancer.

3.2.7 Prior radiation to the breast or thorax.

3.2.8 Collagen vascular disease, specifically dermatomyositis with a CPK level above normal or with an active skin rash, systemic lupus erythematosis, or scleroderma.

3.2.9 Pregnancy or lactation at the time of proposed study entry. Women of reproductive potential must agree to use an effective non-hormonal method of contraception during

therapy such as an intrauterine device or condom with spermicide. (Note: Women of childbearing potential must have a negative serum pregnancy test within 3 weeks of study registration).

3.2.10 Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements.

3.2.11 Prior history of non-breast malignancies unless they have been disease free for 5 or more years and are deemed by their physician to be at low risk for recurrence. Further, patients who have the following cancers treated within the prior 5 years are permitted: carcinoma in situ of the cervix, carcinoma in situ of the colon, melanoma in situ, basal cell or squamous cell carcinoma of the skin.

4.0 PATIENT ASSESSMENTS

4.1 Study Parameters

Assessments	Pre-Treatment	Weekly During RT	At 4-8 weeks following RT	Follow-Up 6 mos after RT completion, 1 year after RT completion then annually
History & Physical Exam (w breast exam) (w check for concomitant therapy)	X[b]	X	X	X
CTCAEv4 Adverse Event Assessment	X Baseline	X	X	X
Acute Skin Reaction Assessment		X	X	X (at 6 mos only)
Late Skin Toxicity Assessment				X
ECOG Performance	X		X	X
Height, Weight	X			
Pregnancy test (serum)	X[c]			
Mammogram	X			X Annually
Pathology Reports	X			
Operative Reports	X			
Coronary angiography CT-scan	X[d, e]			X[e] Once at year 5
Chest CT Scan without contrast for treatment planning	X[d]			
Cosmesis Form– (not for chest wall pts) (see SPM for details)	X			X
Photographs (see SPM for details)	X	X	X	X
Patient survey – QOL (see SPM for details)	X			X 6 months after RT completion, 1 year after RT completion then annually for 5 years.

a. H&P, x-rays, scans, and other testing may be performed more frequently according to physician preference and when symptoms suggest metastatic disease.
b. H&P within 4 months prior to study treatment.
c. Within 3 weeks prior to registration for women of childbearing potential.
d. As part of treatment planning imaging.
e. Strongly recommended, but not mandatory

4.2. Clinical Assessments: Standard of Care and additional investigations.

All proton radiation treatment will be provided according to the present standards of care in radiotherapy for breast cancer patients.

4.2.1 Patient Questionnaire and Cosmesis assessment

A questionnaire will be used to determine quality of life and to demonstrate visually the cosmetic outcome. Patients will not incur any added costs (mailing provided). Additional details may be found in the SPM.

4.2.2 Coronary angiography CT scan (strongly recommended, but not mandatory)

A diagnostic study in routine clinical use for the assessment of coronary artery stenosis. Coronary calcium scanning contributes significantly to the accuracy of CHD detection on top of traditional CV risk factors in asymptomatic women and coronary CT angiography has proven accurate for the diagnosis of significant CHD as well as cost effective in the evaluation of symptomatic women. [74]

Coronary angiography CT scan is invasive (i.v. injection of contrast material) and exposing the patient to added ionizing radiation (CT scan). It is routine clinical care for patients with pre-existing cardiac disorder or symptoms. In addition, it is routine clinical care in patients receiving combined modality therapy including cardiotoxic systemic substances (examples: anthracyclines, Herceptin).

Coronary artery CT scan as part of treatment planning (i.e. at pre-treatment): Acquisition of a coronary artery CT scan is currently not standard in the process of radiotherapy planning for women with breast cancer. However, one of the main rationales for performing proton radiotherapy is risk-reduction of radiation-induced coronary artery stenosis and CAD. Hence, appropriate imaging of coronary arteries as "OAR" is important to the overall study hypothesis and treatment rationale and treatment conduct. Pretreatment coronary artery CT scan should be an integral part of precision proton-radiotherapy for breast cancer. Although this presents a change in paradigm of required diagnostic imaging modalities, it is similar to the introduction of routine MRI fusion with planning CT scans for various high precision stereotactic or radio-surgical photon procedures. In summary, a coronary artery CT should be an integral part of proton radiotherapy for breast cancer patients.

Coronary artery CT scan at 5 years of follow-up: Routine clinical care for patients who developed coronary artery stenosis or symptoms of angina. It is not routine clinical care in patients without known cardiac disease and without cardiac symptoms. However, coronary artery CT scan can assess pre-clinical, asymptomatic coronary artery stenosis. Coronary artery CT scan at 5 years is voluntary.

4.3 Follow-Up Visits

Follow up visits are based on the last treatment day. For example, the first follow up visit is due 4-8 weeks after the last day of radiation treatment. Patients will be followed for survival unless the study is terminated by the Study Chair. It is highly recommended that patients will be seen in person by the treating investigator for all follow-up visits. If however subjects refuse or unable to return to the clinic they must be contacted by phone or email to obtain information needed for data collection. Collaborating medical records must also be obtained including records from other treating physician exams. Any failure to contact subjects for follow-up must be clearly documented in the source record.

4.4 Early Withdrawal of Subjects

Subjects should be withdrawn from the study prior to the expected completion of the study due to reasons outlined below.

4.4.1 When and How to Withdraw Subjects

Proton-Radiotherapy may be discontinued and the patient will continue standard irradiation with photons, for any of the following reasons:

- Unacceptable adverse events (at the discretion of the treating physician(s))
- Patient's withdrawal of consent.
- If at the start of the PT attempts fail to meet the quality standards of radiation treatment of proton therapy in terms of reproducibility of the patient set-up compared to treatment planning pre-set requirements. The patient's care will be immediately transferred to a photon based facility for photon therapy if appropriate. Follow-up assessments may be discontinued for any of the following reasons:
- Patient's withdrawal of consent.
- Patient lost to follow-up

5.0 REGISTRATION

5.1 PCG headquarters must have documentation of each institution's IRB approval of the protocol on file prior to registering patients.

5.2 Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

5.3 Verify the patient meets the eligibility criteria prior study enrollment and start of protocol therapy the patient. The protocol-specific eligibility checklist provided in the Study Procedures Manual (SPM) may be used to document eligibility and place in the participant's medical/research record. To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist and section 3 of this protocol.

5.4 Patients must be registered through the PCG Electronic Data Capture (EDC) system. Patients can be registered only after eligibility criteria are met.

5.5 Treatment plan reviews for the initial 3 cases from the institution will be centrally reviewed by a PCG Medical Physicist and the Study Chair or designee prior to start of treatment. *Further cases from the institution may also be reviewed periodically for quality assurance. See the Study Procedures Manual (SPM) for details.*

6.0 RADIATION THERAPY

As a minimum, a center has to be operational for at least 3 months prior to opening this study for its patients.

Breast size will likely in a subgroup of patients exceed the technical limitations of daily set-up reproducibility. This might be center-specific and will be assessed at the discretion of the treating center.

Women with post-surgical temporary breast expanders or permanent implants will require individual assessment. Depending on the manufacturing product and other treatment planning-specific details the patient may be eligible or may be deemed ineligible.

6.1 Dose Specifications

6.1.1 Mastectomy

Chest wall and regional lymph nodes (axilla levels I-III, supraclavicular): 45-50.4 Gy (RBE) in 25-28 fractions of 1.8 Gy (RBE).

Chest wall scar boost (optional): for a total cumulative dose of 61.2 Gy (RBE) in 1.8 Gy (RBE) per fraction.

With respect to undissected gross axillary apex, infraclavicular and/or supraclavicular node disease, a boost beyond 45-50.4 Gy (RBE) is recommended to a minimum of 54-55.8 Gy (RBE) in chemotherapy responsive disease up to 61.2-66.6 Gy(RBE) for persistently positive lymph node disease. The choice of final dose for these lymph node sites will be left to the discretion of the treating physician.

Internal mammary node chain (IMC) inclusion is recommended for all stage III patients: 45 - 50.4 Gy (RBE) in 25-28 fractions of 1.8 Gy (RBE). A minimum dose of 45 Gy (RBE) to the IMC is mandatory these cases.

In case of inclusion of internal mammary chain (IMC), a 3 level IMC total dose schema will be applied depending on pretreatment positivity of IMC nodes assessed by imaging studies as well as the responsiveness to chemotherapy, as follows:

a) Clinically negative IMC: no boost beyond 45-50.4 Gy (RBE)

b) Clinically positive IMC nodes pre-treatment with response to chemotherapy: boost to a total cumulative dose of 54 - 55.8 Gy (RBE) in 1.8 Gy (RBE) per fraction.

c) Clinically positive IMC nodes pre-treatment with persisting positivity post-chemotherapy: boost to a total cumulative dose of 61.2 - 66.6 Gy (RBE) in 1.8 Gy (RBE) per fraction. The study specifically recommends 61.2 Gy (RBE) as the minimum dose for this subset of patients, however allows a total of 66.6 Gy (RBE) to be used at the discretion of the treating physician.

The mastectomy scar boost should be done preferably with protons, but can be delivered with photons or electrons at the discretion of the treating physician. Photon or electron therapy techniques may be used for the boost dose component only. The total dose and fractionation regimen will be identical between photon and proton boost RT.

The boost dose plans and DVH for either photon or electron technique being contemplated for the boost should be compared to the proton boost plan and DVH before electing to proceed with a photon or electron boost. Photons or electrons can be used as long as there is no significant compromise in the overall sparing of normal tissues, such as heart, LAD and ipsilateral lung. If in doubt the principal investigator should be contacted.

Regional lymph node minimum dose requirements:
Any undissected lymph node region (axilla, infraclavicular, supraclavicular and/or IMC node) – whether post-lumpectomy or post-mastectomy, should receive a minimum dose within the following ranges:
a) 45.0 - 50.4 Gy (RBE) when clinical negative.
b) 54.0 - 55.8 Gy (RBE) in clinically positive but responsive to chemotherapy
c) 61.2 - 66.6 Gy (RBE) for persistently positive lymph node disease

These are levels are meant to determine the minimum doses.
The option to deliver a higher dose beyond these minimum ranges will be left to the discretion of the treating investigator as long as:

1) The total dose prescribed never exceeds 66.6 Gy (RBE) without individual case discussion with the study chair
2) Any organ at risk maximum dose constraint such as maximum dose to brachial plexus of 66 Gy (RBE) must be respected.

6.1.2 Breast Conserving Therapy

Whole breast and regional lymph nodes (axilla levels I-III, supraclavicular): 45-50.4 Gy (RBE) in 25-28 fractions of 1.8 Gy (RBE).

Lumpectomy tumor bed boost to a total cumulative dose of 61.2 - 66.6 Gy (RBE) in 1.8 Gy (RBE) per fraction. A lumpectomy boost dose of up to a total cumulative dose of 66.6 Gy (RBE) may be employed in patients with close or focally positive margins, at the discretion of the treating physician.

With respect to undissected gross axillary apex, infraclavicular and/or supraclavicular node disease, a boost beyond 45-50.4 Gy (RBE) is recommended to a minimum of 54-55.8 Gy (RBE) in chemotherapy responsive disease up to 61.2-66.6 Gy(RBE) for persistently positive lymph node disease. The choice of final dose for these lymph node sites will be left to the discretion of the treating physician.

Internal mammary node chain (IMC) inclusion is recommended for all stage III patients: 45 - 50.4 Gy (RBE) in 25-28 fractions of 1.8 Gy (RBE). A minimum dose of 45 Gy (RBE) to the IMC is mandatory for these cases.

In case of inclusion of internal mammary chain (IMC), a 3 level IMC total dose schema will be applied depending on pretreatment positivity of IMC nodes assessed by imaging studies as well as the responsiveness to chemotherapy, as follows:

a) Clinically negative IMC: no boost beyond 45-50.4 Gy (RBE)

b) Clinically positive IMC nodes pre-treatment with response to chemotherapy: boost to a total cumulative dose of 54 - 55.8 Gy (RBE) in 1.8 Gy (RBE) per fraction.

c) Clinically positive IMC nodes pre-treatment with persisting positivity post-chemotherapy: boost to a total cumulative dose of 61.2 - 66.6 Gy (RBE) in 1.8 Gy (RBE) per fraction. The study specifically recommends 61.2 Gy (RBE) as the minimum dose for this subset of patients, however allows a total of 66.6 Gy (RBE) to be used at the discretion of the treating physician.

Patients with breast conserving surgery without implanted clips at the lumpectomy cavity can receive the final boost to the lumpectomy cavity with proton, photons or electrons, but should preferably be boosted with protons at the discretion of the treating physician. Photon or electron therapy techniques may be used for the boost dose component only. The total dose and fractionation regimen will be identical between photon and proton boost RT.

