Radiothérapie du sein en décubitus ventral : performances de la segmentation automatique de la cible du traitement et des organes à risque

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Résumé (en français)

1. Introduction

Le cancer du sein est le cancer le plus fréquent dans la population féminine et la deuxième cause de décès par cancer chez les femmes dans le monde. Au cours des 30 dernières années, la mortalité due au cancer du sein a diminué, notamment grâce aux diagnostics précoces et à l'efficacité des traitements. Du point de vue clinique, le cancer du sein au stade précoce est défini par une absence de ganglions lymphatiques axillaires au-delà du sein. L'objectif du traitement pour ces patientes, est de parvenir à la guérison et à la survie à long terme.

Une grande partie des patientes précocement diagnostiquées bénéficient d'un traitement conservateur incluant une tumorectomie, une radiothérapie adjuvante, une chimiothérapie et une thérapie endocrinienne. La radiothérapie adjuvante a permis de réduire de façon significative le risque de récurrence locorégionale et le risque de décès par cancer du sein. La radiothérapie sur l'ensemble du sein reste un élément essentiel du traitement conservateur et fait partie des recommandations dans les directives cliniques pratiques.

La radiothérapie peut par ailleurs entraîner une toxicité sur les organes tels que la peau, le cœur et les poumons, diminuer les résultats cosmétiques et provoquer une sténose coronarienne pouvant conduire à une maladie cardiaque ischémique sévère. Les toxicités radio-induites au niveau de la peau sont l'œdème, l'ulcération, l'atrophie, la sclérose, ainsi que la réduction du volume mammaire, qui peut être particulièrement importante chez les femmes ayant une poitrine volumineuse. La toxicité radio-induite cardiaque se manifeste souvent plusieurs années après le traitement et n'est mise en évidence que par un suivi à long terme.

De nombreuses techniques de radiothérapie permettent de relever le défi de réduire le risque de toxicité tout en préservant les chances de contrôle local. Des techniques en

décubitus ventral 0nt été préconisées pour diminuer l'irradiation de la peau, des poumons et du cœur. De cette façon, la totalité du sein s'éloigne de la paroi thoracique, ce qui permet aux champs tangentiels d'éviter les organes intra-thoraciques tout en maintenant la couverture du sein. Les résultats à long terme ont montré un contrôle tumoral équivalant par radiothérapie en décubitus ventral, versus radiothérapie en décubitus dorsal.

Plusieurs études dosimétriques ont été faites sur des patientes simulées dans les deux positions. En ce qui concerne les doses au poumon ipsilatéral, la technique en décubitus ventral s'est avérée être optimale en termes de protection des poumons. Cependant, compte tenu de la variabilité interindividuelle de l'anatomie, d'un déplacement aléatoire des organes, des modifications postopératoires hétérogènes et des différentes capacités entre patientes pour tenir une inspiration forcée pendant le traitement, la comparaison entre les deux techniques reste moins fiable.

Le contourage du volume cible clinique (CTVs) et des organes à risque (OARs), est un acte important dans la planification du traitement de radiothérapie. On observe de grandes variations intra- et inter-opérateurs pour contourer le sein entier et le cœur, ce qui risque d'influencer la reproductibilité des résultats dosimétriques.

Afin de réduire le temps de contourage, d'accroître la fiabilité et d'améliorer la reproductibilité, la segmentation automatique (AS) peut être la solution pour les patientes traitées en position ventrale. AS a déjà été évaluée pour les tumeurs et les cibles telles que le sein, l'endomètre, ainsi que la tête et le cou. Les temps de délimitation avec l'AS ont été réduits, de même que les différences de contourage entre opérateurs. Les seins, le cœur et les poumons sont des organes bien définis et distincts sur le CT de simulation, comparativement aux CTVs pour d'autres localisations anatomiques telles que les régions anorectale, intestinale, ou cervicale.

Le but de cette thèse est d'évaluer les pours et les contre de la position ventrale pour la

radiothérapie du sein *in toto* et la fiabilité de l'AS pour les patientes exposées à ce traitement.

2. Contexte et objectifs

Le dépistage précoce et le traitement complet du cancer du sein augmentent le taux de survie du patient. Les résultats des essais cliniques montrent aussi que le contrôle local de la maladie s'améliore avec radiothérapie adjuvante. Celle-ci est délivrée sur le sein malade avec la patiente habituellement allongée end décubitus dorsale (DD). Cependant, il a été observé que les avantages de la radiothérapie en termes de guérison peuvent être contrés par l'apparition d'effets secondaires délétères au niveau du cœur et des poumons.

En décubitus ventral (DV) la glande mammaire s'éloigne du thorax à cause de la gravité ce qui permet une irradiation de la totalité du sein et une épargne maximale des organes critiques proches tels que les poumons. Cependant, le cœur aussi soumis à la force de la gravité va se déplacer vers la paroi thoracique au lieu de se séparer comme les poumons, au risque de se trouver dans la projection du faisceau chez les patientes traitées en DV.

Afin d'évaluer la meilleure position de traitement, DD *vs.* DV, deux CTs et deux plans de traitement on été effectués pour chaque patiente au prix d'une plus grande exposition au rayonnement et doublant, en conséquence, la charge de travail de la planification. Celle-ci débute par une délinéation (segmentation) précise de la cible ou cibles et des organes à risque (OARs), tels que les poumons, le cœur, et le sein non-atteint. Ces organes doivent être protégés le plus possible de l'irradiation reçu par la/les cible/s à traiter.

La segmentation manuelle sur les images CT des cibles du traitement et des OARs est un processus fastidieux et long. Un outil de segmentation automatique peut réduire le temps de contourage et améliorer la reproductibilité du contourage entre observateurs. Un de ces outils est basé sur un atlas-bibliothèque des cas anatomiquement divers et d'un algorithme d'enregistrement capable de reconnaitre les OARs d'une patiente choisie pour qu'une délinéation automatique puisse avoir lieu.

Dans un premier temps, nous avons évalué comparativement la répartition de dose en position DD *vs.* DV chez 282 patientes. Ceci a permis d'identifier certaines caractéristiques anatomiques permettant de prédire la meilleure position de traitement pour une patiente déterminée.

Dans un deuxième temps, nous avons procédé à l'évaluation de la segmentation automatique appliquée exclusivement à des patientes traitées en position de DV. La cible (le sein atteint ou *clinical target volume*, CTV) et les OARs, tels que le cœur, l'artère coronaire antérieure descendante gauche (LADA), l'artère coronaire droite (RCA), les deux poumons et le sein non-atteint (controlatéral) on fait l'objet de cette évaluation. Des paramètres volumétriques et d'orientation spatiale (*similarity indexes*) ont été utilisés pour analyser la similitude ou les différences entre segmentation automatique et la délinéation manuelle. Nous avons présumé que l'introduction de l'information sur les différences de surface corporelle (*body mass index*, BMI) et de taille de soutien gorge (*breast cup size*, BCS) entre les patientes devrait pouvoir améliorer les performances de l'algorithme de segmentation.

3. Matériel et méthodes

L'étude de dosimétrie comparative entre les positions DD et DV a porté sur 282 femmes qui ont bénéficié d'une radiothérapie adjuvante après chirurgie mammaire conservatrice. Chaque patiente a subi un double CT. Pour les patientes atteintes d'un cancer du sein gauche le CT en DD a été effectué en conditions d'inspiration forcée. La dose prescrite a été de 47,25 Gy en 21 séances journalières, 4 jours par semaine. Le traitement a été délivré toujours par une technique employant deux champs tangentiels, parallèles et opposés. La distribution de la dose dans le CTV ainsi que dans les OARs respectifs a été quantifiée et représentée par histogrammes reliant la dose au volume (*dose-volume histograms*, DVH). Nous avons élaboré un algorithme permettant évaluer comparativement les doses reçus par les OARs et la cible.

Des priorités hiérarchisées pour les OARs ont été établies en accord avec l'importance et sévérité du risque de toxicité avec les doses grandissantes avec des index de pondération.

L'étude de contourage automatique s'est porté sur 40 patientes atteintes d'un cancer du sein sur les quelles des CT de planification en DV avaient été effectués. Treize de ces patientes ont servi pour créer la bibliothèque anatomique avec une répartition selon volume de poitrine (de petit à grand) et latéralité du sein atteint (gauche *vs.* droit). Les autres 27 patients ont servi à tester individuellement la segmentation automatique.

Un logiciel (VODCA) a été employé pour calculer l'index de similarité (*dice similarity coefficient*, DSC) entre les volumes et comparer les différences entre les volumes contournés. Le contourage manuel de la cible et des OARs a été comparé aux volumes respectifs après segmentation automatique, avec ou sans édition postérieure des contours. Les DVH on servi à obtenir des données sur la distribution de la dose dans un volume d'un OARs concret. Ainsi des paramètres tels que la dose moyenne et la dose reçu par le 2%, 5% et 10% des OARs ont pu être estimée pour chaque type de segmentation manuelle, automatique ou automatique avec optimisation manuelle.

4. Résultats

L'étude de dosimétrie comparative a été effectuée sur 138 patientes traitées sur le sein gauche, dont 113 (soit 81,9%) en inspiration bloquée (DD), et 144 patientes traitées sur le sein droit (toutes en respiration libre). Des très faibles différences (<1%) en faveur du DD ont été observées sur le cœur, le poumon contralateral, les deux seins et le lit tumoral du sein atteint. Cependant, le traitement en DV avait réussi à réduire la dose de 6.39% sur le poumon ipsilateral et de 1.29% sur le corps entier (dose intégrale). En effet, d'un point de vue dosimétrique la position de traitement en DV a été avantageuse chez 180 patientes (64%) vs. 102 (36%) pour lesquelles la position en DD a été meilleure. Le gain dosimétrique entre DD

et DV représenté par «Δ» a montré que la position en DD a été avantageuse chez 87,6%, 75,5% et 95,4% des patientes pour le cœur, le poumon controlatéral et le sein non-atteint (contralateral), respectivement; cependant le traitement en DV a été avantageuse chez 98,9% et 85,1% des patientes pour le poumon homolateral et la dose intégrale au corps, respectivement. Dans le but de réduire la pratique de double planification (DD et DV), DV devrait être toujours préférée pour les traitements du sein droit ou ceux du sein gauche effectués en conditions de respiration libre ; pour les traitements sur le sein gauche en conditions de respiration bloqué en inspiration profonde, la position DD devrait être considérée la meilleure option.