Regional lymph node minimum dose requirements:

Any undissected lymph node region (axilla, infraclavicular, supraclavicular and/or IMC node) – whether post-lumpectomy or post-mastectomy, should receive a minimum dose within the following ranges:

a) 45.0 - 50.4 Gy (RBE) when clinical negative.
b) 54.0 - 55.8 Gy (RBE) in clinically positive but responsive to chemotherapy

c) 61.2 - 66.6 Gy (RBE) for persistently positive lymph node disease

These are levels are meant to determine the minimum doses.
The option to deliver a higher dose beyond these minimum ranges will be left to the discretion of the treating investigator as long as:
1) The total dose prescribed never exceeds 66.6 Gy (RBE) without individual case discussion with the study chair
2) Any organ at risk maximum dose constraint such as maximum dose to brachial plexus of 66 Gy (RBE) must be respected.

The boost dose plans and DVH for either photon or electron technique being contemplated for the boost should be compared to the proton boost plan and DVH before electing to proceed with a photon or electron boost. Photons or electrons can be used as long as there is no significant compromise in the overall sparing of normal tissues, such as heart, LAD and ipsilateral lung. If in doubt the principal investigator should be contacted.

6.2 Technical factors

6.2.1 Proton plans will be generated for treatment purposes. Photon plans will be generated for treatment comparisons only. Hence, it is not required for photon plans (3-D, IMRT, Tomotherapy plans) to be completed prior to start of therapy.

This protocol is designed to permit patient accrual at multiple proton centers. At present, there are several proton beam delivery systems in use. They can be divided in principle in passive scattering technology and active scanning technology – with several variations within these two groups. In addition, individual centers are presently undergoing technological innovation adaptation to introduce spot scanning technology.

All proton delivery systems in clinical use are permissible as long as treatment specifications are met. The specific delivery system will be recorded to permit adverse event analysis in relationship to equipment.

During the entire treatment and on maximally 3 occasions, it will be permitted to apply 3-4 fractions per week due to logistical or technical reasons. An interruption of treatment for > consecutive 5 days (including weekends) will be considered a minor violation. An interruption of treatment for >10 days will be considered a major violation. This specifically applies to logistical or technical reasons only. Interruption due to medical reasons will be recorded but will not be censored as violation. In case of interruption for more than 10 days one additional fraction of 1.8 Gy (RBE) will be added corresponding to the target at the time (entire field versus boost).

For the purpose of comparison one of 3 modalities, 3-D, IMRT or Tomotherapy plans, will also be generated for the initial 20 patients . There is no requirement to generate this comparison plan before accepting and treating a patient with protons on this protocol. The guidelines for IMRT comparison plan on this study will conform to the policies set by the Advanced Technology Consortium (ATC) and the National Cancer Institute (NCI) http//atc.wustl.edu/home/NCI/NCI_Guidelines.html.

6.2.2 Each of the target volumes and organs at risk (OAR) listed below must be delineated on every slice of the planning CT scan in which that structure exists.

6.3. Diagnostic imaging and treatment planning imaging for coronary artery contouring

This study may incorporate diagnostic imaging for optimal visualization of coronary arteries with routine chest Treatment Planning CT scan obtained at the time of simulation for treatment planning purposes.

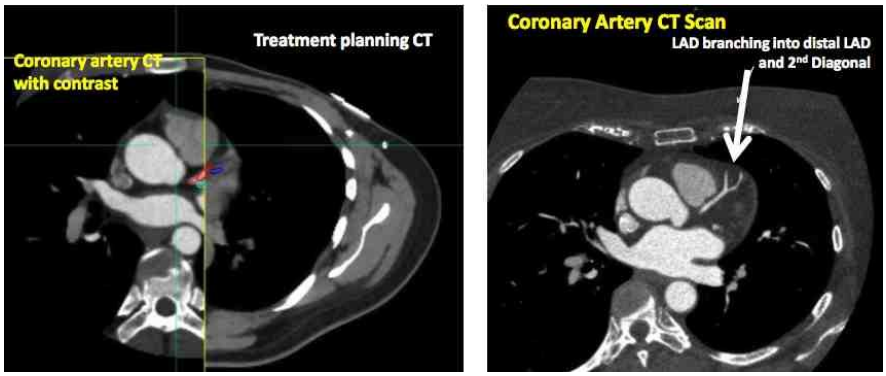
6.3.1 Conventional chest CT for treatment planning purposes without contrast

A conventional Chest-CT scan without contrast the proximal segments of the coronaries can generally be identified using slice thickness < 3mm: The proximal half of the RCA, left coronary artery and proximal LAD including the take-offs of D1 and D2 can be identified. However, the distal portions of the RCA and the LAD segments at highest risk for radiation damage, i.e., the distal segments of LAD towards the apex and the path of the diagonal branches are usually not readily identifiable or only with ambiguity. Hence, a conventional CT scan is in principle helpful but ultimately the resolution is insufficient to perform the task at hand. As surrogate for direct imaging of the coronaries, their known anatomic compartments can be identified. In case of the RCA, it is the right atrial-ventricular groove and in case of LAD the inter-ventricular groove. Both compartments are usually identifiable with or without contrast due to its fat content in contrast to the myocardium. However, the diagonal branches of the LAD (D1, D2) are in immediate contact and overlying the myocardium, without a specific "fat compartment" – thus cannot be indirectly identified. Treatment planning Chest CT with contrast are permissible, but will not replace the need for a Coronary Artery CT scan.

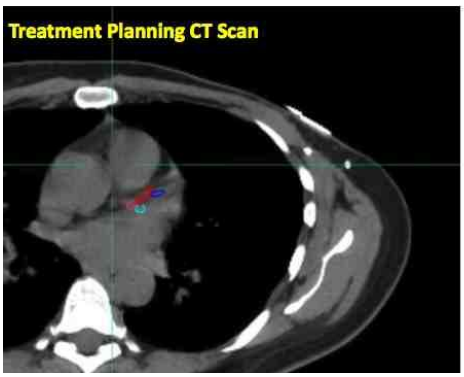
6.3.2 Coronary artery CT scan (strongly encouraged, but not mandatory)

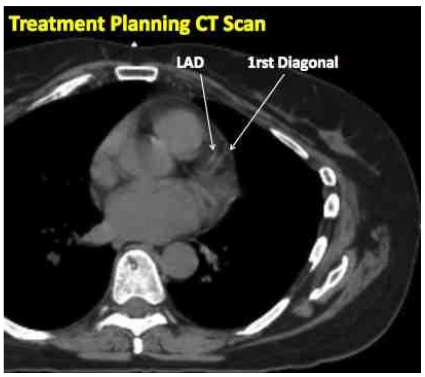
A dedicated, triple contrast cardiac CT or coronary artery CT scan is readily available in diagnostic radiology departments and routinely used by cardiologists for differential diagnosis. Coronary artery CT with fast image acquisition readily permits visualization of the coronary arteries including diagonal branches of the LAD and including the distal path of all coronaries. A coronary artery CT scan is presently the most suitable non-invasive modality to adequately image coronary arteries and their branches at risk for stenosis. The coronary artery CT scan can be readily fused with a planning CT scan. The advantage of the planning CT scan is that due to its relatively slow acquisition, it already "averages out" cardiac motion.

A diagnostic coronary artery CT scan as performed routinely in diagnostic departments can be reliably fused with the treatment planning CT scan. Coronary artery CT scan enables visualization of all blood vessels:

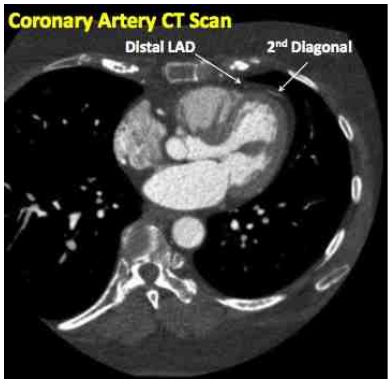


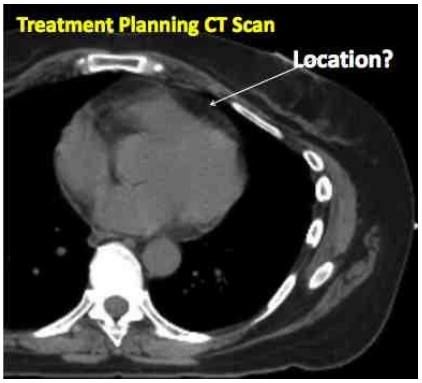
However, even a non-contrast treatment planning CT scan permits visualization and contouring of proximal coronary arteries:





Main advantage of a coronary artery CT scan is the visualization of distal segments of coronary arteries. Specifically distal segments of LAD and the 2nd diagonal branch are closest to chest wall, thus at highest risk of receiving significant radiation dose:





6.4 Localization, Simulation and Immobilization

6.4.1 Simulation and treatment will be performed in the supine position.

6.4.2 Patients should be optimally positioned with alpha cradle casts, breast boards, wing boards and / or other methods of immobilization at the discretion of the treating institution.

6.4.3 A treatment planning CT scan in the treatment position will be required to define the targets and normal structures. The recommended slice thickness is $\leq$ 2 mm. However, up to 3 mm slice thickness is acceptable. The CT scan should extend cephalad to start at or above the mandible. The caudal or inferior limit should be sufficiently extended beyond the infra-mammary fold to encompass the entire volume of both lungs.

6.4.4 Radio-opaque markers should be placed on external landmarks at the acquisition of the CT scan to facilitate contouring segmentation of the CT data-set. The markers are to be used for topographic anatomical reference and should identify:

1) The lumpectomy or mastectomy incision (scar)
2) The outline of the palpable breast tissue circumferentially at least from 2 o'clock to 10 o'clock.
3) The superior border of the breast tissue at 12 o'clock based on palpation. Additional markers to define the borders of "clinical" tangent fields (e.g. based on the palpable breast tissue and boney landmarks) may be helpful.

The choice of markers type should be carefully considered with efforts to minimize CT artifact. External skin localizing marks, which may include permanent tattoos, are recommended for radiation daily localization and set-up accuracy.

6.5 Treatment Planning / Target Volumes

6.5.1 The definitions for GTV, CTV, PTV and normal structures used in this protocol generally conform to the RTOG – endorsed consensus guidelines for delineation of target and normal structures for breast cancer. [75]

For proton therapy, dosimetric expansions lateral to the beam direction are necessary to account for internal motion, patient set-up errors, and the inherent errors of the patient alignment system. The expansion of a CTV to a PTV addresses this need lateral to the proton beam direction. Distal and proximal expansions on the CTV are necessary to account for range uncertainties characteristic to proton therapy.

Lateral expansions used to eliminate the possibility of a geometric miss are quantified in unit of physical distances while margins added distal and proximal, a result of range uncertainties, need to be added in units of water equivalent thicknesses (WET). For this reason, when using protons for treatment, the distal/proximal margin will not be equivalent to lateral margins. The generic concept of using a PTV to access appropriate target coverage is therefore not completely applicable in the case of proton therapy. This will be addressed in 6.6.1. For cross protocol documentation consistency, the PTV will be generated using standard methods of uniform expansions to the CTV, but will not be used to determine appropriateness of target coverage.

6.5.2 Target volumes and normal structures:

6.5.2.1 *Chest wall target volume definition (post-mastectomy):*

Chest Wall Gross Tumor Volume (GTV):

In general, a GTV is defined as any visible and/or palpable disease prior to start of radiotherapy defined by physical examination, computed tomography and ancillary imaging studies, for example magnetic resonance imaging, PET scanning etc. For this study no visible or palpable disease will be expected post-operatively on the chest wall. Any visible GTV in regional lymph node areas will be contoured per instructions in regional target definition (section 6.5.2.3).

Chest Wall Clinical Target Volume (CTV):

The CTV is meant to approximate the limits of the previous breast. Clinical reference markers should be taken into account to help define the cranial, caudal, medial and lateral extent.

The cranial extent will be defined by clinical reference plus the second rib insertion, while the caudal limit will be the theoretical infra-mammary breast fold using the contralateral breast as a clinical reference in addition to apparent loss of breast tissue/chest wall on CT scan. The anterior border will be defined as the skin surface. The posterior limit will be defined as the soft tissues anterior to the external border of the ribs and inter-coastal muscles. The lateral border will be defined by clinical means to include the previous breast, typically beyond the lateral edge of the pectoralis muscles but excluding the latissimus dorsi muscle. The medial border will be the costo-sternal junction and typically shall not cross midline. The entire mastectomy scar shall be included in case of mastectomy.

For the purpose of topographic clinical correlation, radiopaque markers defining the cranial, caudal, medial and lateral limits are encouraged. This scan with topographic markers can be acquired either immediately following or preceding the actual planning scan to avoid image artifacts created by the markers on the planning scan and then subsequently have both scans fused. Alternatively, one can opt to acquire the planning scan with the markers in place, at the discretion of the treating physician.

Chest Wall Planning Target Volume (PTV):
The PTV will be generated by expanding the CTVs uniformly by 7 mm. The PTV will be limited anteriorly and laterally by the skin surface.