En ce qui concerne l'étude de segmentation automatique en DV, la définition manuelle du CTV (référence) et AS (+ édition/correction), ont révélé un DSC>0.95. En effet, l'index de similarité plus élevés et les seins plus tombants ont montré que les cibles avec un DSC >0.965 présentaient les meilleurs résultats dosimétriques. Une corrélation entre DSC et latéralité ou volume n'a pas été observée. Une corrélation entre le DSC avec le ratio de surface du CTV en contact avec l'air sur le total de la surface du CTV (RSA) a été aussi observée (augmentation des valeurs de DSC avec les valeurs de RSA plus élevés). Le temps moyen pour éditer/corriger les contours du CTV obtenus par AS a été de 5.22 minutes, significativement plus court que la moyenne de temps nécessaire pour le contourage manuel du CTV (12.4 minutes).

En ce qui concerne la AS du cœur et des vaisseaux coronariens l'utilisation du BMI et du BCS a permis d'optimaliser le contourage automatique. Comme pour la AS du CTV décrit dans le paragraphe précédant la AS du cœur et coronaires l'index moyen de similarité était >0.9 après édition. Cependant, en raison de la structure complexe et étroite des vaisseaux coronariens une nouvelle structure a été créé a partir de la LADA et la RCA en élargissant leur diamètre d'1 cm (vaisseaux + 1cm). L'index de similarité de ces nouvelles structures a été de

⩾0.8 après édition/correction des contours après AS. Le temps moyen de contourage avec AS du CTV et des OARs a été un 60% inferieur comparé au temps nécessaire pour un contourage manuel de ces mêmes structures. En effet, si dans notre étude le temps moyen nécessaire pour contourer manuellement tous les OARs a été de 27,5 minutes ce même temps après AS + correction a été de 11.4 minutes. La différence dans la moyenne de dose reçue par les OARs après AS a été estimée à <1.5% comparé au contourage manuel.

Dans l'étude comparative DD vs. DV avec un nombre important de patientes nous avons pu constater que la position en DV était l'idéale pour le poumon et pour réduire la dose intégrale au corps entier des patientes. Sans doute le premier choix pour les cancers siégeant le sein droit. Cependant, en raison de la position avancée du cœur el les artères coronariennes avec le DV, les tumeurs siégeant le sein gauche sont mieux traitées en DD, spécialement ceux chez des patientes ne pouvant pas bloquer la respiration en phase d'inspiration profonde. Un CT de planification en DD et en DV pour une patiente déterminée ne se justifie que chez des patientes avec des tumeurs gauches qui ne peuvent pas tenir leur respiration bloquée en inspiration profonde, aussi chez des patientes avec comorbidités de l'appareil cardio-vasculaire et/ou respiratoire (*e.g.*, fonction pulmonaire anormale).

Dans le chapitre concernant la segmentation automatique du CTV chez les patientes planifiées et traitées sur le sein en DV, nous rapportons un DSC moyen de 0,91 pour la AS ce qui est comparable aux données rapportées dans la littérature pour des patientes traitées aussi pour un cancer du sein mais en DD. AS a comme avantages le fait de réduire la variabilité de contourage entre observateurs ainsi qu'une réduction importante du temps de contourage. Des index de similarité (>0.965) et les seins plus tombants ont présentés les meilleurs résultats dosimétriques après AS.

Utiliser la BMI et le BCS effectue un stockage hiérarchique de la bibliothèque d'atlas AS. Aide à optimiser les esquisses AS, Pour améliorer la fiabilité du débridement de la

radiothérapie du cancer du sein, surtout le contour du cœur. AS application générée contour cardiaque, Tout aussi fiable que la position en décubitus a été rapporté Croquis en supination, La valeur *Dice* peut être augmentée à 0,94. Le temps pris pour tirer le cible et OARs a été réduit de 40% quand le Sr a utilisé l'AS avec l'édition manuelle, par rapport au contourage manuel seul. Cette réalisation a été possible grâce à l'élargissement de la base de données avec des cas d'atlas supplémentaires et établi une classification claire basée sur les indices de la BMI et les BCS.

5. Discussion

Depuis que le Memorial Sloan-Kettering Cancer Centre a publié sur la première irradiation mammaire en décubitus ventral (DV) en 1994, six études dosimétriques, avec un nombre de patientes par étude non-inférieur à 40, ont fait état de comparaisons dosimétriques duales (ventrales et dorsales). L'épargne sur le poumon est reconnue à l'unanimité, tandis que pour d'autres structures les données sont contradictoires. Notre étude est spécialement contributive car elle est moins biaisée par la présence excessive de seins de grande taille, comme cela était le cas dans la plupart des études dosimétriques précédentes, et donc potentiellement applicable à une population de patientes plus large, donc moins sélective.

Nos résultats ont montré que la distribution de dose était plus favorable chez les patientes traitées en décubitus dorsal (DD) par rapport au cœur, le sein-cible ou PTV, le lit tumoral, le sein controlatéral et le poumon controlatéral. Cependant, en tenant compte de la variabilité entre les patientes des organes évalués et les cibles respectives, le DV semble associé à un gain dosimétrique global chez 63,8 % des patientes dans l'étude.

Comme illustré dans la figure 2, la position de traitement en DD a été surtout avantageuse pour les femmes atteintes d'un cancer du sein gauche et aptes à endurer un traitement en inspiration profonde bloquée (acronyme de l'anglais, deep inspiration breath

hold, DiBH) pour le sein gauche. L'un des points forts de l'étude a été le nombre de patientes recrutées.

De nos jours, une radiothérapie idéale devrait tenter d'optimiser les probabilités de contrôle de la tumeur tout en minimisant les risques de complications pour les tissus non tumoraux. Nous avons estimé le bénéfice potentiel d'un traitement en DV vs. DD (ou viceversa) en développant un algorithme basé sur des paramètres de pondération préétablis et «arbitraires», selon l'importance des organes en question (cœur > CTV-lit tumoral > poumon = CTV-sein = sein controlatéral = autres structures) nous permettant ainsi de quantifier l'avantage ou le désavantage dosimétrique d'une position de traitement par rapport à l'autre (⊿Wsum). En effet, selon cet algorithme le cœur deviendrait 4x plus important et le lit tumoral 2x plus important que le CTV-mammaire. Nous avons également prédéterminé une contrainte pulmonaire plus restrictive V20Gy de 10%.

Dans la deuxième étude portant sur le contourage, nous avons investigué la faisabilité de la segmentation automatique (AS) chez les patientes traitées sur le sein en DV. Le temps total nécessaire pour dessiner le CTV et les OAR chez ces patientes a été réduit par un facteur de 30-40%. Les temps de contourage du CTV ont été comparables à ceux rapportés par Reed et al. En DD, mais suggèrent que le contourage de la cible en DV pourrait être plus facile.

Afin d'optimiser le contourage des OARs et d'économiser du temps, nous avons élargi la bibliothèque (atlas) avec des cas additionnels pour affiner le match entre les patientes testées et disposer ainsi d'une casuistique plus ample et variée. Le recrutement des patientes s'est fait selon la taille des bonnets de A à F et trois niveaux distincts de BMI, ce qui s'est traduit par deux sets de 18 patientes (droite et gauche). Pour optimiser les résultats d'AS, il était important d'introduire dans l'algorithme des paramètres qui pourraient mieux décrire l'atlas.

L'indice de similarité AS après contourage du CTV-sein était comparable aux données rapportées dans la littérature pour le DD. Cependant, ces dernières études avaient suggéré une

influence négative de la taille du sein sur les résultats du contourage automatique, ce qui n'a pas été mis en évidence dans notre étude. Les causes pouvant expliquer cette différence pourraient être; (1) soit la division de la base de données de l'atlas en trois groupes de CTV stratifiés par leur taille, (2) soit une meilleure performance des algorithmes utilisés par l'outil AS, et/ou (3) par la position de traitement en DV. Les disparités entre observateurs sont un facteur important dans la pratique clinique du contourage d'organes ou des cibles sur l'imagerie. Dans l'étude sur le traitement par CTV menée par AS, les résultats montrent une meilleure couverture de la cible et une plus grande épargne des tissus sains.

Dans la troisième étude, celle concernant la segmentation automatique du cœur et des vaisseaux coronariens (i.e., acronymes de l'anglais, left anterior descending artery, LADA et right coronary artery, RCA), les variables BMI et la taille du soutien-gorge (acronyme de l'anglais, breast cup size, BCS) ont permis de mieux sélectionner les cas à partir de l'atlas pour un meilleur échantillonnage de patientes, permettant un contourage optimal du cœur et des vaisseaux coronariens. Cette alternative c'est révélée meilleure qu'avec l'échantillonnage des patientes stratifiées par volume mammaire, comme c'est habituellement le cas pour l'AS du CTV mammaire.

L'AS du cœur en DV peut se révéler aussi fiable que les données rapportées dans la littérature pour les patientes planifiées et traitées en DD. En effet, dans la présente étude, après AS et correction manuelle du contourage cardiaque, les paramètres de similarité (Dice) entre la dosimétrie sur les volumes contourés manuellement par l'expert (Sr) et l'AS ont été optimales et presque égales à 1 (0,91-0,94), ce qui compare favorablement face aux données d'AS en DD de la littérature et avec le bénéfice ajouté de que ces dernières méthodes seraient plus chronophages (e.g. 30 min/cas) que le nôtre. Curieusement, la différence moyenne de dose au cœur en DD entre la AS non-corrigée et la segmentation manuelle est de -0,1 %, ce qui est similaire à notre expérience en DV d'AS (i.e. +0,1 %), malgré les différences

anatomiques du cœur par rapport à la paroi thoracique antérieure lorsque les patientes sont allongées sur le ventre ou sur le dos, respectivement.