6.5.2.2 *Whole Breast and Lumpectomy volume definition (post-lumpectomy):*

Whole Breast Clinical Tumor Volume (CTV):
The CTV of the whole breast will include all visible breast parenchyma seen on planning CT scan. The breast CTV will be limited to inside the skin surface. The posterior limit will be defined as the soft tissues anterior to the external border of the ribs and inter-coastal muscles. With the exception for this posterior limit definition, the breast CTV should otherwise follow the consensus guidelines.
Whole Breast Planning Target Volume (PTV):
Breast PTV: Breast CTV + 7 mm expansion (exclude heart and do not cross midline). After expansion, the volume extending outside of the skin surface must be edited to crop the PTV volume to the skin surface.
Lumpectomy Boost volumes (Seroma, CTV and PTV)
Lumpectomy Seroma:
Contour using all available clinical and radiographic information including the excision cavity volume, architectural distortion, lumpectomy scar, seroma and/or extent of surgical clips (clips are strongly recommended).
Lumpectomy CTV: Lumpectomy seroma + 1 cm 3D expansion.
The anterior and anterolateral limit of the CTV should be inside the skin surface. If after 3D expansion of the seroma to obtain the CTV, the CTV is extending into the ribs and/or intercostal muscle, the CTV should be cropped so that the posterior limit of the CTV will be the anterior aspect of the rib and/or intercostal muscle. The CTV should not cross midline.
Lumpectomy PTV: Lumpectomy CTV + 7 mm 3D expansion (excludes heart).
Analogous to the breast PTV, after expansion, the volume extending outside of the skin surface must be edited to crop the PTV volume to the skin surface.
Posteriorly, the volume will be cropped to the anterior limit of the ribs (excludes boney thorax and lung).

6.5.2.3 *Regional lymph node CTVs (selective inclusion of IMC in stage III):*
The regional lymph node contouring will follow the RTOG breast atlas which requires individual CTV delineation of the supraclavicular, axilla levels I, II and II, in addition to the internal mammary nodes (IMC). Obs.: The non-inclusion of one or more of lymph node CTV (sites/levels) will be at the discretion of the treating physician before the final CTV is expanded to generate the PTV. For example, patients who have had extensive level I-II axillary dissection will not necessarily need levels I-II included in the treating CTV. Similarly, a lateral quadrant tumor with 1 axillary lymph node involved would not necessarily need the IMN CTV included in the treatment volume.

The anatomic limits for each lymph node region are defined as follows:

Supraclavicular

- Cranial: caudal to the cricoid cartilage
- Caudal: junction of the brachiocephalic – axillary veins/caudal edge of the clavicle head
- Anterior: sternocleidomastoid muscle (SCM)
- Posterior: Anterior aspect of the scalene muscle
- Lateral: lateral edge of the sternocleidomastoid muscle and more caudally the junction of the 1st rib –clavicle
- Medial: Excludes esophagus, thyroid and trachea. Obs.: the following structures should be excluded from the supraclavicular PTV to minimize

excess dose to normal tissues: esophagus, ipsilateral thyroid, trachea, and ipsilateral lung. Therefore, some or all of the medial border of the CTV will be contoured in a way to avoid abutting or overlapping with those structures. Similarly, when expanding the CTV to generate the PTV, the CTV may not be able to be expanded medially.. As a consequence, the medial limits (borders) of the CTV and PTV will be similar in many cases. Cropping the PTV medially is another option to reach the end result. There is no defined preset distance gap between the esophagus wall and medial limits of the PTV, but a 5 – 10 mm separation will likely be required in many cases to minimize the esophagus dose exposure (and more closely resemble historical supraclavicular fields). Evidently, target coverage will always be prioritized, such as in patients with grossly positive supraclavicular nodal disease where maximum esophageal sparing may not be possible.

Axilla level I

- Cranial: axillary veins cross the lateral edge of the pectoralis minor muscle
- Caudal: pectoralis major muscle insert into ribs
- Anterior: plane defined by the anterior surface of the pectoralis major and the latissimus dorsi muscles
- Posterior: Anterior surface of the subscapularis muscle
- Lateral: Medial border of the latissimus dorsi muscle
- Medial: lateral border of the pectoralis minor muscle

Axilla level II

- Cranial: axillary veins cross the medial edge of the pectoralis minor muscle
- Caudal: axillary vessels cross the lateral edge of the pectoralis minor muscle
- Anterior: anterior surface of the pectoralis minor muscle
- Posterior: Ribs and intercostal muscles
- Lateral: lateral border of the pectoralis minor muscle
- Medial: medial border of the pectoralis minor muscle

Axilla level III

- Cranial: Pectoralis minor insert into cricoid
- Caudal: axillary veins cross the medial edge of the pectoralis minor muscle
- Anterior: posterior surface of the pectoralis major muscle
- Posterior: : Ribs and intercostal muscles
- Lateral: Medial border of the pectoralis minor muscle
- Medial: thoracic inlet

Internal mammary chain

- Cranial: Superior aspect of the medial 1st rib
- Caudal: cranial aspect of the 4th rib
- Anterior, posterior, lateral and medial should include the internal mammary / thoracic vessels.

Contouring comments:

Supraclavicular: caudal border meant to approximate the superior aspect on the breast/chest wall border

Axillary level I: Caudal border is clinically at the base of the anterior axillary line

Axillary level II: caudal border is the same as the cranial border of level I

Axillary level III: caudal border is the same as the cranial border of level II

Internal mammary lymph nodes: encompass the internal mammary /thoracic vessels

Regional Lymph Node PTV: Regional Lymph Node CTV + 7 mm expansion. After expansion, the PTV must be edited and cropped to the skin surface. Posteriorly, the volume will be cropped to the anterior limit of the ribs (excludes boney thorax and lung).

Obs.: the following structures should be excluded from the supraclavicular PTV to

minimize excess dose to normal tissues: esophagus, ipsilateral thyroid, trachea, and ipsilateral lung. In order to accomplish the goal of excluding these structures from any overlap with the target, some or all of the medial border of the PTV and CTV will be similar. The supraclavicular PTV should also exclude the vertebral body.

6.5.2.4 CTV Minus Skin

Once individual CTV's are defined as stated above, a combined CTV is to be created for treatment planning purposes. The combined CTV is the volumetric sum of all applicable CTV's but cropped by 5mm from the skin surface. This structure will be defined as CTV Minus Skin.

6.5.2.5 PTV Minus Skin

Once individual PTV's are defined as stated above, a combined PTV is to be created for treatment planning purposes. The combined PTV is the volumetric sum of all applicable PTV's but cropped by 5mm from the skin surface. This structure will be defined as PTV Minus Skin.

6.5.2.6 Normal structures contouring:

6.5.2.7 Contralateral breast

Refer to the contouring atlas

6.5.2.8 Ipsilateral lung

May be contoured with auto-segmentation with manual verification

6.5.2.9 Contralateral lung

May be contoured with auto-segmentation with manual verification

6.5.2.10 Heart including Coronary Arteries

Heart:

The heart shall be contoured beginning just inferior to the level in which the pulmonary trunk branches into the left and right pulmonary arteries (PA). Above the PA, none of the heart's 4 chambers are present. All the mediastinal tissue below this level should be contoured, including the great vessels (ascending and descending aorta, inferior vena cava) and defined as "heart". The heart should be contoured on every contiguous slice thereafter to its inferior most extent near the diaphragm. If one can identify the esophagus, this structure should be excluded from the heart. One does not need to include the pericardial fat, if present. Contouring along the pericardium itself, when visible, is appropriate.

Coronary Arteries:

This study defines the coronary arteries as "organs at risk (OAR's). The coronary arteries will be *contoured* individually following fusion of appropriate diagnostic imaging (coronary artery CT scan) with the planning CT-scan, and will be an integral part of the treatment planning process. Alternatively, if a coronary artery CT scan cannot be obtained, a standard coronary artery CT scan will be fused with the treatment planning CT scan. Typically, on a non-contrast treatment planning CT scan the proximal portions of coronary arteries can be readily identified and contoured. The distal portions will be contoured by extrapolating the fused standard coronary artery CT scan.

The heart has three main coronary arteries (see normal coronary artery anatomy, Appendix IV): The left main or left coronary artery (LCA), which branches immediately after origin into the left anterior descending (LAD) artery as well as the circumflex coronary artery (Cx). A third branch is the right coronary artery (RCA).

The RCA shall be contoured from its origins to its distal end. The segments at highest risk of radiation damage are the proximal segments of the RCA. LCA as well as LAD shall be contoured including the 2 diagonal branches (D1, D2) of the LAD which

provide blood supply to the lateral portions of the left ventricle, i.e., the anterolateral heart. At highest risks are the distal segments of LAD including apex of the heart and the second diagonal branch. Whenever a third diagonal branch of the LAD (D3) is visible it should be contoured. (For details see Appendix XX, Atlas of sequential, axial CT images providing guidelines for outlining the RCA, Cx, LCA, LAD, D1, D2 and D3).

All patients will have a diagnostic coronary angiography CT prior to start of proton therapy. This scan will be fused with the planning CT scan and coronary arteries will be delineated as OAR accordingly.

6.5.2.11 Other Structures to be contoured on planning CT scan:

- Thyroid
- Esophagus
- Brachial Plexus
- Skin: The skin will be defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head).

6.6 Dose specifications

6.6.1 CTV Minus Skin

In proton delivery, treatment to PTV expansions may not adequately ensure appropriate target coverage or may over treat areas of healthy tissue where dose is not necessary. In directions perpendicular to a treatment beam, the PTV can be used as an aid to design aperture margins. In the directions distal and proximal to the target, margins to the CTV for proton range uncertainties should be used to define the necessary margins.

With these concepts in mind, it is up to the treating institution to ensure that a method is in place to ensure appropriate coverage of the CTV Minus Skin in conditions of potential set-up errors AND potential range errors. This can be accomplished by through several methods including: 1) optimizing fields to PTV perpendicular to the beam direction and to the CTV distally, then adding distal and proximal margins as needed as a function of individual field ranges, 2) performing robustness analysis, or 3) including robustness into the cost function of an inverse planned treatment. The choice of the method is up to the treating institution and may be dictated by the treatment delivery method (PBS, vs. non-PBS).

Appropriate dose coverage is evaluated under conditions of minimum possible dose to the CTV Minus Skin when considering set-up errors and range uncertainties.

CTV Minus Skin (Also applicable for Boost CTV's)

≥ 95% of the CTV Minus Skin should receive 100% of the prescribed dose.

≥ 90% of the CTV Minus Skin receiving 100% of the prescribed dose will be acceptable.

Minimum Dose to CTV Minus Skin

≥ than 99% of the CTV Minus Skin shall receive >95% of the prescribed dose.

Maximum CTV Minus Skin dose:

The maximum dose should be ≤ 115% of the prescribed dose to ≤ 1 cc volume. A maximum dose of ≤ 120% of the prescribed dose to ≤ 1 cc volume will be acceptable.

6.6.2 PTV Minus Skin will be recorded to maintain a baseline consistency with comparative photon protocols. If appropriate measure have been taken to ensure compliance with CTV Minus Skin dose constraints, PTV Minus Skin target dose should be easily achieved without additional adjustment to the plan.

PTV Minus Skin (Also applicable for Boost PTV's)

≥ 95% of the PTV Minus Skin should receive ≥ 95% of the prescribed dose. ≥ 90% of the PTV Minus Skin receiving ≥ 90% of the prescribed dose will be acceptable.

Maximum PTV dose:

The maximum dose should be ≤ 115% of the prescribed dose to ≤ 1 cc volume. A maximum dose of ≤ 120% of the prescribed dose to ≤ 1 cc volume will be acceptable.

6.6.3 Dose Volume Constraints for Normal Tissues

6.6.3.1 The dose to the following normal tissues will be recorded and analyzed but no individual dose volume constraints will be assigned:

Coronary arteries: (See Appendix IV)
RCA
LAD
1st and 2nd Diagonal branch of LAD
Thyroid
Esophagus

6.6.3.2 Heart

It is anticipated that proton therapy will significantly reduce exposure of the heart and the Coronary arteries: RCA, LAD, 1st and 2nd Diagonal branch of LAD (See Appendix IV). Efforts will be made to reduce the dose to the heart and coronaries both in the lower dose range of 5 Gy (V5) and higher dose range of 20 Gy (V20) or higher. The maximum dose to 1% volume (Gy) to the heart and coronaries will be documented.

6.6.3.3 Ipsilateral Lung

Ipsilateral lung volume receiving 20 Gy (V20) shall be limited to ≤ 33% of the lung volume whenever possible.

In addition, smaller dose partial volumes will be evaluated. The ipsilateral lung volume receiving 5 Gy (V5) should also be minimized preferably to ≤ 42% of the lung.

6.6.3.4 Contralateral Lung

The contralateral lung volume receiving a dose of 5 Gy (V5) should be ≤ 10% of the lung volume.

6.6.3.5 Contralateral Breast

Efforts will be made to minimize the dose to the contralateral breast whenever feasible without compromising target coverage and cardiac structure sparing. The mean doses as well as various partial volume dose ranges will be tracked.

6.6.3.6 Brachial Plexus:

The maximum point dose to the brachial plexus should not exceed 66 Gy(RBE).

6.7 Treatment Planning

Proton Treatment plans shall be performed on the treatment planning CT. The images used for proton planning shall come from CT scanner with a device specific calibration to convert Hounsfield Units to the appropriate parameters required by the planning system. The procedure and verification of the accuracy of the imaging and planning system are at the discretion of the participating institution.

Field arrangements for comparison plans (3D, IMRT or Tomotherapy) are at the discretion of the treating physician. Multiple beam arrangements are to be designed during the comparison treatment planning process to produce an optimal comparative plan that meets the dose-volume constraints of the study.

Field Selection for Proton Plans

The beam arrangement, and number of beams shall be chosen at the discretion of the participating institution as long as the necessary dose volume constraints mentioned above can be met. In preliminary feasibility studies using uniform scanning as a treatment delivery method, this typically included two daily fields for the breast/chest wall region, matched to two daily fields to the axilla, nodal region. Due to the large area being treated, matched fields may be required. If matched fields are used, at least two match lines are required to minimize uncertainty in the matched area and to decrease hot or cold spot at the match.

Typical field arrangements may include:

Breast / Chest wall:

(2) enface proton fields.
Gantry angles:
Left Medial Anterior Oblique: ~15 to 30 degrees to the lateral from vertical
Left Lateral Anterior Oblique: ~15 to 30 degrees anterior to lateral
Include the Chestwall / breast CTV and IMN

Supraclavicular / Axilla:

(2) enface proton fields.
Gantry angles:
Left Medial Anterior Oblique: ~15 to 30 degrees to the Lt lateral from vertical
Right Medial Anterior Oblique ~15 to 30 degrees to the Rt lateral from vertical

Distal range modifications to conform the distal edge of the proton dose to the target regions may be done in the form of field specific compensators or energy stacking with spots. Appropriate techniques shall be used to compensate for situations of non-ideal patient alignment and minor patient motions. This method is often termed "smearing" of the distal edge. Smearing distances shall be set to a value at least as large as the PTV expansion, or 7mm. If the participating institution's planning system does not include the option for adding smearing, alternative methods to account for set-up errors and motion may be used.

6.8 Method of Assigning Subjects to Treatment Groups

All subjects will receive the same treatment. The study objective is to demonstrate the feasibility and long-term outcomes of proton radiotherapy. No control group will be used. The rates of acute and late toxicity will be compared with published results.

6.9 Timing of Radiotherapy

The day 1 of the study will be the first day of delivered radiotherapy. The study strongly encourages the start of proton therapy < 12 weeks after the last surgery (including re-excision) or last chemotherapy cycle.

6.10 Patient positioning and Immobilization

Patients shall be treated in the supine position using the identical immobilization method and devices used during the treatment planning CT simulation.

6.10.1 Determining reproducibility of daily positioning

Accurate daily positioning of the patient is essential for accurate treatment delivery. The participating institution shall use their preferred method of localization to optimize reproducibility of daily positioning. The preferred method should include considerations such as accuracy, patient comfort, acquisition time, and radiation dose.

PTV expansions of 7mm are added to CTV targets to account for patient motion and patient set-up errors. The positioning systems shall be used to ensure this expansion is appropriate.

6.10.2 Organ Motion Management

The field arrangement used to treat patients with proton portals will be primarily perpendicular to the chest wall excursion. Previous studies have demonstrated that proton plans based on a perpendicular approach are much less sensitive to the breathing motion.

There are several devices that are commercially available to monitor patient motion or validate the respiratory cycle motion (i.e. Vision RT, C-Rad). There are also several methods minimize the effects of respiratory motion during beam delivery such as beam gating or breath hold. Such systems or methods may be used to further limit the effects of organ motion at the discretion of the participating institution.

6.10.3 Patient Specific Treatment Verification

It is expected that each participating institution will have a through Quality Assurance program in place to verify that the planned dose will be identical to delivered dose from the proton source, within some institutional specific tolerance. Each center shall use their standard QA procedures for patient specific fields. These procedures may contain such tests as absolute field dose output, portal shape accuracy, compensator design accuracy, spot pattern position and intensity accuracy.

6.11 Dose Calculation and Reporting

D95% CTV Minus Skin (Dose received by 95% of the CTV Minus Skin) reported under conditions of the minimum possible dose to the CTV Minus Skin when considering set-up errors and range uncertainties.

D99% CTV Minus Skin (Dose received by 99% of the CTV Minus Skin) reported under conditions of the minimum possible dose to the CTV Minus Skin when considering set-up errors and range uncertainties.

D(1.0cc) CTV Minus Skin (Maximum Dose to 1.0cc of CTV Minus Skin) reported under conditions of the minimum possible dose to the CTV Minus Skin when considering set-up errors and range uncertainties.

D95% PTV Minus Skin (Dose received by 95% of the PTV Minus Skin) of the delivered plan

D90% PTV Minus Skin (Dose received by 90% of the PTV Minus Skin) of the delivered plan

D(1.0cc) PTV Minus Skin (Maximum Dose to 1.0cc of PTV Minus Skin) of the delivered plan

These should be derived from Dose Volume Histograms.

The maximum and mean doses as well as the defined previously dose volume constraints to all critical organs indicated in Section 6.5 shall be calculated and reported. Dose Volume Histograms for all critical organs shall be submitted. In addition, for the whole treatment, the volume of an organ (in cc) receiving a dose greater than the constraint shall also be reported.

6.12 Quality Assurance Documentation

Within six weeks of the end of radiotherapy, the following documentation shall be filed in the patient's medical record:

- A completed and signed 'Clinical treatment summary' form, summarizing the prescription and delivered doses for the whole proton treatment.
- A copy of the patient's radiotherapy record including the prescription, and daily and cumulative doses to all required areas and reference points.
- Weekly photographs of the patient to be taken during the on treatment visit for documentation of acute effects and subsequent correlation with cosmesis.

6.13 Radiation Toxicity

The Common Toxicity Criteria for Adverse Events (CTCAE) v4.0 from the National Cancer Institute (NCI) will be used for toxicity grading. In addition a separate Acute Skin Reaction Assessment and the Late Skin Toxicity Assessment will be used for assessing skin reactions. All patients will be seen weekly by the radiation oncologist during radiation therapy. See appendix III for further details.

7.0 DRUG THERAPY

Chemotherapy and other systemic therapy may be done at the discretion of treating institution. Neo-adjuvant chemotherapy is allowed.

8.0 SURGERY

Surgical tumor removal is not specific part of this trial, but standard of care is considered routine clinical care for this patient subgroup. All the patients will enter this trial following surgery. The following, general routine clinical care must have been met in order to permit study inclusion.

8.1 Surgical Removal of the Primary Tumor

Surgical treatment of the breast must have been a mastectomy or lumpectomy with sentinel lymph node biopsy and / or axillary dissection, at the discretion of the treating institution. The margins of the resected specimen must be histologically free of tumor. Re-excision of surgical margins is permitted.

8.2 Operative reports

All detailed operative reports must be included in the patient's file and applicable information reported in the electronic CRF.

9.0 OTHER THERAPY

Permitted supportive therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication. These therapies

include physical therapy, rehabilitation and medication, e.g. steroids, anti-emetics, anticoagulants, anti-diarrheal, analgesics, hematopoietic growth factors and nutritional supplementation.

10.0 PATHOLOGY

A detailed pathology report must be included in the patient's source record and applicable information will be collected on the case reports form.

11.0 DATA COLLECTION

Patients must be registered/enrolled through the PCG Electronic Data Capture (EDC) system. All required study information will be entered and verified in the EDC system. Detailed guidelines for patient study entry and electronic case form (eCRF) completion can be found in the Study Procedures Manual. Timelines for data submission must be followed closely in order to assure human subject safety.

The PI must make study data accessible to the PCG Study Monitor, to other authorized representatives of the study chair, and to the appropriate regulatory authority inspectors. The data in the EDC will be checked against source documents at the study site by the Study Monitor on a periodic basis based on the PCG Headquarters Monitoring Plan.

12.0 STATISTICAL CONSIDERATIONS

12.1 General considerations

It is the goal of this study to provide proton therapy today to subgroup of women with breast cancer at significant risk of developing radiation induced late adverse events, i.e. clinically symptomatic side effects from irradiation of non-target, normal tissues. All pre-clinical, treatment planning comparisons indicate a decrease or essentially elimination of normal tissue irradiation by use of protons. Organs and tissues can only develop radiation damage when they receive radiation dose. Most radiation damages are non-stochastic, i.e. the risk of damage increases with increasing dose. Consequently, reduced radiation dose will decrease this risk. This is a well-established fact and paradigm of radiation oncology. Aim of this study is to collect these important data in a prospective, long-term study design.

The three major components of any cancer therapy are disease control, survival, and reduction in complications, i.e. side effects or adverse events, related to therapy.

12.2 Disease control and survival

The present study design exchanges external beam radiotherapy, based on photons or a combination of photons and electrons with proton therapy. Target volume definition (CTV, GTV), total dose delivered and dose per fraction will remain identical to the presently recommended standard of care for Stage II and III breast cancer patients. Hence, we expect a disease outcome similar to results achieved by use of external, non-proton radiotherapy. The concept of use of proton therapy in lieu of photon therapy while maintaining identical therapy prescription has been in routine clinical practice for about 2 decades – most notably in prostate cancer and pediatric malignancies. There has not been a single report that would question the validity of this concept or would provide data to the contrary. In summary, this study does incorporate disease-control related parameters and shall report results based on those endpoints. However, it is not the goal of this study to demonstrate superior disease control by proton therapy. Disease control parameters will be collect prospectively and results will be compared with published multi-center external beam RT trials.

Treatment failure and survival, time to local and regional failure, time to distant metastasis and specific and overall survival will be documented. Events will be calculated from the first day of PT.

The definition of treatment failure is histological evidence of recurrent carcinoma, either invasive or non-invasive (except LCIS) in the ipsilateral breast. Clinical evidence of carcinoma by physical examination and/or mammograms will not be construed as evidence of treatment failure without biopsy proof but will be considered as suspicious for recurrence and the date of failure will be determined as the first documented clinical indication of recurrence (backdated). Ipsilateral breast recurrences will be considered local (infield) if they occur within the prescription isodose volume; they will be considered peripheral if they occur between the prescription isodose volume and a volume 2 cm outside of the prescription isodose volume. Ipsilateral recurrences will be considered non-contiguous or extra field if they are beyond the peripheral volume described above.
Clinical evidence of ipsilateral axillary, infra-clavicular, internal mammary or supraclavicular recurrences will be considered as suspicious for recurrence, and confirmed histologically if feasible. Distant metastases will not be considered a treatment failure unless accompanied by ipsilateral breast or regional recurrence.

12.3 Primary Endpoint

Determination of the rates of acute and late toxicities (acute and late adverse events as defined in 12.5 and 12.6) resulting from proton therapy radiation treatment.

12.4 Exploratory Endpoints

12.4.1. Compare dosimetrically the dose volume histogram of the PT plans with conventional external beam plans (either photon/electron IMRT plans, 3D-photon plans, or Tomotherapy plans).

12.4.2. Incidence rates of local control, regional control, metastatic status and disease free overall survival.

12.4.3. Compare the different dose volume histogram (DVH) parameters for the targets (D2, Dmean, Dmin, D95, V95, V110) and different OARs (as described later) of the PT plans with the corresponding values of the 3D-CRT, IMRT and Tomotherapy plans.

12.4.4 Determine dose distribution of proton therapy to coronary arteries, heart, ipsilateral and contralateral lung, and contralateral breast.

12.4.5 Determine the incidence of clinically symptomatic coronary artery disease, cardiac morbidity and mortality in general and incidence of secondary malignancy, including contralateral breast cancer.

12.4.6 Evaluate quality of life results.

12.5 Acute adverse events

It is a goal of the study to determine acute toxicities after PT. It is anticipated that PT-induced toxicities occur overall with less frequency and severity compared to photon-based radiotherapy – or in the case of skin toxicity at least not with increased severity. No proton-specific toxicities are anticipated.

However, it is recognized and well known fact, that temporary expanders can be a source of increased acute side effects of skin or subcutaneous soft tissues. Patients with temporary expanders in place will be censored according to their side effects, but will be analyzed separately. They will not be part of the patients assessed for early toxicity assessment of proton therapy. Patients with permanent implants placed at the time of mastectomy are eligible for the protocol and cosmesis and adverse events.

Assessment of objective parameters of status of skin and subcutaneous tissues (serial photos) as well as of subjective parameters (symptoms, quality of life questionnaire) will be used to quantify acute adverse event endpoints. Repeat cosmetic evaluation will be performed by the radiation oncologist and the patient using established RTOG criteria at regular intervals, i.e., using standard questionnaires and photographs.