Dans les cas de cancer du sein gauche, la D2% cardiaque, pouvait être très différente entre les plans de traitement faits sur les volumes de référence contourés manuellement par l'expert (Sr) et les plans de traitement faits sur les volumes cardiaques définis à l'aide d'AS non-corrigée. L'explication la plus vraisemblable de cette différence par rapport aux seins du côté droit est que le cœur, penchant du côté gauche, est en contact avec la paroi thoracique et exposé à des doses plus élevées en DV.

Dans notre étude les indices de similarité des contours des vaisseaux coronaires tracés par AS étaient faibles par rapport aux volumes contourés manuellement par l'expert (Sr). Ceci est en partie attribuable aux caractéristiques anatomiques de la LADA et la RCA qui, par leur taille longiligne, arborescente et de petit diamètre, en plus des artefacts causés par les battements du cœur et les mouvements respiratoires, ont rendu difficile une identification fidèle sur les images CT. La RCA a été encore plus difficile à reproduire que la LADA (indice de conformité plus faible), comme l'ont également observé Feng et al., lors de l'analyse d'images cardiaques pratiquées en DD. Le contourage LADA a toujours été un défi, même pour des observateurs expérimentés lesquels, malgré l'emploi de l'imagerie CT dynamique, n'ont pas réussi à améliorer l'identification de la LADA. Nous avons réussi à améliorer les paramètres de similarité dosimétrique (Dice > 0.8) en ajoutant 1 cm de marge autour des artères coronariennes contournées manuellement ou par AS, selon les recommandations de Kirby et al.

Il est important également de signaler le fait que le contourage du sein controlatéral, non-cible, n'a pas été toujours facile après l'AS. Cependant, nous avons réussi à améliorer les paramètres de similarité (Dice >0,9) après correction du contourage automatique du sein controlatéral. En effet, en DV, le sein controlatéral est souvent comprimé de façon aléatoire

durant le traitement. Le sein controlatéral n'est pas une contrainte majeure pour les traitements conformationnels 3D et la planification de champs tangentiels, mais pourrait le devenir si des techniques par arc-thérapie volumétrique modulée devaient être utilisées pour traiter les patientes en DV dans le futur.

Abstract

Prone setup has been advocated as a technique to improve organ sparing for whole breast radiotherapy without impairing breast dose coverage. However, the advantage of prone over supine is not easy to be predicted because of factors such as anatomic variability, organ displacement, and post-surgical changes between patients.

The first study aimed to assess one-person prone *vs.* supine planning dose volume histogram comparisons summing organ at risks and targets. While lying prone was associated with a dosimetric gain for the majority of patients, the supine position was preferable for left breast patients who could be reliably treated in deep inspiration breath hold.

The second study, explored the potential advantages of automatic-segmentation for patients lying prone before radiotherapy planning of the target (the breast) and organs at risk (the heart and the coronary vessels). It has been shown that contouring times were reduced with automatic-segmentation compared to manual segmentation.

Breasts with high similarity-indexes and high pendulousness presented the best dosimetric results when planning the treatment with tangential fields. Introducing body-mass-index and breast cup-size in the selection algorithm of patients from the library improved the automatic-segmentation of the breast and organs at risk. The reviewed/edited automatically-segmented structures of the heart and coronary vessels, the later with 1cm expansion, reached high similarity and low mean dose differences compared to manual segmentation.

I. Introduction

1. Epidemiology

Breast cancer is the most common malignancy and the second leading cause of cancer death among women worldwide [1]. In the US, 231,840 new breast cancer cases were diagnosed in 2015 (29% of all female cancer cases) accounting for 40,290 breast cancer deaths and 15% of all female cancer deaths (Figure 1) [2].

Breast cancer incidence rates are higher in more developed countries and lower in Africa and Asia. These differences may be due to differences in risk factors and to early screening. Older age, early menarche, hormone therapy, and a positive family history of breast cancer are associated with a higher risk for breast cancer [3,4]. Physical activity, a healthy body weight, and breastfeeding are associated with a lower risk for cancer development. Mammography screening programs are widely used in developed countries helping to detect breast cancer in its early stages of development hence improving the chances of cure reducing cancer death rates [1,2].

(a) Estimated new cases

Females

Breast	231,840	29%
Lung & bronchus	105,590	13%
Colon & rectum	63,610	8%
Uterine corpus	54,870	7%
Thyroid	47,230	6%
Non-Hodgkin lymphoma	32,000	4%
Melanoma of the skin	31,200	4%
Pancreas	24,120	3%
Leukemia	23,370	3%
Kidney & renal pelvis	23,290	3%
All Sites	**810,170**	**100%**

(b) Estimated deaths

Females

Lung & bronchus	71,660	26%
Breast	40,290	15%
Colon & rectum	23,600	9%
Pancreas	19,850	7%
Ovary	14,180	5%
Leukemia	10,240	4%
Uterine corpus	10,170	4%
Non-Hodgkin lymphoma	8,310	3%
Liver & intrahepatic bile duct	7,520	3%
Brain & other nervous system	6,380	2%
All Sites	**277,280**	**100%**

Figure 1. Ten leading cancers in female in the US (2015).（a） Estimated new cases（b） Estimated deaths [2].

2. Histological anatomy

The breast is a cutaneous exocrine gland located on either side of the upper thoracic wall. Breast have no anatomic capsular tissue surrounding the region, it is composed of skin, glandular parenchyma and subcutaneous tissue (Figure 2). The glandular parenchyma is mainly composed of lobules and milk ducts, and breast cancer generally develops from glandular tissue. Hormones such as estrogens, progesterone, prolactin, and growth hormone may interact with the mammary gland causing tissue to develop and eventually secreting milk [5].

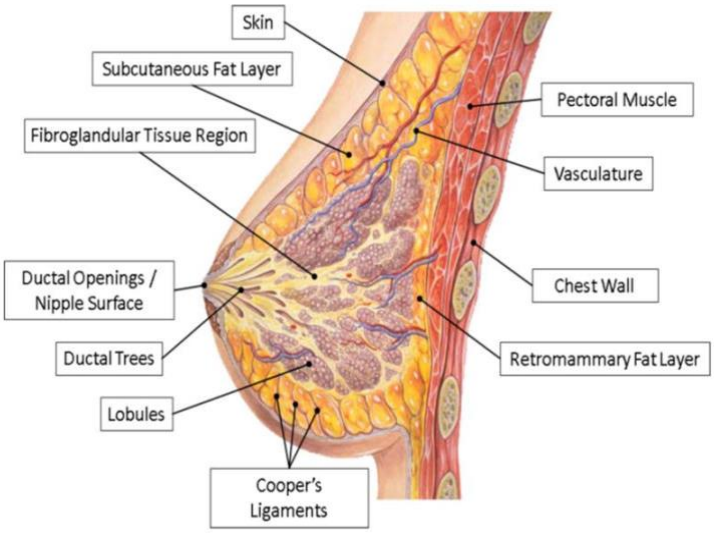

Figure 2. Normal breast anatomy [6].

The subcutaneous tissue is constituted of fatty tissue, fibrous ligament tissue, and blood vessel, as well as lymph vessels and nerves. These tissues envelop and give support to the mammary gland **(**Figure 2**)**. The breast is crossed by a complex vessel and lymphatic network. The arterial supply is derived from the internal mammary, lateral thoracic and posterior intercostal arteries. The venous blood drains towards the axillary, subclavian, intercostal, and internal thoracic veins**.** In the breast, there is an inter-communicating lymphatic plexus located in the dermis (cutaneous plexus), in the superficial subcutaneous, in the pectoralis major muscle fascia (fascial plexus), and in the mammary gland (glandular plexus). The

breast lymph drains through the lymphatic plexuses to reach the axillary lymph nodes and the internal mammary nodes**.**

The breast shape varies among individuals influenced by gravity and the presence of subcutaneous tissue. In a supine position the breast flattens on top of the chest wall; lying prone the breast moves away from the chest wall increasing its shape (Figure 3).

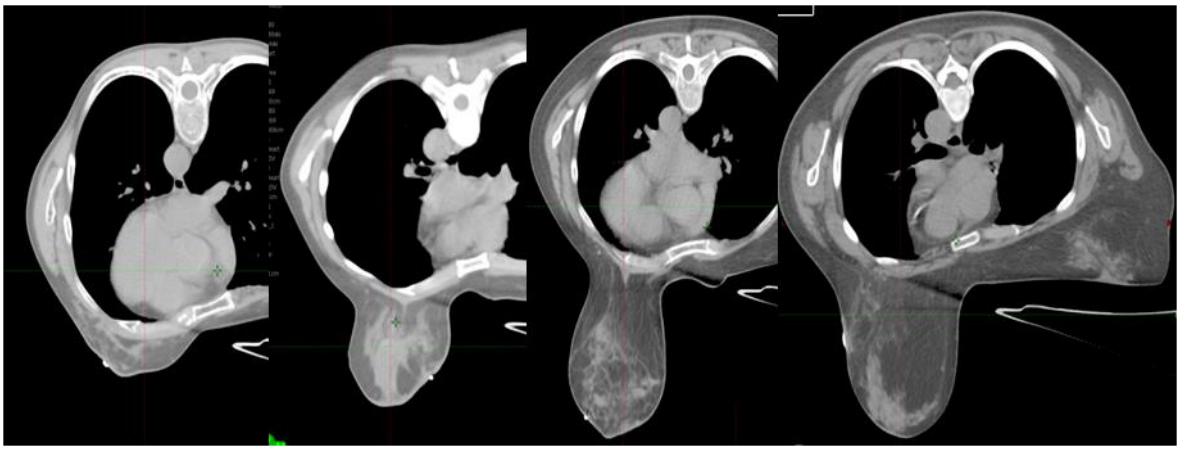

Figure 3. CT images of shape changes of the breast in patients lying prone.