In contrast to photons, protons by and large lack the initial dose "build up" characteristic of megavoltage photon irradiation. A higher degree of skin erythema can be observed in clinical practice if a single proton field is used "en face" compared to an equivalent photon field.

In purposely conservative consideration of this uncertainty an assessment of acute skin toxicity will be performed early in this trial.

12.6 Late adverse events.

It is a goal of the study to determine late toxicities after PT. It is anticipated that PT-induced toxicities occur with less frequency and severity compared to photon-based Radiotherapy – or in the case of skin toxicity at least not with increased severity. No proton-specific late toxicities are anticipated.

The endpoints for late adverse events, i.e. adverse events requiring a minimum of 5 years, but likely even 10 or more years to be clinically expressed, are primarily cardiac morbidity, cardiac mortality, and second malignant neoplasm.

There is no conceivable reason to assume that a reduced radiation dose by proton radiation will result in an increased risk of late events. No incident has ever been reported in the literature after more than 70,000 patients have been treated worldwide with proton therapy for more than 3 decades. Rather to the contrary, i.e. reduced radiation dose to normal tissues by use of protons has consistently led to decreased rates and severities of adverse events. Hence, the study is designed to primarily collect prospectively endpoint results on late toxicity incidence and severity (cardiac morbidity and mortality, second malignancy, pulmonary morbidity, cosmetic and functional outcome, and QOL impairment).

12.7 Patient Accrual

Approx. 230,000 women are diagnosed with breast cancer each year in the US http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-030975.pdf. Approx. 33% of newly diagnosed patients are categorized as having regional disease -stage II-III (75,900 patients). Hence, the annual incidence number of newly diagnosed breast cancer patients in the US potentially eligible for this study is 75,900 women.

Patient Accrual Assumptions: At a minimum the study will be open at 3 Proton Therapy Centers in late 2012 and 4 Centers by July 2013.

Conservatively 1-2 patients are estimated to be referred to each Center per month. Assuming a 50% accrual rate and realistic assumptions of "ramp-up" time for this protocol, we estimate 1 patient per 1-2 months per center to be accrued into the protocol. Anticipating opening of the protocol in the fall of 2012, this results in accrual estimates of:

Q4 '12 – Q2 '13: 12 patients
Q3-Q4 '13: 18 patients
Q1 '14 – end of study: 12 x 4 /year = 48 patients / year.

12.8 Sample Size and Study duration

The study is designed to detect a 10% difference in the cardiac morbidity- and cardiac mortality- free survival rate between the experimental group treated and the historical control survival of 75% at 10 years, with a significance level of $\alpha = .05$ and a statistical power of 0.80. A one-sided binomial test will be used to investigate the primary endpoint of FFF. Thus, a total of 145 patients are required for accrual within 5 years for a 80% power and a 95% level of significance. Considering 50% attrition due to patients' ineligibility, lacking data, or lost to follow-up, the total sample size needed is 218 patients. A total of 220 patients will be allocated to the study. The experimental group is defined as patients being treated with proton therapy for left-sided breast cancer. Right-sided breast cancer patients are permitted on this study but do not count towards the number of patients required for accrual. The majority of patients (estimated 90%) are projected to be accrued with left-sided breast cancer.

The ability of the present study design based on proton therapy to compare incidence and severity of late adverse events with conventional photon therapy is limited. The incidence of cardiac mortality, cardiac morbidity, and of second malignancy induction following conventional external beam therapy is presently not sufficiently defined for this subgroup of patients, but additional data are expected to emerge within the next years as studies mature. None of the large, multicenter cooperative group trials involving large patient numbers have provided sufficient data to determine the disease stage-adjusted expected incidence of cardiac morbidity for this high-risk patient cohort. Recent publications based on patients treated at University of Pennsylvania and at the Mofitt Cancer Center suggest a differential in incidence rate at 10 years of approx.. 10% and at 15 years of approx. 15% in cardiac morbidity for left-sided versus right-sided breast cancer following radiotherapy. However, these patient cohorts included in majority Stage II patients. We expect to accrue in the majority Stage III patients and patients referred specifically for protons due to inability of photon therapy to reduce cardiac dose .

In summary, it is presently difficult to accurately define a "disease stage adjusted "historic control group incidence rate" after conventional therapy, against which proton therapy data could be compared with. We believe that our assumptions are conservative. In addition,, it is expected that during the course of this study, one or several breast cancer research institutions and multicenter cooperative groups worldwide will analyze their long-term data retrospectively or prospectively. It is anticipated that results on the long term incidence of these endpoints will become more detailed. At such time, the trial specifications of our study duration and patient number enrollment shall be reevaluated based on calculated expectations of adverse event reduction by protons compared to the then available results on incidence and severity following conventional external beam therapy.

12.9 Early Stopping of Study Due to Grade 3 or Higher SAE of Skin Toxicity

It is expected that at most 20% of patients will experience a grade 3 or higher severe adverse event of the skin, defined as confluent, moist desquamation, pitting edema, ulceration, hemorrhage, or necrosis. The study will not be continued if 50% or greater grade 3 or higher severe adverse events are seen in the first 20 patients treated. The null hypothesis (H_0) is that the regimen is not safe versus the alternative hypothesis (H_A) that the regimen is safe. Let p denote the proportion of patients who have not experienced a grade 3 or higher severe adverse event among the first 20 analyzable patients (patients who received proton therapy treatment). The hypotheses are therefore:

$$H_0: p \leq 0.50 \text{ vs. } H_A: p \geq 0.80$$

Based on the above hypotheses, the sample size was initially calculated with Fleming's One Sample Multiple Testing Procedure for Phase II Clinical Trials (1981), at a significance level of 0.05 and 80% statistical power. Using these criteria, a sample size of 15 would be needed to adequately assess acute skin toxicity. However, Fleming's design, based on the normal approximation, could be misleading and result in larger than planned alpha levels and lower power when small sample sizes are computed. Therefore, additional confirmatory computations were made using an exact binomial distribution (A'Hern, 2001), and returned a sample size of 18. The sample size of 18 was adjusted for attrition or unanalyzable cases by 10%; a sample size of 20 patients would be required for adequate assessment of SAE skin toxicity. Patient assessment for instances of grade 3 or higher skin toxicities will be performed at each RT session, and at 4 and 8 weeks following RT. If a patient has indications of grade 3 or higher skin toxicity, reporting of the adverse event will be performed according to the criteria set forth in Appendix III. Although a patient may have more than one reported occurrence of skin toxicity during treatment, the patient will be counted only once as having the SAE of skin toxicity for measurement of SAE as relates to early stopping of the study. The study will be discontinued if a total of 13 patients show indications of grade 3 or higher skin toxicity.

12.10 Statistical and Analytical Plan

An initial analysis will be performed after 20 patients have been treated to judge acute toxicity (primarily skin and soft tissue toxicity). A second, interim analysis will be performed to judge early-late (primarily skin and soft-tissue) toxicity incidence and severity once 20 patients have been followed for a minimum of 1 year after completion of proton therapy.

Subsequent analyses will be performed at mean follow up of 36 months and 60 months for the entire cohort to estimate rates of tumor- and disease control and early- late toxicities. Analysis of late effect endpoints will occur at mean follow-up of 15 years

12.10.1 Primary Analyses

To determine the rates of acute and late toxicity, toxicities resulting from radiation treatment will be collected and graded. Descriptive measures using frequency and percentages of acute toxicity data will be compiled. Determination of the rate of incidence of cardiac mortality, morbidity, and second malignant neoplasms with historical control percentages at interim and final analyses will be performed with one sample binomial tests.

12.10.2 Exploratory Analyses

a) To compare dosimetrically the dose volume histogram of the PT plans with conventional external beam plans (3D, IMRT and/or Tomotherapy plans) for the initial 20 patients enrolled. A comparison of the different dose volume parameters will be performed using contingency tables.

b) Local control, regional control and metastatic status of the photon therapy patients will be reported as percentages. Disease-free and overall survival will be analyzed using actuarial life tables and Kaplan Meier analysis.

c) All the different dose volume histogram (DVH) parameters for the targets (D2, Dmean, Dmin, D95, V95, V110) and different OARs (as described later) of the PT plans will be analyzed and compared with the corresponding values of the 3D-CRT, IMRT and/or Tomotherapy plans. Analysis will be performed according to the pre-clinical analysis performed. An estimation of NTCP with the different plans will be calculated, to evaluate the potential benefits of protons in the patient cohort. Correlation study has no influence on the accrual of patient numbers or duration of study.

12.11 Handling of Missing Data

Patients withdrawing consent prior to the end of treatment will be excluded from the analysis for feasibility . Dropouts during the follow up phase will be analyzed up to the date the last information was available and not replaced.

12.12 Handling of Missing Data

In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and racial/ethnic minorities in clinical research, we will include patients of any racial/ethnic minority in our study. However, given that the majority of breast cancers involve women, patients for this study will be female. Based on previous accrual statistics, we project that 81% of the women in the study will be white, 15% black or African American, 3% Hispanic, 0.5% Asian, 0.3% Pacific Islander, and 0.2% American Indian or Alaskan Native.

13.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

This study is to be conducted according to the applicable international standards of Good Clinical Practice (GCP) (International Conference on Harmonization guidelines), the current version of the Declaration of Helsinki, and applicable NIH requirements.

This study will be conducted in full compliance with the Institutional Review Board regulations in 21 CFR 56. This study will be conducted in full compliance with the informed consent regulations in 21 CFR 50. Only staff members who have completed approved human subject protection training will obtain informed consent from the study participants.

Written informed consent and authorization of use and disclosure of PHI (as applicable in the US) must be obtained from each patient before performing any Screening/Baseline evaluations that are specifically study related (outside the scope of routine care). One copy of the signed informed consent document and authorization will be given to the patient, and the investigative site will retain the original document. (If original consent is electronically saved it must be a verified copy of the original). The consent document must contain the 20 elements of informed consent described in ICH E6 4.8. The authorization for use and disclosure of PHI must contain the elements required by 45 CFR 164.508(b) for valid authorizations.

13.1 Study Data Storage and Confidentiality

Raw and collected research data will be stored in locked cabinets at all times. If electronic forms are used they are kept in a password protected form. Electronic data will be in compliance with FDA CFR Title 21 Part 11.

No study documents will be destroyed without prior written approval from the sponsor. If the site investigator relocates, retires, or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed-upon designee, such as another investigator or the institution where the study was conducted.

All information regarding the nature of the proposed investigation provided by the study chair to the investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the patient, or the appropriate regulatory authority) must be kept in confidence by the investigator.

The anonymity of participating patients must be maintained. Patients will be identified by their initials and assigned patient numbers in CRFs and other documents submitted off site. Documents that will not be submitted off site and that identify the patient (e.g., the signed informed consent document) must be maintained in strict confidence by the

investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the CRA, or sponsor representatives.

13.2 Risk Benefit Assessment

By definition this study is determined as greater than minimal risk. Patients treated in the protocol will have the potential benefit of treatment with state of the art technologies and thorough treatment quality assurance that is not available in common clinical practice. The risks of the treatment or the acute or long term side effects with this technology (proton therapy) and thorough quality treatment assurance should be lower than with conventional treatment as delivered with photon radiation in common clinical practice. However, a data safety monitoring board will review the potential harmful effects of the treatment and stopping rules are in place in the protocol.

APPENDIX I

ECOG PERFORMANCE SCALE

0 Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100).

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).

3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).

4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).

5 Dead.

APPENDIX II

AJCC STAGING SYSTEM- BREAST, 7TH EDITION

Primary Tumor (T) , Clinical and Pathological

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
Tis (DCIS)	Ductal carcinoma *in situ*
Tis (LCIS)	Lobular carcinoma *in situ*
Tis (Paget's)	Paget's disease of the nipple is NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted
T1	Tumor </= 20 mm in greatest dimension
T1mi	Tumor </= 1 mm in greatest dimension
T1a	Tumor >1 mm but </= 5 mm in greatest dimension
T1b	Tumor >5 mm but </= 10 mm in greatest dimension
T1c	Tumor >10 mm but </= 20 mm in greatest dimension
T2	Tumor >20 mm but </= 50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)*
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma**

**Note*: Invasion of the dermis alone does not qualify as T4.

***Note:* Inflammatory carcinoma is restricted to cases with typical skin changes involving a third or more of the skin of the breast. While the histologic presence of invasive carcinoma invading dermal lymphatics is supportive of the diagnosis, it is not required, nor is dermal lymphatic invasion without typical clinical findings sufficient for a diagnosis of inflammatory breast cancer.