3. Diagnosis and screening

A palpable breast lump is the most common symptom of breast cancer. A painless, hard lump that has irregular edges is typically associated with the diagnosis. While the tumor develops other signs and symptoms may appear such as: skin dimpling, breast swelling, orange peel skin texture, skin ulceration, nipple retraction, blood stained nipple discharge, and enlarged axillary lymph nodes.

Breast screening can help to detect the tumor in its most early stage before any clinical symptom appear [7]. Breast self-examination, clinical breast exam, and mammography are important screening studies. Breast mammography is recommended for any 50 to 74 years-old average-risk woman every one to two years. It should also be recommended for 40-49 years-old high-risk women [8].

3.1 Imaging examination

Mammography helps to evaluate the lump size, location, and guide the needle biopsy for tissue sampling and histopathological examination [9,10]. Ultrasonography is often required in the work-up after mammography and is especially helpful in young women (<40 years), whose breasts are too dense for a correct assessment with mammography [9]. Magnetic Resonance Imaging (MRI) of the breast is a sensitive method to detect breast/chest wall lesions and the presence of axillary lymph nodes [11]. MRI studies can also help to guide the surgical approach or the target definition for post-lumpectomy radiotherapy [9,10].

Positron-emission tomography (PET) provides metabolic information of tumor tissue. PET combined with CT or MRI is a useful tool in staging advanced breast cancer and assessing the disease extent when metastasis are suspected [12].

3.2 Pathologic diagnosis

Breast cancer is a highly heterogeneous group of neoplasia with well-defined histopathological subtypes, different immunohistological profiles, and a wide genetic expression variability that may lead different responses to treatment and prognosis [13,14]. A thorough pathological profile can provide the basic information for individualized treatments [15,16].

Ductal and lobular carcinoma account for 65% of all diagnosed tumors [17]. They originate in the glandular epithelial cells and penetrate the basement membrane of ducts or lobular alveolar tissue and invade into mesenchymal tissue [13]. Ductal carcinoma *in-situ* (DCIS) is a non-invasive form of breast carcinoma characterized by proliferating malignant epithelial cells bounded to the basement membrane of the ducts [13,14]. DCIS may develop to invasive carcinoma [18,19]. The evolution of invasive carcinomas is to spread through the regional lymphatic vessels and to distant organs later on.

The histological grade of carcinomas is closely related to the clinical prognosis. Evidence shows that high tumor-grade carcinomas are associated with a higher risk of local recurrence and/or distance metastases compared to intermediate-grade (grade 2) or low-grade (grade 1) ones. Several molecular tumor markers such as estrogen receptor (ER) and progesterone receptor (PR) expression are also assessed at diagnosis to influence the decision of further endocrine therapy [20]. Last but not least, the expression of human epidermal growth factor receptor (HER2) in tumors cells is tested to help to decide if any targeted treatment with specific antibodies such as trastuzumab is necessary [13].

Profile assays of gene expression have been introduced for early-stage breast cancer providing additional information concerning potential aggressive behavior that will recommend or not the adjunction of (neo-)adjuvant chemotherapy [21].

3.3 Disease staging

Clinical and pathologic staging provides baseline prognostic information, helping to identify local or systemic treatment strategies and compare outcome results across institutions and clinical trials. Clinical staging is performed with the information collected on physical exam, on biopsy examination, and on imaging; pathologic staging is based on findings of surgery, and histopathologic examination. The most commonly used staging classification is the one proposed by the American Joint Committee on Cancer [22]. This classification system is based on the size of the primary tumor and on the eventual spread to the skin or to the chest wall; the involved regional lymph node depending on regions and number of lymph nodes involved; and the presence or absence of distant metastasis (bones, lungs, liver, or brain) [22]. (Appendix 1, Tables).

4. Early-stage breast cancer and the treatment principles

A large proportion of breast cancer patients have their disease diagnosed at an early-stage thanks to an efficient screening and to a better education of women [23]. From the clinician's view, early stage breast cancer is defined as the cancer that has not spread beyond the breast and/or the axillary lymph nodes. The treatment goal for these patients is to achieve cure. Early breast cancers include tumors such as ductal carcinoma *in-situ* and invasive subtypes with stages I, II, or IIIA (T3,N1,M0) [22].

The treatment for most early-stage breast cancers includes tumorectomy, mastectomy, adjuvant radiation, and systemic treatment with endocrine therapy, chemotherapy, and eventually immunotherapy. Conservative surgery is deemed to remove the macroscopic disease in the breast while radiotherapy aims to eliminate the potentially existing microscopic tumor foci nearby. Chemotherapy or endocrine therapy can eliminate tumor cells growing distantly. The chosen treatment strategy depends on factors that include the primary tumor clinical and pathologic characteristics, the axillary lymph nodes status, the multi-gene profile, the HER2 status, the ER/PR receptor status, and whether there is metastatic disease or not. Patient's age and menopausal status are also important patient related factors that influence the choice of treatment [24].

5. Radiotherapy for early-stage breast cancer

5.1 Roles and effects of radiotherapy in early-stage breast cancer

Whole-breast radiotherapy after lumpectomy is an essential component of the conservative treatment strategy. In 2005, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported a meta-analysis of several randomized trials [25], comparing radical mastectomy with conservative surgery followed by breast radiotherapy. Six trials included

3107 patients with a 10-year follow-up. The comparison was unable to show any difference in 10-year local recurrence (6.2％ *vs.* 5.9％) ， in mortality (22.9％ *vs.* 22.9％), and in overall survival (71.5％ vs. 71.1％) between both cohorts. Based on the results from these studies, conservative surgery followed by whole breast irradiation replaced gradually total mastectomy and has become, and still is, the standard local therapy for most patients with early breast cancer [24].

In order to assess the benefits of radiotherapy in the conservative breast treatment setting, the EBCTCG reported again in 2011 the results of a meta-analysis with 10’801 patients from 17 randomized trials [26]. Radiotherapy significantly reduced the 10-year risk of any (*i.e.*, loco regional or distant) first recurrence and the 15-year risk of breast cancer death. In women with node-negative breast cancer, radiation reduced those risks from 31.0% to 15.6% and from 20.5% to 17.2%, respectively, while in women with node-positive disease, radiation reduced these risks from 63.7% to 42.5% and 51.3% to 42.8%, respectively.

5.2 Toxicity of whole breast radiotherapy in early-stage breast cancer

Radiation-induced toxicity to the skin, heart, and lungs exposed to irradiation are key factors in patients treated with curative intend. Acute reactions in the skin are erythema, edema, pruritus, moist desquamation, and occasionally ulceration. Chronic changes may include atrophy, sclerosis, and breast volume reduction. This toxic events may result in a poor cosmetic outcome that may be especially important in women with large breasts [27]. Radiotherapy-induced heart toxicity often manifests many years after radiation and was not fully recognized until several high-quality articles were published [28,29]. A retrospective study observed a higher cardiac mortality ratio for women with left-sided tumors compared to right-sided ones in women undergoing radiotherapy starting 10 years and afterwards [30]. In 2011, Nilsson et *al.*[29] conducted a population study to investigate coronary artery stenosis

in patients with a history of irradiation for breast cancer that underwent coronary angiographies. The later showed that mid and distal left anterior descending arteries (Figure 5A, segments 7, 8) and proximal right coronary arteries (Figure 5A, segments 1 and 2) were especially touched by severe stenosis. Among patients irradiated to the left breast the left anterior descending artery was often included in the tangential radiation fields (Figure 5B).

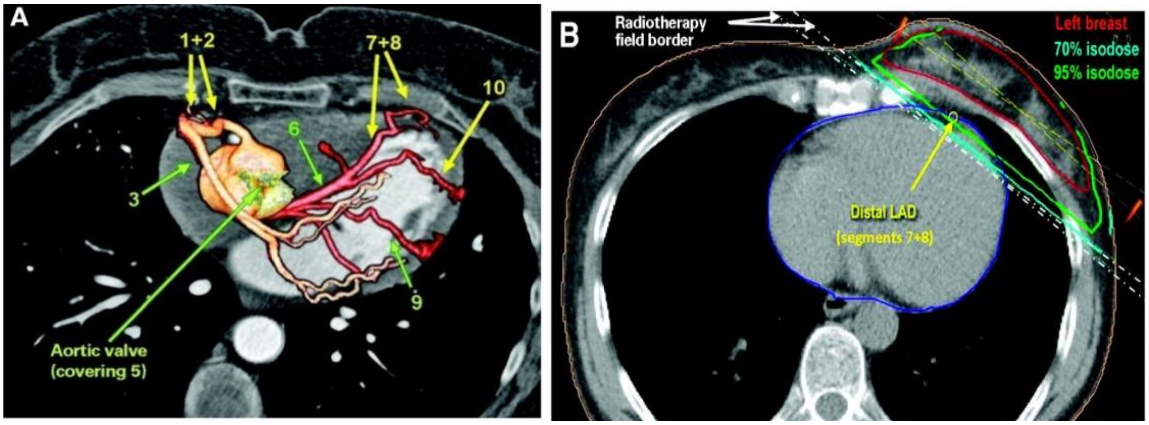

Figure. 5. **(A)** Coronary angiogram superimposed on CT of heart illustrating anatomy of coronary arteries with branches of right coronary artery (orange) and left circumflex and left anterior descending arteries (red); numbered arrows indicate segments. **(B)** CT dose-planned left tangential breast irradiation showing distal left anterior descending arteries (yellow circle) and radiation fields[29].

Another study by Darby et *al.*, reported the risk of ischemic heart disease in 2'168 women after radiotherapy for breast cancer [28]. Results showed that the rate of major coronary events *(i.e.*, myocardial infarction, coronary revascularization, or death from ischemic heart disease) increased by 7.4% per Gray (mean radiation dose to the heart).

Lung acute radiation-induced toxicity is radiation pneumonitis that often occurs within several weeks after completion of radiotherapy. Chronic radiation-induced lung cancers may occur starting 10 years after breast irradiation the risk lasting 30 years and longer [31]. Kaufman et *al.*, investigated the radiation-related mortality from second-primary lung cancer in treated breast cancer patients [32]. The mortality hazard ratio from lung cancer (ipsilateral *vs.* contralateral) increased with time and was 1.05, 2.04, and 3.87 at <10, 10–20, and >20 years, respectively.

6. Prone whole breast radiotherapy

6.1 Prone position was introduced in 1994

Whole breast irradiation was initially implemented with patients lying supine with the breast flattening on the chest wall and its contents including the tumor bed coming close to the chest wall [33]. In 1994, the Memorial Sloan-Kettering Cancer Center (MSKCC) first reported on a prone position technique for whole breast irradiation in women with large breasts [34]. A special breast couch was designed on top of which the patient was positioned prone with the irradiated breast hanging down through a dedicated couch aperture. Lying prone breasts move away from the chest wall by gravity. In the first cohort of 56 patients investigators elaborated isodose distributions generated in a transverse plane in both prone and supine positions. With the former high dose regions were decreased (better homogeneity). After 3 years' follow-up, the MSKCC group reported the clinical results with minimal skin toxicity, good breast cosmesis, and good tumor control [35].

Prone breast positioning devices are nowadays commercially available. Kirby et *al.*, reported a randomized study of supine *vs.* prone whole breast radiotherapy comparing set-up errors with CBCT and respiratory motion [36]. Although, set-up errors were greater in patients treated prone compared to those treated supine (chest-wall and clip displacement) patients treated prone showed reduced respiration motion than those treated supine (4D-CT).

6.2 Disease control and dosimetric study

Long-term disease control results of prone *vs.* supine whole breast radiotherapy have shown to be equivalent. Lauren et *al.*, reported excellent clinical result after a median of 4.9 years follow-up in 245 women with 248 early-stage invasive or *in-situ* breast cancers [37]. The 5-year local breast tumor recurrence rates was 4.8%; the 5-year disease-free survival,

disease-specific survival, and overall survival rates were 89.4%, 97.3%, and 93%, respectively. Regarding skin acute toxicity, whole-breast irradiation in prone position for large breasts has resulted in reduced acute moist skin desquamation, dermatitis, edema, pruritus and pain [38]. There is also a significant dose sparing effect from prone position to the ipsilateral lung. Nonetheless, under the influence of the gravity the heart moves anteriorly towards the chest wall and presents a larger contact surface with the chest wall when treated prone [39]. This is a clear drawback of prone treatments for patients with left-sided tumors as the heart risks to be more exposed using tangential beams than it might be in supine [40].

Several dosimetric studies with patients simulated both in supine and prone positions have been published. Table 5 presents some of these studies (only those with >45 patients) [41-46]. When focusing on ipsilateral lung doses, prone was found to be the optimal lung sparing system. Regarding the heart, the left anterior descending coronary artery, and the contralateral breast the comparison between prone and supine was less reliable. Considering factors such as anatomical variability between individuals, organ displacement differences, and post-surgical changes, the potential dosimetric benefit of prone *vs.* supine or viceversa can only be determined in a patient-to-patient basis. This entails two CTs (one prone, one supine) and two treatment planning calculations with the drawback of a double irradiation exposure from the CTs to the patient and an increased workload for radiation oncologists and dosimetrists. Clinical factors that can help to select beforehand which position would be most advantageous for any given patient.

6.3 Delineation target and OARs

Contouring the clinical target volume (CTVs) and OARs requires expertise. Large intra- and inter-observer variations exist at contouring the whole breast and the heart [47,48] strongly influencing dosimetry and dose distribution. Existing consensus guidelines and

contouring atlas may improve inter-observer agreement for supine treated patients [47,49]. For patients treated prone consensus is more difficult to reach between authors regarding contouring matters [44,50].

Table 5 Dosimetric studies of supine-prone breast radiotherapy reporting dual CT-planning with ≥ 40 patients.

Author, publication year	Patients N	Left breast N	Structure analyzed							Breast volume (ml)
			Breast PTV	lung ipsilateral	Heart	LAD	Breast contralateral	Tumor bed	Lung contralateral	
Varga *et al.,* 2009 [41]	61	34	S	P	≈	N/A	S	N/A	N/A	N/A
Kirby *et al.,* 2010[42]	65	30	N/A	P	≈	S	N/A	N/A	N/A	896
Lymberis *et al.,* 2012 [43]	100	53	N/A	P	P	N/A	N/A	N/A	N/A	735
Krengli *et al.,* 2013 [44]	41	17	S	P	≈	≈	N/A	N/A	N/A	525
Varga *et al.,*, 2014 [45]	138	138	≈	P	P	P	≈	N/A	N/A	962
Wurschmidt, *et al.,* 2014 [46]	46	13	N/A	P	≈	S	N/A	N/A	N/A	1718

P: favors prone. S: favors supine. ≈: no signigicant difference. N/A: not available. LAD: left anterior descending coronary.

In the present study, in order to identify the optimal treatment position, patients have been simulated one by one both, supine and prone with the drawback of long contouring times as drawing the PTV and OARs had to be done twice. In order to reduce the contouring time, increase the contouring reliability, and improve the inter-observer reproducibility, automatic segmentation (AS) may be the solution for patients treated prone.

7. Automatic segmentation solutions

Computer-assisted AS and deformable image registration techniques have been recently introduced in radiotherapy practice with the aim to improve contouring efficiency and reduce

the inter- and intra-individual variations in delineated contours [51-55]. For AS purposes a library has to be build-up first with a variety of patient models including all structures of interest on CT simulation images thus helping to create a reference atlas. Structures will be selected from the library and registered with the real patient CT images with deformable image registration algorithms. The process of selecting and transferring all involved contours is little time consuming. In order to optimize the patient matching with cases from the atlas collection, the later can be stratified by tumor location, tumor stage, and patient's specific physical characteristic. Automatic generated contours can always be edited manually before final validation [51,54].

Atlas-based automatic segmentation has already been evaluated for tumors and sites such as breast [53], endometrium [51], prostate, and head/neck [52]. Delineation times with AS were reduced as well as inter-observer contouring differences. The breast, heart, and lungs are well defined and contrasted organs on simulation CT compared to CTVs in other anatomical sites such as anorectal, bowel, and head and neck regions [52,53]. Reed *et al.*, [56], evaluated the performance of an atlas-based AS to contour the whole breast in supine position. Several breast cancer experts tested the system and it could be observed that inter-observer variations with AS were reduced compared to manual delineation. Furthermore, Lorenzen et *al.*, [57] investigated AS of the heart for breast cancer treatment planning and also observed results comparable to manual delineation in terms of dose distribution and spatial similarity. The best results were obtained by using 8-9 atlas cases to reach comparable performances. Nevertheless, AS of the heart was time-consuming (30 min/case) more than the average 5-10 minutes needed for manual segmentation. Contouring efficiency and contouring time reduction should be the main goals of AS.

8. Study aims

The purpose of this thesis is to assess the pros and cons of prone position for whole breast radiotherapy and the contouring reliability of AS in patients lying prone for this purpose.

Two areas of work have been identified:

- A dosimetric study: 282 breast cancer patients with a dual planning (supine and prone) fully eligible for a comparative dosimetric evaluation with dose volume histograms (DVH). It was aimed to evaluate whether or not a change from supine to prone was associated with a comparative dosimetric gain thus the lowest dose to the OARs (heart, lungs, and contralateral breast) while the PTV received the prescribed dose with an optimal homogeneity.

- A contouring study: we assessed an atlas-based AS software, the Smart Segmentation Knowledge Based Contouring (Varian Medical Systems, Palo Alto, California) system, for patients treated prone for whole breast irradiation. We selected 40 CT planning images aiming to evaluate the time saving, the reliability, and the accuracy of atlas-based automatic delineation in front of manual contouring for the CTV, the heart, the left anterior descending coronary artery, the contralateral breast, and both lungs. Patient-related anatomical patterns were assessed to improve the accuracy of segmentation process for an optimal atlas modeling.

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10. Abbreviations and Acronyms

Abbreviations	French name	English name
DD	décubitus dorsale	dorsal decubitus
DV	décubitus ventral	ventral decubitus
OARs	organes à risque	organs at risk
AS	atlas-bibliothèque segmentation automatique	atlas-based automatic segmentation
CTV	volume cible anatomo-clinique	clinical target volume
LADA	artère coronaire antérieure descendante gauche	left anterior descending coronary
RCA	artère coronaire droite	right coronary artery
BMI	surface corporelle	*body mass index*
BCS	taille de soutien-gorge	*breast cup size*
DVH	Histogramme du dose-volume	dose volume histogram
DSC	index de similarité	*dice similarity coefficient*
DiBH	inspiration bloquée	deep inspiration breath hold
TNM	la tumeur primitive, le ganglion lymphatique et les métastases	the primary tumor, lymph node, and metastasis
ER	récepteur d'oestrogènes	estrogen receptor
PR	récepteur de progestérone	progesterone receptor
HER2	récepteur du facteur de croissance épidermique humain 2	human epidermal growth factor receptor 2
OS	survie globale	overall survival
NCCN		National Comprehensive Cancer Network
CT	tomodensitométrie	computer tomography
PET	tomographie par émission de positron	positron-emission tomography

MRI	imagerie par résonance magnétique	breast magnetic resonance imaging
DCIS	carcinome canalaire in situ	ductal carcinoma in situ
EBCTCG		Early Breast Cancer Trialists' Collaborative Group
RT	Radiothérapie	radiotherapy
MSKCC		Memorial Sloan-Kettering Cancer Center
CBCT		cone beam computer tomography
RTOG		Radiation Therapy Oncology Group

11. Appendix tables: The 2002 TNM Classification

Table 1. American Joint Committee on Cancer Definition of Primary Tumor (T)—Clinical (cT) and Pathological (pT)

T Category	T Criteria
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS) [a]	Ductal carcinoma in situ (DCIS)
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
T1	Tumor ≤ 20mm in greatest dimension
T1mi	Tumor ≤ 1mm in greatest dimension
T1a	Tumor > 1mm but ≤ 5mm in greatest dimension (round any measurement from >1.0 – 1.9 mm to 2 mm)
T1b	Tumor > 5mm but ≤ 10mm in greatest dimension
T1c	Tumor > 10mm but ≤ 20mm in greatest dimension
T2	Tumor > 20mm but ≤ 50mm in greatest dimension
T3	Tumor > 50mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualify as T4
T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4
T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema of the skin that does not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma

a Lobular carcinoma in situ is a benign entity and is removed from TNM staging in the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, eighth edition.