Regional Lymph Nodes (N) Clinical

NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastases
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastases
N2a	Metastases in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected*** ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal

	mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph nodes

Regional Lymph Nodes (N) Pathological

pNX*	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically
pN0(i-)	No regional lymph node metastases histologically, negative IHC
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
pN0(mol-)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
pN0(mol+)	Positive molecular findings (RT-PC) but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases; or metastases in 1 to 3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected**
pN1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a	Metastases in 1 to 3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
pN1b	Metastases in internal mammary nodes with Micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected**
pN1c	Metastases in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected**
pN2	Metastases in 4 to 9 axillary lymph nodes; or in clinically detected*** internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN2a	Metastases in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastases in clinically detected*** internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN3	Metastases in 10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected*** ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive level I, II axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected**; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected*** ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected**
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

*Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(sn).

***Note: Not clinically detected* is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

****Note: Clinically detected* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in site specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.
Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunehistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated

Distant Metastasis (M) Clinical

M0	No clinical or radiographic evidence of distant metastases (no pathologic M0; use clinical M to complete stage group)
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow or other non-regional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Distant Metastasis (M) Pathological

M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Anatomic Stage/Prognostic Groups (Clinical and Pathological)

Group	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1mi	M0
	T1	N1mi	M0
IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0

IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

* T1 includes T1mi
** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.
Stage Unknown

APPENDIX III

ADVERSE EVENT REPORTING

Federal Regulations require that investigators report adverse events and reactions in a timely manner. This reporting improves patient care and scientific communication by providing information to the study chair and PCG headquarters; whereby, new findings can be more widely disseminated to investigators and scientists.

ADVERSE EVENT REPORTING GUIDELINES

Definitions and Terminology
An adverse event (AE) is typically defined as any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a protocol-specified medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (e.g., attribution of unrelated, unlikely, possible, probable, or definite). This may be a new event that was not pre-existing at initiation of any protocol-specified treatment/procedure(s), a pre-existing event that recurs with increased severity or frequency subsequent to commencement of any protocol specified treatment/procedure(s), or an event though present at commencement of any protocol-specified treatment/procedure(s) becomes more severe following initiation of these treatment(s)/procedure(s). Each AE is a unique representation of a specific event used for medical documentation and scientific analysis.

For the BRE008-12 protocol all baseline events and then only possibly, probably or definitely related adverse events are collected.

Grading of Adverse Events
Unless otherwise specified, the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 is used to grade severity of adverse events. All appropriate site personnel should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Reporting Adverse Events
Adverse Event collection is included in PCG's Electronic Data Capture (EDC) system for the BRE008-12 protocol. Additional information regarding data entry can be found in the Study Procedures Manual.

SERIOUS ADVERSE EVENT REPORTING GUIDELINES

Definitions and Terminology

A Serious Adverse Event (SAE) is an adverse experience occurring during the course of the study or during planned follow-up that meets any of the following criteria:

- results in death
- is life threatening (places the patient at immediate risk of death from the experience as it occurred);
- requires inpatient hospitalization (> 24 hours) or prolongs an existing hospitalization
- results in persistent or significant disability/incapacity (substantial disruption of one's ability to carry out normal life functions);
- or is a congenital anomaly/birth defect.

For the BRE008-12 protocol, ONLY SAE's possibly, probably or definitely related to protocol therapy are collected. In addition, the BRE008-12 protocol requires all grade 3 and above non-hematologic toxicities to be reported as SAEs.
Medical and scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. Important medical events that may not meet the strict definition of a SAE could still be significant enough to require reporting. For instance, situations that may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the SAE definition above. They should also usually be considered serious.

Reporting Serious Adverse Events (SAE)
SAE reporting is safety related, separate from and in addition to data management toxicity reporting requirements on the case report form. For the **BRE008-12** study, investigators and other site personnel must **report all possibly, probably or definitely related SAEs within 1 business day of discovery of the event.**

SAEs should be reported on an SAE form via email to safety@pcgresearch.org. If email is unavailable, PCG Headquarters should be notified by phone to alert that an SAE has occurred and a SAE report form will be forthcoming.

It is expected that all information may not be available at the time of the initial SAE report is submitted. A follow-up report with complete information is expected within 10 days of the initial report. As new information related to the SAE is made known to the investigator, the SAE report should be updated and resubmitted to PCG Headquarters. All supporting source documentation, if requested, must be emailed to the CRA at PCG Headquarters as soon as available. SAEs will also be recorded in the PCG Electronic Data Capture system. In addition to notifying PCG, the Investigator is responsible for reporting SAEs to the IRB per their requirements.

Additional information regarding adverse event collection is available in SPM.

Appendix IV

A) Coronary Artery Anatomy (Ref 1)

I. Overview

Overview of the coronary arteries in the anterior projection (Figure 1).

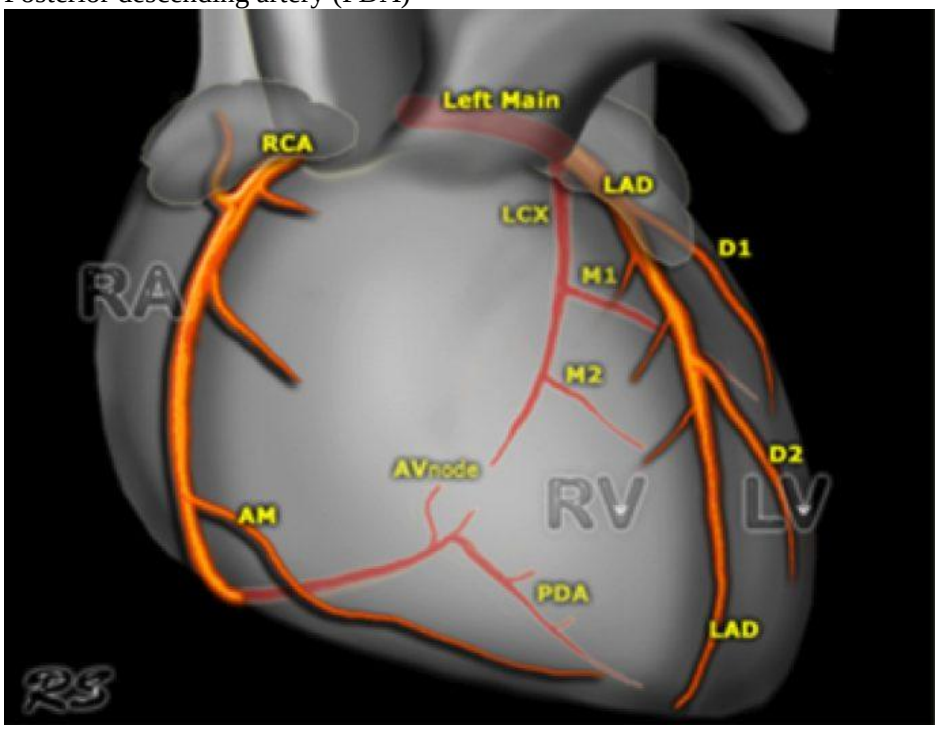
- Left Main or left coronary artery (LCA)
  - Left anterior descending (LAD)
    - diagonal branches (D1, D2)
    - septal branches
  - Circumflex (Cx – labeled LCX))
    - Marginal branches (M1,M2)
- Right coronary artery
  - Acute marginal branch (AM)
  - AV node branch
  - Posterior descending artery (PDA)
- 

Figure 1

II. Left Coronary Artery (LCA) (Fig. 2)

The left coronary artery (LCA) is also known as the left main. The LCA arises from the left coronary cusp. The aortic valve has three leaflets, each having a cusp or cup-like configuration. These are known as the left coronary cusp (L), the right coronary cusp (R) and the posterior non-coronary cusp (N). Just above the aortic valves there are anatomic dilations of the ascending aorta, also known as the sinus of Valsalva. The left aortic sinus gives rise to the left coronary artery. The right aortic sinus which lies anteriorly, gives rise to the right coronary artery. The non-coronary sinus is positioned on the right side.

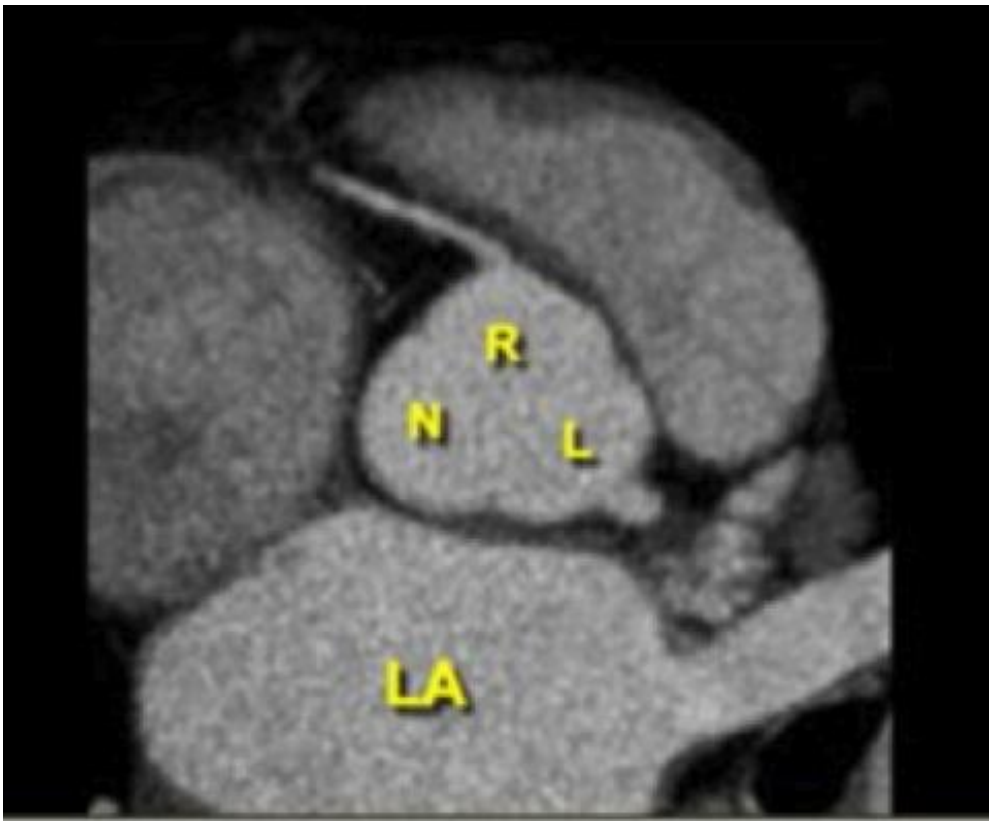


Figure 2
The LCA divides almost immediately into the circumflex artery (Cx) and left anterior descending artery (LAD) (Fig. 3). The LCA travels between the right ventricle outflow tract anteriorly and the left atrium posteriorly and divides into LAD and Cx.

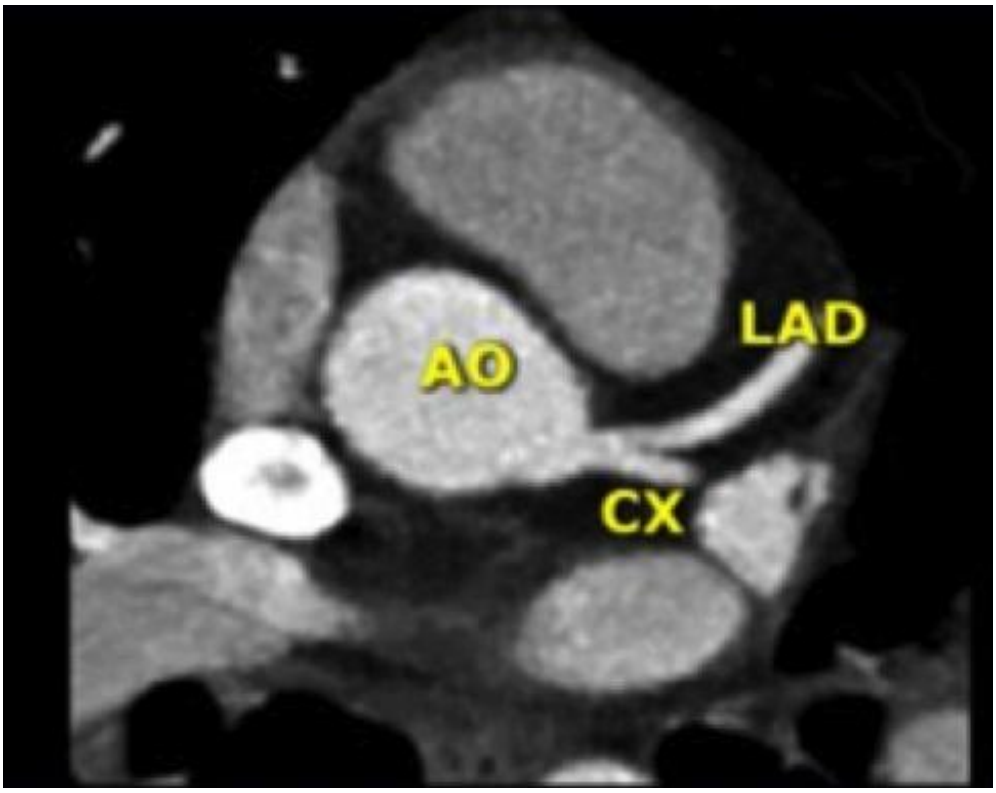


Figure 3

III. Left Anterior Descending (LAD)(Fig. 4)

The LAD travels in the anterior interventricular groove and continues up to the apex of the heart (Fig. 4A). The LAD supplies the anterior part of the septum with septal branches and the anterior wall of the left ventricle with diagonal branches. The LAD supplies most of the left ventricle and also the AV-bundle.