Table 2. American Joint Committee on Cancer Definition of Regional Lymph Nodes—Clinical (cN) and Pathological (pN)

Category	Criteria
cN[a]	
cNx[b]	Regional lymph nodes cannot be assessed (eg, previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral level I and II axillary lymph node(s)
cN1mic	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
cN2	Metastases in ipsilateral level I and II axillary lymph nodes that are clinically fixed or matted; or in ipsilateral internal mammary lymph nodes in the absence of axillary lymph node metastases
cN2a	Metastases in ipsilateral level I and II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary lymph nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I and II axillary lymph node involvement; or in ipsilateral internal mammary lymph node(s) with level I and II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)
pN[d]	
pNX	Regional lymph nodes cannot be assessed (eg, not removed for pathological study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph node(s)
pN0(	Positive molecular findings by reverse transcriptase-polymerase chain

mol+)		reaction (RT-PCR); no ITCs detected
	pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or clinically negative internal mammary lymph nodes with micrometastases or macrometastases by sentinel lymph node biopsy
	pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
	pN1a	Metastases in 1-3 axillary lymph nodes, at least one metastasis larger than 2.0mm
	pN1b	Metastases in ipsilateral internal mammary sentinel lymph nodes, excluding ITCs
	pN1c	pN1a and pN1b combined
	pN2	Metastases in 4-9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
	PN2a	Metastases in 4-9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)
	pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary lymph nodes
	pN3	Metastases in 10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive level I and II axillary lymph nodes; or in more than 3 axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
	pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
	pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary lymph nodes by imaging); or pN2a in the presence of pN1b
	pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Abbreviation: ITCs, isolated tumor cells. [a] The (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel lymph node biopsy or fine-needle aspiration/core needle biopsy, respectively. [b] The cNX category is used sparingly in patients with regional lymph nodes that were previously surgically removed or if there is no documentation of physical examination of the axillar. [c]cN1mi is rarely used but may be appropriate in patients who undergo sentinel lymph node biopsy before tumor resection, which is most likely to occur in patients who receive neoadjuvant therapy. [d] The (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel lymph node biopsy or fine-needle aspiration/core needle biopsy, respectively, with NO further resection of lymph nodes.

Table 3. American Joint Committee on Cancer Definition of Distant Metastasis （M）—Clinical (cM) and Pathological（pM）

M Category	**M Critera**
M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or and no deposits no greater than 0.2mm detected microscopically or by using molecular techniques in circulating blood, bone marrow, or other nonregional lymph node tissue in a patient without symptoms or signs of metastases
M1	Distant metastases detected by clinical and radiographic means (cM) and/or histologically proven metastases larger than 0.2mm (pM)

[a]Note that imaging studies are not required to assign the cM0 category.

Table 4. American Joint Commission on Cancer breast cancer TNM Anatomic Stage Groups [a]

WHEN T IS…	AND N IS…	AND M IS….	THEN THE STAGE GROUP IS…
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

[A] The Anatomic Stage Group table should only be used in global regions where biomarker tests are not routinely available. Cancer registries in the United States must use the Prognostic Stage Group table for case reporting.

II. Study 1: Dosimetric Gain Analysis of Prone-Free Breathing and Supine-Deep Inspiration Breath Hold for Left-Whole Breast Radiotherapy

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Abstract

Background and purpose: Prone setup has been advocated as a technique to improve organ sparing in whole breast radiotherapy without impairing breast dose coverage. The present study evaluates the dosimetric gain of prone setup and aims to identify patients' characteristics that can predict the gain.

Methods: Breast cancer patients treated in 2010-2013 who had a dual planning in supine and in prone position were retrospectively identified. Radiation to heart, lungs, breasts, tumor bed, and body were evaluated by dose volume histogram (DVH). A global penalty score was computed as a weighted sum of supine-prone differences of the mean doses to organ at risks (DOAR) and the mean absolute dose deviation from prescription to targets (DPTV). Recursive partitioning was used to identify significant classifiers.

Results: A total of 282 patients were accrued, 138 lefts, of whom 113 had supine setup in deep inspiration breath hold (DiBH), 144 right breast cancer. Heart, contralateral lung, breasts, and tumor bed presented small dose differences <1% in favor of supine position. Ipsilateral lung and body presented 6.34% and 1.29% dose difference, respectively, in favor of prone position. The global score showed that 180 (64%) patients had a dosimetric advantage with prone, versus 102 (36%) with supine position. Partitioning analysis found DiBH to be the only significant predictor favouring supine treatment position.

Conclusion: Prone was associated with a dosimetric gain in the majority of patients. Supine position appeared advisable only in left breast patients who could be treated in DiBH.

Keywords: Breast cancer, radiation treatment planning, supine, prone, N-of-1, dose volume histogram, dual-CT, breath control, deep inspiration breath-hold, dosimetric gain.

Introduction

Breast cancer is the leading cause of cancer incidence and disability in women [1]. Death rates have been stable or decreasing [2], reflecting early detection and improved treatment. Improved survival indicates the growing need for treatment research to reduce the risk of treatment sequels. Randomized clinical trials have repeatedly shown the importance of adjuvant radiotherapy for the local control of breast cancer [3-6]. The survival benefit has however been modest. Most notably in older clinical trials, the advantage of local control was offset by an increased risk of heart and lung toxicity [7, 8].

Many radiotherapy techniques have addressed the challenge to reduce the risk of toxicity while preserving the chance of anticancer control [9-12]. Prone radiotherapy has been advocated as a lung and heart sparing technique [13]. In prone setup, the breast hangs down through an opening. The breast and its contents fall away from the chest wall, allowing tangential fields to avoid intrathoracic organs while maintaining coverage of the breast [14, 15]. However, under the influence of the gravity in prone position, the heart also moves anteriorly closer to the chest wall and presents with a larger contact surface with the chest wall [16]. Radiation dose sparing of the heart might be less than expected or might even be disadvantageous [10]. The dosimetric implications of prone positioning will depend on the location of the breast target tissues relatively to the heart and chest wall [17].

Considering the variability of individual anatomies, of organs displacements, of post-surgery changes, the advantage of prone or supine position can only be determined by individual planning comparison. Individual planning comparison entails twice CT-simulation and twice dosimetry. The drawback is the burden of a double CT exposure on the patients and the increased workload on the radiotherapists and the dosimetrists. There is a need for clinical tools to determine beforehand which position would be most advantageous for any given patient.

In this study, the primary objective was to evaluate whether or not a change of radiation treatment setup from supine to prone was associated with a dosimetric gain, meaning the lowest radiation dose to non-target organs (heart, lungs, contralateral breast) while giving the prescribed dose to the tumor bed and the ipsilateral breast. The secondary objective was to search for clinical characteristics that could predict the dosimetric gain.

Materials and methods

Patients were retrospectively selected through the Geneva University Hospitals' radiotherapy database. Selection criteria were women referred in 2010-2013 for adjuvant radiotherapy after breast conserving surgery for completely resected primary breast cancer, in whom CT simulation and treatment planning were done prone and supine. The study received Institutional Review Board approval and was registered under ClinicalTrials.gov Identifier NCT02237469.

Referred patients were seen at consultation. The clinical examination included an assessment of the patient's mobility and breast deformability. Patients with left breast cancer were timed for the ability to stably sustain DiBH for 20 seconds, and were further instructed with a nurse to breath-hold exercises at home. The patients received information about the treatment procedures and gave written consent prior to simulation.

At simulation, the patient was positioned supine on an inclined breast board with arms extended above head. Breath-hold capability was re-ascertained in left breast cancer patients. CT-images with 3 mm slices were acquired without contrast. The scan range covered the entire lungs and breasts, from the top of the lungs to 5 cm caudal to the breasts or to the base of the lungs, whichever was the most caudal.

Thereafter the patient was positioned prone using the Bionix Prone Breast System in 2010-2012 and the Varian Pivotal Prone Breast Care since 2013. The contralateral breast

rested on a 5 degrees foam wedge. The ipsilateral breast was inspected to hang unhindered and centered through an ipsilateral opening in the couch support. CT-images were acquired with the same parameters as supine. Posterior and lateral positioning marks were tattooed.

An evaluation score recorded the patient's subjective feelings of pain, fear, anxiety, and discomfort, and position preference at the end of simulation.

For treatment planning, the breast clinical target volume (CTV) was drawn cranially up to 1 cm below the sternoclavicular joint, caudally to the farthest visible breast contour, medially to the perforating mammary vessels or to the edge of the sternum, laterally to the lateral breast-skin fold, posteriorly to but not beyond the surface of the pectoralis muscle or ribs and intercostal muscles, anteriorly to 5 mm under the skin surface [18-20]. The tumor bed CTV was based on combined clinical, radiological and surgical-pathological data. Planning target volume (PTV) equated CTV without expansion. Delineation of the contralateral breast included the skin surface. Delineation of the heart included the pericardium and the basis of the large vessels [21], but not above the top of the left atrium. Delineation of the lungs and the body's external contour used automatic segmentation.

Dose prescription generally was 47.25 Gy to the breast in 21 fractions, 4 fractions/week [22]. Treatments were planned without boost using Varian Eclipse with constraints of 95% of prescribed dose covering 95% of breast PTV and covering 100% of tumor bed PTV, breast PTV V107% < 2 cc, ipsilateral lung V20 Gy < 10%, heart near max D2% < 15 Gy, and heart mean dose < 3 Gy. Treatment beams were required to avoid the contralateral breast. Combination of wedges, field in field compensation, mixing different photon energies, and heart block were allowed.

To evaluate the treatment plans, dose volume histograms (DVH's) were expressed on relative doses and relative volumes. The mean dose (D_{OAR}) to OARs and the absolute deviation from prescribed dose (D_{PTV}) to PTVs were used as penalty indicators of OAR and

PTV doses. The dosimetric gain (Δ) from supine to prone was computed as the difference between the D_{OAR}'s for OARs, and as the difference between the D_{PTV}'s for PTVs:

$$\Delta\,(\text{OAR}) = D_{OAR}(\text{OAR supine}) - D_{OAR}(\text{OAR prone})$$

$$\Delta\,(\text{PTV}) = D_{PTV}(\text{PTV supine}) - D_{PTV}(\text{PTV prone})$$

A negative Δ would indicate better doses with supine (no prone dosimetric gain), a positive Δ would indicate better doses with prone dosimetric gain.

In order to define an indicator of overall dosimetric gain, we defined a composite index ΔWsum as a weighted sum of the changes from supine to prone:

$$\Delta_{Wsum} = (4\,\Delta_{Hrt}) + (\Delta_{Hrt}/6)_3 + \Delta_{Lips} + \Delta_{Lctl} + (2\,\Delta_{Tbed}) + \Delta_{PTV} + \Delta_{Bctl} + \Delta_{Body}$$

Where Δ_{Body} was computed using body's mean dose (%) x body volume (cc) / 20,000 (cc) to adjust for different scanning lengths. The Δ_{WSum}'s weights indicate that we assigned higher priority to the heart than the Danish Breast Cancer Cooperative Group [23].

Data analyses used abstracted patient's data: age, height, weight, body mass index (BMI), bra cup size, breast tumor laterality, quadrant location, histopathological type and grade, clinical T-stage, planning breast and heart volumes, use of DiBH or not, patients' preference, and the position actually selected for the patient's treatment.

The relationship between patients' characteristics and Δ outcomes were analyzed using the analysis of variance with Δ on a continuous scale, and using contingency tables with Δ binarized as supine better (ΔOAR or ΔPTV <= 0) vs. prone better (ΔOAR or ΔPTV > 0). The Student t-test was used for significance testing of continuous variables. The Chi-square test was used for significance testing of contingency tables. Recursive partitioning was used to identify potentially meaningful hierarchies of characteristics to predict the outcomes [24, 25]. All statistical computations used R version 3.1.2 [26]. Recursive partitioning used the package "party" [24].

Results

We identified 290 patients who underwent dual CT simulation. Eight were excluded: 5 bilateral synchronous breast cancer, 1 volumetric modulated arc therapy, and 2 non-finalized prone planning. The remaining 282 patients constitute the study population.

Table 1 summarizes the patients' characteristics. The age distribution was comparable to registry data except for an underrepresentation of the >65 years old age by 5-10% [27]. BMI overweight and obesity were found in 52.6% (32.4% + 20.2%) of the non-missing cases, higher than the expected 38% prevalence [28]. DiBH was realized in 113 patients, representing 81.9% of 138 patients with left breast cancer. Patients' preference was supine in 52.6% of the cases. The actually delivered treatment was distributed evenly between supine and prone setup, in 47.9% and 52.1% of the patients, respectively.

Figure 1 provides a visual comparison of heart, lungs, breasts, and tumor bed DVHs for the whole study population, right and left cases confounded. All structures other than the contralateral lung displayed large variability. The variability affected more prone by the heart, tumor bed and breasts (preponderant thin blue lines). The variability affected more supine by the ipsilateral lung (preponderant thin red lines). The differences in mean doses were however small, all Δ's were <1%, except by the ipsilateral lung where the mean dose received supine exceeded by 6.34% the dose received prone. The body received a higher dose in supine position, $\Delta = +1.29\%$, $P < 0.001$ (Figure 2).

Table 2 details the Δ's. Supine was advantageous to the heart, the contralateral lung, and the contralateral breast in 87.6%, 75.5%, and 95.4% of the cases, respectively. Prone was advantageous to the ipsilateral lung and the body in 98.9% and 85.1% of the cases, respectively. Δw_{sum} showed an overall dosimetric advantage with prone in 63.8% (180 of 282), and with supine in 36.2% (102 of 282) patients, $P<0.001$.

Subgroup associations found by univariate analyses are summarized in Table 3. By patient's characteristic (browsing from row to row), higher weight and higher BMI were associated with improved prone dose distribution for the heart, the ipsilateral lung, and the breast PTV. Larger bra cup size and likewise larger breast volumes were associated with improved prone doses. Right tumor laterality and free breathing were associated with better doses in prone to the heart and the contralateral lung. By structure (browsing from column to column), there were no significant associations between tumor bed doses and patient's characteristics. The contralateral breast was associated with weight and breathing mode. Better body dosimetry associated with prone position was not affected by laterality or by breathing mode, but changed significantly with weight, BMI, breast volume, and with tumor quadrant localization. By ΔW_{sum}, significant subgroup associations were found with laterality, breathing mode, and breast volume, but not with other characteristics.

Recursive partitioning with specific outcomes identified a weight of 72 kg as a classifier subsidiary to non-DiBH for the heart, laterality as classifier for the ipsilateral lung, and a breast volume of 450 cc (figure rounded) as classifier for the breast PTV (Figure 3.A-C). Supine was increasingly unfavorable to the body with breast volume breakpoints of 680 cc and 1250 cc (Figure 3.D). No classifier were retained regarding the tumor bed PTV, the contralateral lung, and the contralateral breast.

Recursive partitioning using ΔW_{sum} for overall outcome suggested breathing mode (significant) and breast volume (non-significant) as classifiers (Figure 4). The boxplots show ΔW_{sum} according to the classifiers. Patients without DiBH were most likely to benefit from prone setup, regardless of any other characteristic (Figure 4's Node 2, positive boxplot). Patients with DiBH could be separated into a group with breast volume $\leq$220 cc (figure rounded) most likely to benefit from supine (Node 4, negative boxplot), and a group with a

volume >220 cc who had equal chance to benefit from one or the other position (Node 5, boxplot centered on 0).

Discussion

Since Merchant et al.'s original communication on prone breast irradiation in 1994 [29], 29 publications have reported same-patient dual prone and supine dosimetric comparisons [30-58]. Six reported on 40 or more patients, the largest included 138 patients (Table 4). The prone sparing effect on the lung is unanimously recognized, but for other structures the evidence has been conflicting. We believe that our study is a substantial contribution, which furthermore is less biased toward large breasts, therefore potentially applicable to a majority of patients.

Our study shows that dose distribution was better for supine treated patients with regard to heart (this has been reported in small series [36, 51, 54, 56], but not in the larger series of Table 4), breast PTV [37, 49], tumor bed PTV (not reported elsewhere), contralateral breast [37], and contralateral lung (not reported elsewhere).

The patients received very low heart doses. Heart toxicity has long been known to radiation oncologists [59, 60]. Heart sparing techniques were already implemented very early on. In our department, heart block became standard when Raj et al.'s report suggested that it was safe [61]. Experience learned with a body plethysmograph system [62] further allowed us to implement DiBH in our left breast cancer patients [63]. The average difference in mean heart doses was less than 1% of prescribed dose, that is, less than 0.5 Gy in a conventional whole breast treatment of 50 Gy. Likewise, the dose differences of contralateral lung, breasts and tumor bed PTV were exceedingly small (Figure 1).

Prone was associated with improved dose sparing to the lung. We reflect that the heart has received major attention [10-12]. However, in the modern radiotherapy of early

breast cancer, care given to sparing the heart has come to the point that no measurable effect can be demonstrated. In the "Tomobreast" randomized breast cancer trial comparing post-operative conventional radiation treatment with Tomotherapy, prospective heart monitoring found no measurable effect, whereas lung monitoring found early deterioration of lung function in the conventional treatment arm [64, 65]. The importance of lung sparing should not be overlooked.

The body dose difference was proportionally small, 1.29%, nevertheless represented an average of 250 cc body volume receiving an excess dose in supine as compared to prone (Figure 2). Supine excess doses to non-target tissues have been reported [44, 48]. In supine position, tangential fields have to extend far laterally and posteriorly (Figure 5, left). In prone position, the tangential fields do not extend that far back (Figure 5, right).

Prone was associated with an overall dosimetric gain in 63.8% patients (Table 2). DiBH (confounded with left breast laterality) was the foremost predictive factor of a dosimetric gain (Figure 3). Supine was advantageous in women with left breast cancer who could sustain DiBH [54, 56]. A 220ml breast volume cutoff was suggested as a possible predictor among the DiBH patients. That volume corresponds to the smallest bra cup size in our patients (Table 5). We rejoin Zhao et al. who showed that breast volume by itself failed to reliably predict the optimal position [66], and Ramella et al. who found a dosimetric benefit in all patients subgroups irrespective of breast volume [44].

Prone can be more demanding than supine setup [46]. However, reproducibility difficulties were not an obstacle to implementing prone. Inter-fractional errors were addressed by daily imaging and daily correction. Intra-fractional errors required no extra management. In the Ghent prospective trial, no significant differences in random and systematic errors were found between prone and supine setup [46]. Positioning reproducibility has not been found to be an issue [47, 67]. Few problems were encountered. In 4 patients, a repeat prone CT

simulation was done mid-therapy without requiring setup change. Setup was modified in 3 cases, 2 from supine to prone (1 DiBH patient who could not hold breath anymore, 1 whose planning was revised), and 1 from prone to supine due to increased discomfort on the prone couch.

Limitations include the retrospective data and selection bias. Patients' age and BMI indeed showed a trend to select younger overweight patients. About 10-15% of our patients eligible for breast radiotherapy did not receive dual CT simulation, the reasons were not recorded. Left anterior descending coronary delineation was not part of our standard contours. Sethi et al. showed that outcome differed considerably between 3-field vs. 4-field vs. intensity modulated radiotherapy (IMRT) [45]: our plans did not explore these possibilities. DVHs do not provide spatial information [68]. The actual treatment given to patients depended on 3-dimensional dose distributions which the present study did not reviewed.