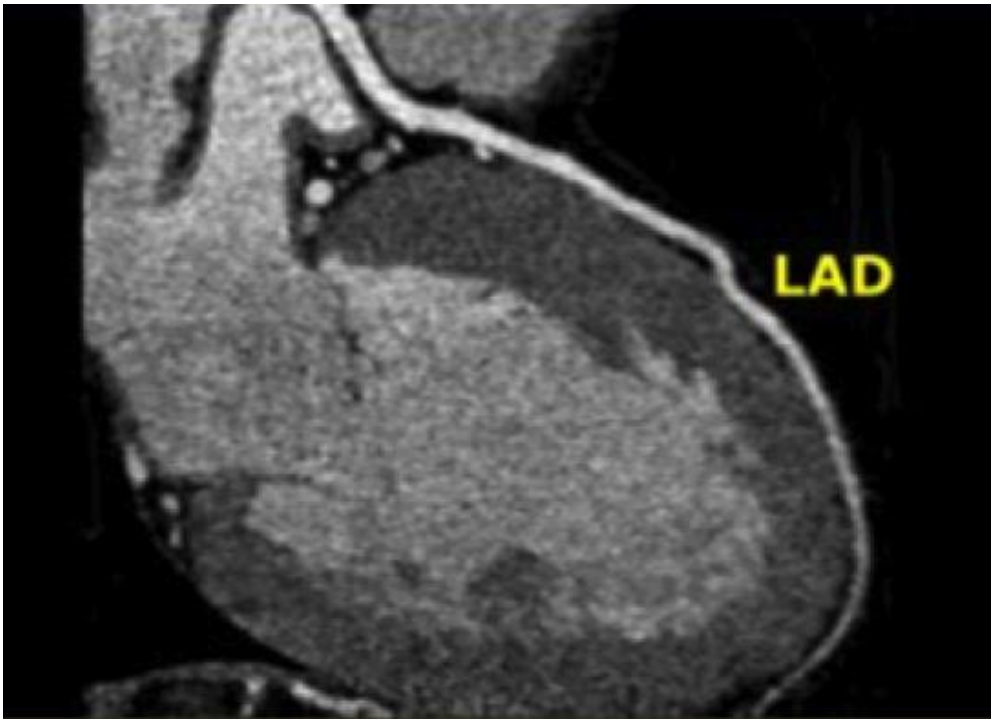


Figure 4 – A CT image of the LAD in RAO projection

The diagonal branches come off the LAD and run laterally to supply the antero-lateral wall of the left ventricle. The first diagonal branch (D1) serves as the boundary between the proximal and mid portion of the LAD . There can be one or more diagonal branches: D1, D2, etc. (Fig. 4B)

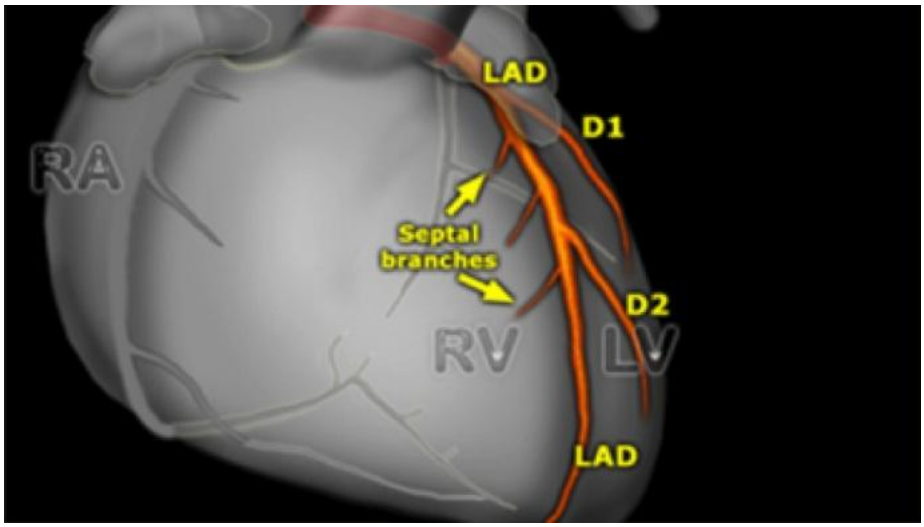


Figure 4 – B

IV. Right Coronary Artery (RCA) (Fig. 5)

The right coronary artery arises from the anterior sinus of Valsalva and courses through the right atrioventricular (AV) groove between the right artium and right ventricle to the inferior part of the septum (Fig. 5A). In 50-60% the first branch of the RCA is the small conus branch that supplies the right ventricle outflow tract. In 20-30% the conus branch arises directly from the aorta. In 60% a sinus node artery arises as second branch of the RCA that runs posteriorly to the

SA-node. The next branches are some diagonals that run anteriorly to supply the anterior wall of the right ventricle. The large acute marginal branch (AM) comes off with an *acute* angle and runs along the *margin* of the right ventricle above the diaphragm. The RCA continues in the AV groove posteriorly and gives off a branch to the AV node. In 65% of cases the posterior descending artery (PDA) is a branch of the RCA (right dominant circulation). The PDA supplies the inferior wall of the left ventricle and inferior part of the septum.

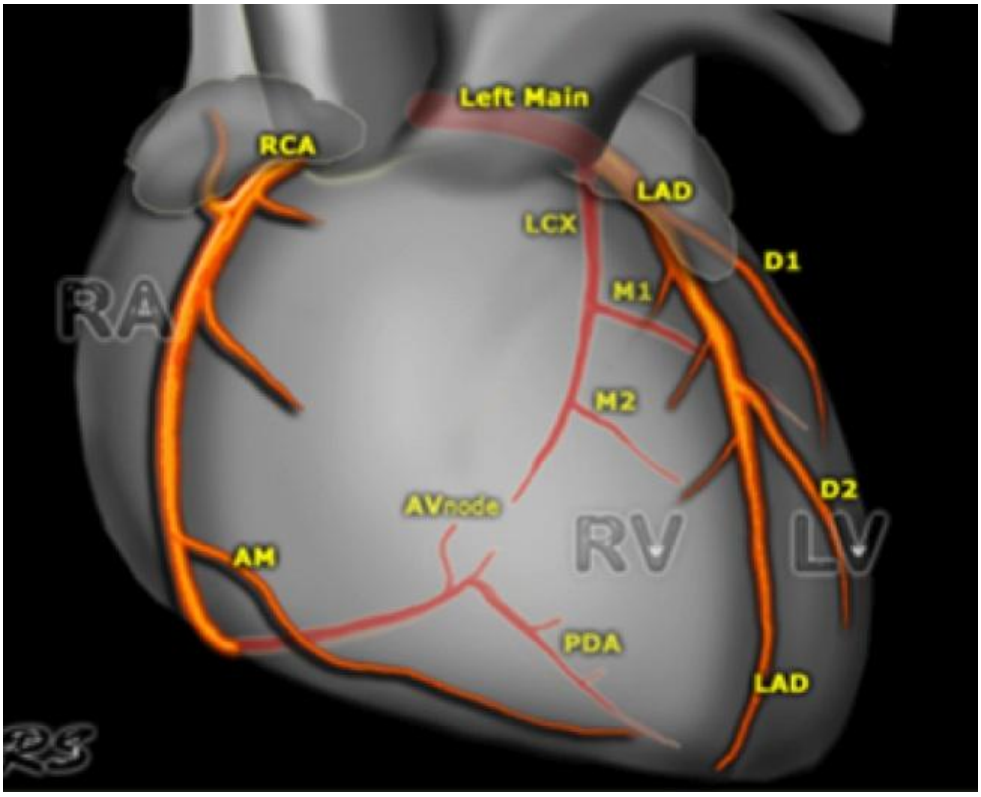


Figure 5 - A
RCA, LAD and LCx in Anterior projection

In the most common situation the RCA comes off the right cusp and will provide the conus branch at a lower level (not shown). On the image next to it, we see a conus branch that comes off directly from the aorta (Fig. 5A&B).

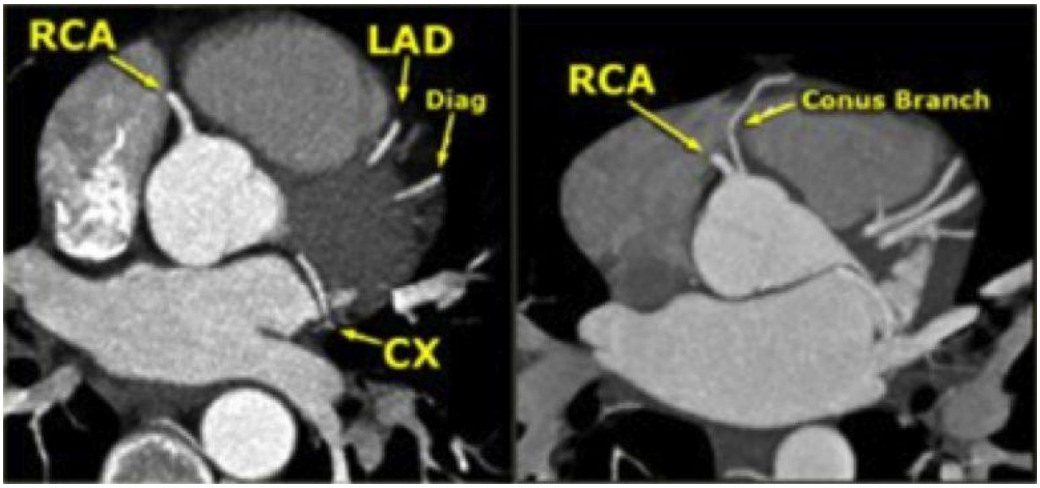


Figure 5 – B & C

V. Coronary Anomalies

Coronary anomalies are uncommon with a prevalence of 1%.

Coronary anomalies can be differentiated into anomalies of the origin, the course and termination.

- Anomalies of the origin
  - Anomalous origin of coronary artery from pulmonary artery
  - Single coronary artery
  - Origin from 'non-coronary cusp'
- Anomalies of the course
  - Myocardial bridging
  - Duplication
- Anomalies of termination
  - Coronary artery fistula
  - Extra-cardiac termination

The most common and clinically significant anomaly is an anomalous origin of the LCA from the right sinus of Valsalva and the LCA courses between the aorta and pulmonary artery (Fig. 6). [76]

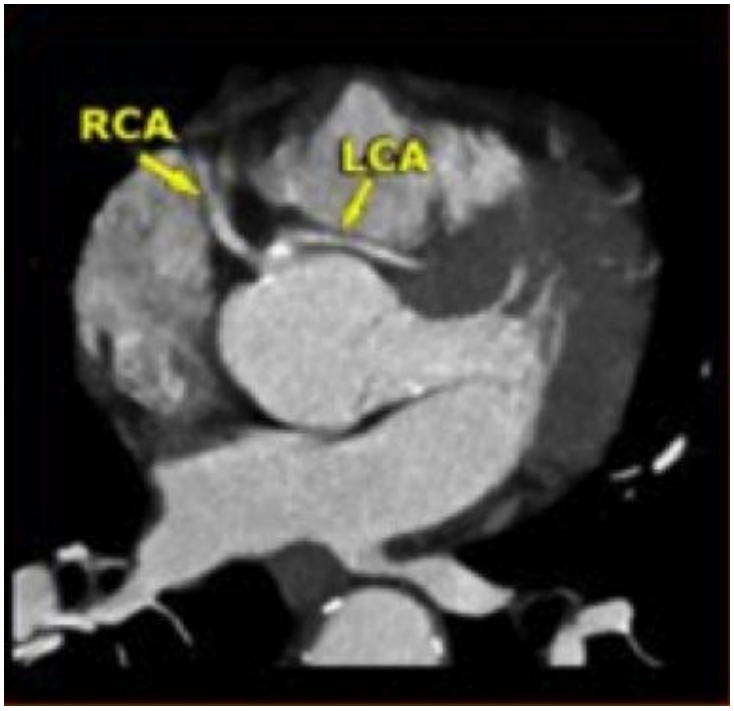


Figure 6

B) Coronary Artery CT Scan Atlas

The sequential CT scans shown in the contouring atlas below illustrates the various levels of the heart starting above the origin of the RCA and the LCA, extending to at the distal LAD at the heart apex. This provides a guide to defining the:

Left main coronary artery (LCA)

- Left anterior descending coronary artery (LAD)
  Diagonal branches (D1, D2)
- Right coronary artery (RCA)
- Circumflex (Cx)

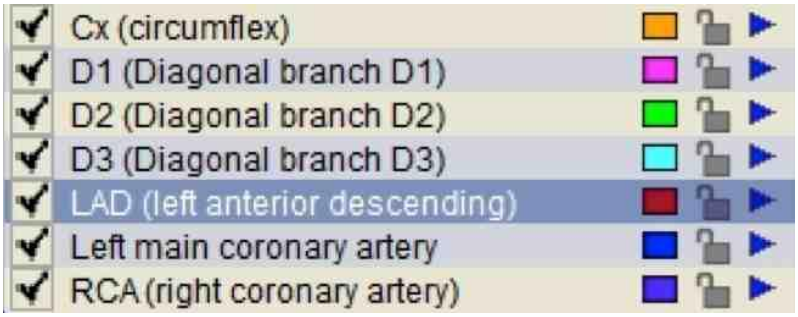
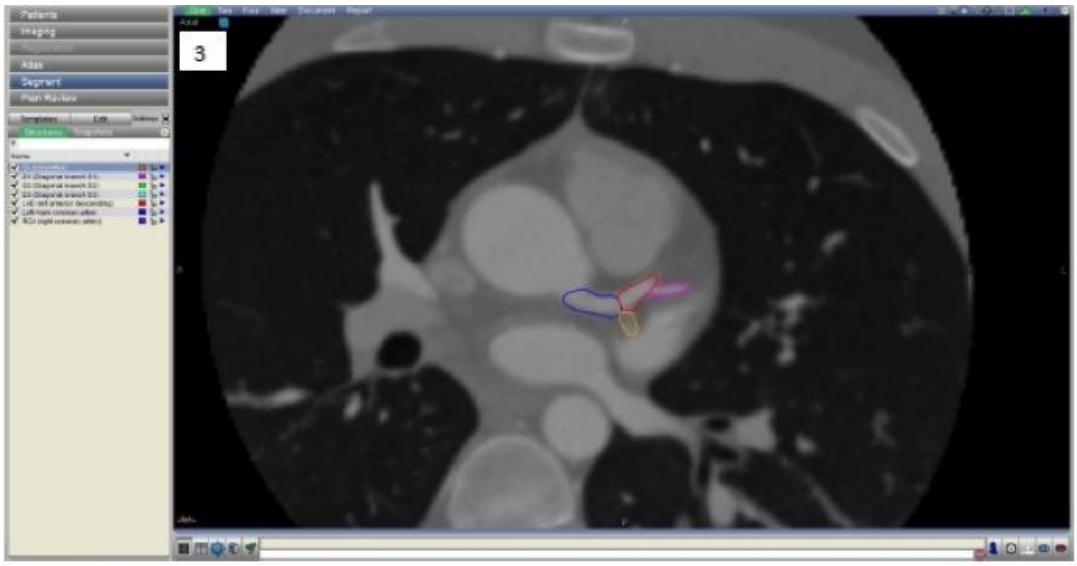


Image 3 magnified below shows the LCA (blue) leading to the origin of the LAD (red) and circumflex artery (orange). The origin of the first diagonal branch off the D1 branch (pink) is also shown. Image 4 shows the origin of the second diagonal branch D2 (green):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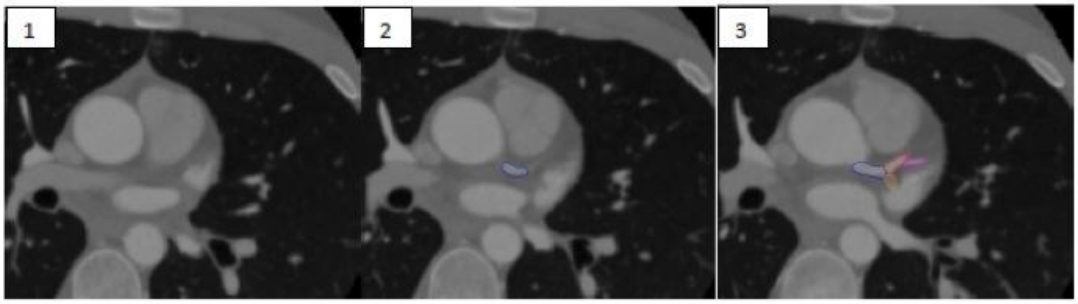
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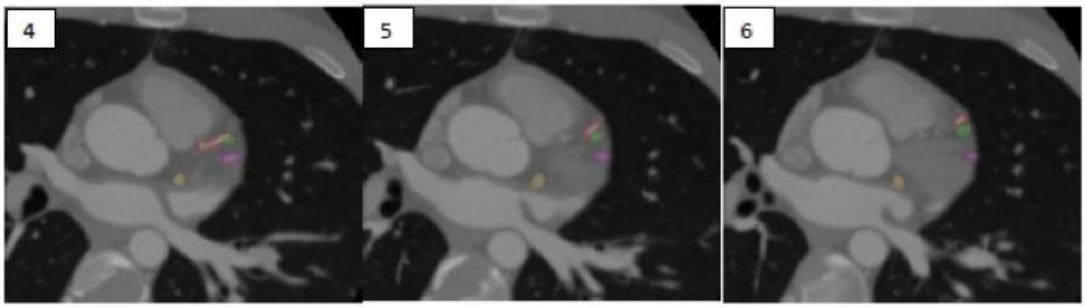
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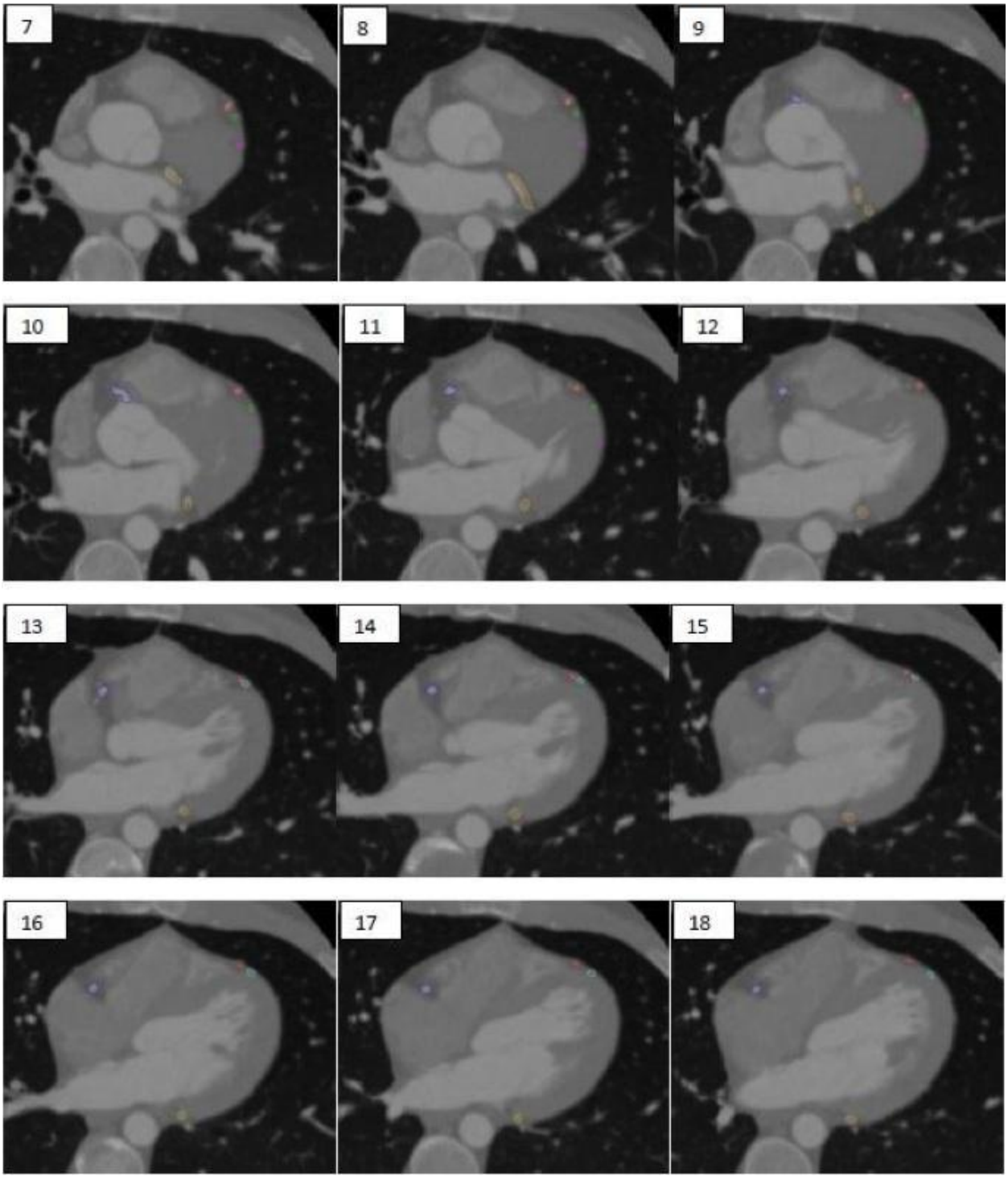
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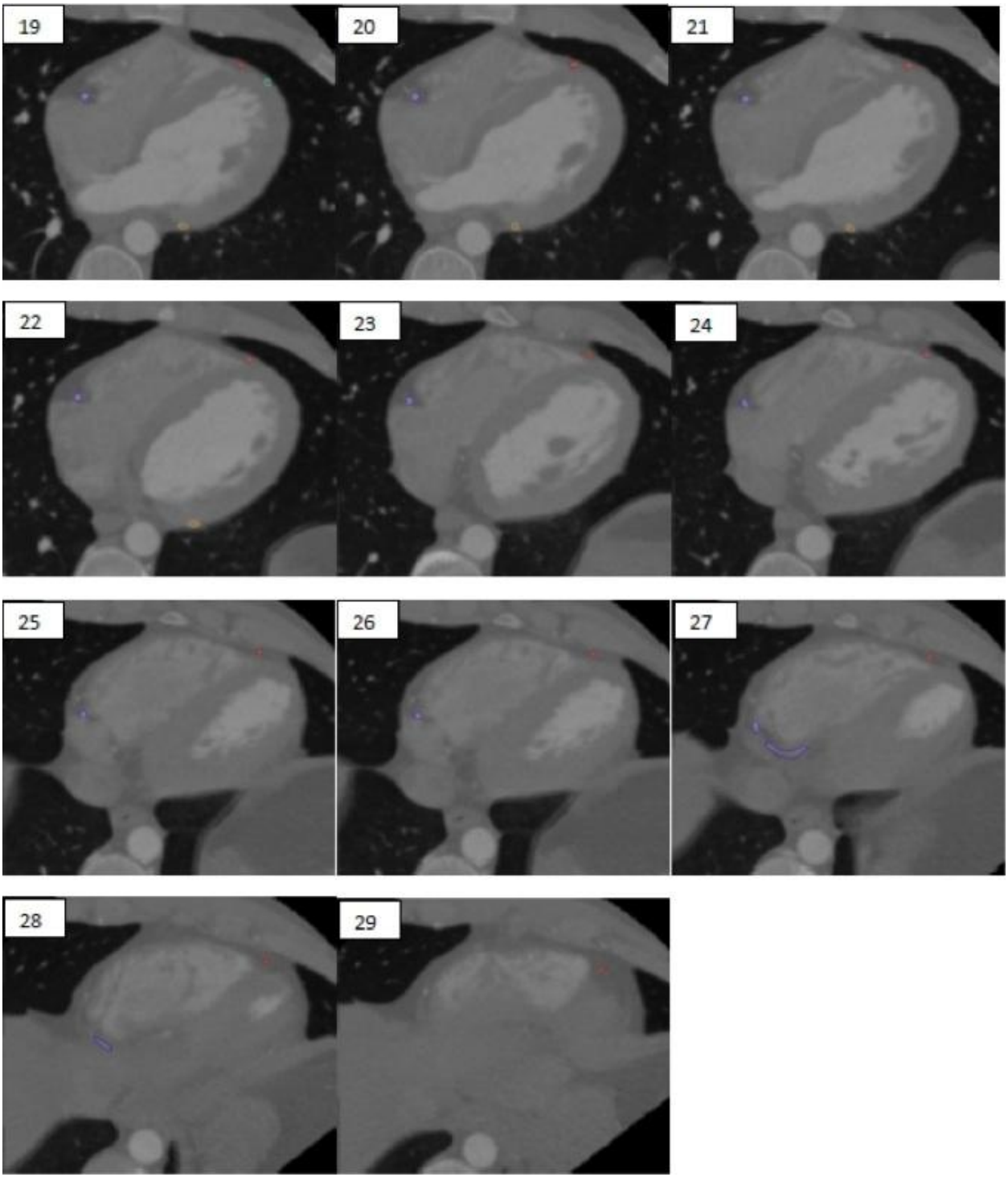
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