Strengths of the study include the large number of patients. Beyond that, we would like to emphasize the one-person comparisons. Randomization in a clinical trial aims 'that subjects receiving the intervention are similar to those in the comparison group, both in regard to any other care they receive and in regard to other characteristics which might influence the outcome' [69]. Our prone and supine treatment plans were done with intent to treat. Known or unknown characteristics whether patient related or operator-related such as delineation inaccuracies would exactly balance out in the dual plans. Confounding factors between the treatments arms would distribute evenly since each patient was her own control. Data collection was retrospective, but on all other accounts the present study is akin to the class of N-of-1 trials [70].

We commented that organ displacements were not predictable. The situation might change with new imaging in breast cancer workup [71]. Dual position preoperative breast imaging are actively researched, MRI from prone to supine [72], FDG-PET/CT from supine

to prone [73-75]. In their review of PET/MR, Tabouret-Viaud et al. have shown the first published cases of preoperative PET/MR and prone CT-planning registration [71]. For patients who would still require dual CT-planning, perspectives might be imaging with new generations of intelligent low-dose CT [76].

Conclusion

One-person dosimetric comparisons showed an overall advantage with prone position in the majority of patients. To reduce dual CT-planning, prone setup might be considered first in patients with left breast cancer who cannot hold breath in deep inspiration and in patients with right breast cancer. In patients with left breast cancer who can maintain deep inspiration, supine in deep inspiration breath hold might be considered as the first option. In a patient with cardiac or pulmonary comorbidity, immediate dual CT-planning would be advisable.

Table 1. Patients' characteristics.

characteristics	N	%
Age (years)		
<= 50	81	28.7
51 – 65	113	40.1
> 65	88	31.2
Body mass index (BMI, kg/m2)		
<= 25	113	40.1
26 - 30	77	27.3
>30	48	17.0
Missing	44	15.6
Laterality		
Left	138	48.9
Right	144	51.1
Tumor location		
Central and inner	59	20.9
Outer	145	51.4
Other	78	27.7
Deep inspiration breath hold		
DiBH: No	169	59.9
DiBH: Yes	113	40.1
Heart volume (ml)		
<= 450	95	33.7
451 – 550	111	39.4
> 550	76	27.0
Breast volume (ml), supine		
<= 400	97	34.4
401 – 600	83	29.4
601 – 800	52	18.4
> 800	50	17.7
Actual treatment position		
Supine	135	47.9
Prone	147	52.1
Couch		
Bionix	229	81.2
Pivotal	53	18.8
Patient's preference		
Supine	102	36.2
No preference	45	16.0
Prone	47	16.7
Missing	88	31.2

Table 2. Summary of supine-prone planning comparisons

Outcome	Penalty	Patients

Evaluation	Supine	Prone	Difference supine – prone	Supine better (Δ ≤ 0)		Prone better (Δ > 0)		Chi2 *P*-value
				N	%	N	%	
Heart	1.76	2.68	$\Delta Hrt = -0.92$	247	87.6	35	12.4	< 0.001
Lung ipsilateral	8.67	2.33	$\Delta Lips = +6.34$	3	1.1	279	98.9	< 0.001
Lung contralateral	0.59	0.70	$\Delta Lctl = -0.12$	213	75.5	69	24.5	< 0.001
Breast contralateral	0.86	1.77	$\Delta Bctl = -0.92$	269	95.4	13	4.6	< 0.001
Breast PTV	2.39	2.66	$\Delta PTV = -0.27$	182	64.5	100	35.5	< 0.001
Tumor bed PTV	1.77	2.04	$\Delta Tbed = -0.28$	148	52.5	134	47.5	0.404
Body (normalized to 20,000 ml)	7.87	6.58	$\Delta Body = +1.29$	42	14.9	240	85.1	< 0.001
Global score			**$\Delta Wsum = +1.95$**	**102**	**36.2**	**180**	**63.8**	**< 0.001**

The Penalty is defined as: mean dose D_{OAR} (%) for organ at risk (heart, lungs, breast contralateral), absolute dose deviation from prescription D_{PTV} (%) for target volumes (breast PTV, tumor bed PTV).

The Difference supine–prone is defined as: $\Delta_{Structure}$ = (Structure's Penalty supine –Structure's Penalty prone)

The Global score is defined as: $\Delta_{Wsum} = (4\,\Delta_{Hrt}) + (\Delta_{Hrt}/6)_3 + \Delta_{Lips} + \Delta_{Lctl} + (2\,\Delta_{Tbed}) + \Delta_{PTV} + \Delta_{Bctl} + \Delta_{Body}$.

Table 3. Subgroup analyses: dosimetric outcomes by patients' characteristics.

Characteristic		N	Heart		Lung ipsilateral		Lung contralateral		Tumor bed		Breast PTV		Breast contralateral		Body		Composite index	
			% prone better	Δ_{Hart}	% prone better	Δ_{Luip}	% prone better	Δ_{Luco}	% prone better	Δ_{Tbed}	% prone better	Δ_{Bptv}	% prone better	Δ_{Brco}	% prone better	Δ_{Body}	% prone better	Δ_{Wsu}
ALL		282	12.4	-0.92	98.9	6.34	24.5	-0.12	47.5	-0.28	35.5	-0.27	4.6	-0.92	85.1	1.29	63.8	1.9
Weight (kg)	≤ 60	82	6.1	-1.31	96.3	6.21	29.3	-0.14	52.4	-0.14	28.0	-0.46	8.5	-0.71	86.6	0.98	56.1	0.2
	61-75	115	12.2	-0.87	100.0	6.64	18.3	-0.13	46.1	-0.37	31.3	-0.24	0.9	-0.96	84.3	1.24	64.3	2.1
	> 75	65	23.1	-0.60	100.0	6.17	27.7	-0.08	49.2	-0.33	52.3	-0.09	3.1	-1.19	86.2	1.72	67.7	3.4
***P*-value**			0.009	0.028	0.036	0.545	0.149	0.309	0.678	0.697	0.004	0.106	0.020	0.069	0.894	0.005	0.309	0.26
BMI (kg/m²)	≤ 25	113	8.0	-1.26	98.2	6.36	27.4	-0.12	48.7	-0.28	33.6	-0.35	6.2	-0.75	86.7	1.12	57.5	0.3
	26-30	77	15.6	-0.64	100.0	6.49	19.5	-0.10	48.1	-0.09	28.6	-0.21	1.3	-1.15	85.7	1.29	66.2	3.5
	>30	48	27.1	-0.63	100.0	6.19	29.2	-0.10	50.0	-0.44	52.1	-0.09	4.2	-1.06	81.3	1.64	70.8	3.1
***P*-value**			0.006	0.018	0.328	0.882	0.361	0.758	0.978	0.571	0.023	0.325	0.256	0.099	0.663	0.106	0.216	0.16
Cup	A	9	0.0	-0.88	88.9	4.74	22.2	-0.16	66.7	-0.21	22.2	-0.18	11.1	-0.63	77.8	0.75	33.3	0.5
	B	102	8.8	-1.11	99.0	6.20	24.5	-0.10	49.0	-0.25	38.2	-0.25	2.9	-0.76	84.3	1.16	59.8	1.1
	C	79	16.5	-0.95	100.0	6.23	20.3	-0.12	45.6	-0.35	35.4	-0.30	2.5	-1.23	88.6	1.35	62.0	1.1
	D	19	36.8	-0.46	100.0	7.46	42.1	-0.09	47.4	-0.35	36.8	-0.13	10.5	-0.99	84.2	1.71	84.2	5.3
	E	5	40.0	-0.32	100.0	7.71	60.0	-0.01	60.0	0.15	80.0	0.92	0.0	-0.67	80.0	2.15	80.0	9.1
***P*-value**			0.005	0.588	0.026	0.198	0.127	0.718	0.782	0.980	0.295	0.099	0.344	0.195	0.859	0.230	0.091	0.45
Laterality	Left	138	10.9	-1.30	98.6	5.81	17.4	-0.15	46.4	-0.34	36.2	-0.36	7.2	-0.90	86.2	1.32	56.5	-0.4
	Right	144	13.9	-0.56	99.3	6.85	31.3	-0.09	48.6	-0.22	34.7	-0.18	2.1	-0.93	84.0	1.26	70.8	4.2
***P*-value**			0.556	0.000	0.970	0.006	0.010	0.049	0.798	0.580	0.888	0.139	0.075	0.855	0.725	0.694	0.017	0.00
Quadrant	Cent	20	5.0	-0.59	100.0	6.03	15.0	-0.16	45.0	-0.14	30.0	-0.36	5.0	-0.81	65.0	0.85	65.0	2.9
	LIQ	8	12.5	-2.14	100.0	5.39	12.5	-0.21	25.0	-0.94	37.5	-0.14	0.0	-0.76	62.5	0.92	50.0	-6.1
	LOQ	20	20.0	-0.66	100.0	7.52	35.0	-0.05	60.0	0.14	40.0	-0.28	10.0	-0.57	85.0	1.63	70.0	5.8
	UIQ	31	19.4	-0.57	100.0	6.75	38.7	-0.06	41.9	-0.58	32.3	-0.15	3.2	-1.43	93.5	1.87	67.7	3.5
	UOQ	125	12.0	-1.07	99.2	6.26	23.2	-0.12	48.0	-0.38	43.2	-0.16	5.6	-0.79	85.6	1.28	64.8	1.2
	Other	78	10.3	-0.86	97.4	6.19	21.8	-0.14	48.7	-0.07	24.4	-0.47	2.6	-1.05	88.5	1.14	60.3	2.1
***P*-value**			0.579	0.104	0.761	0.492	0.252	0.253	0.643	0.535	0.153	0.434	0.720	0.094	0.034	0.099	0.890	0.20
DiBH	Yes	113	3.5	-1.57	98.2	5.75	16.8	-0.15	46.9	-0.33	32.7	-0.48	8.8	-0.85	88.5	1.40	54.0	-1.5
	No	169	18.3	-0.49	99.4	6.74	29.6	-0.10	47.9	-0.24	37.3	-0.13	1.8	-0.96	82.8	1.22	70.4	4.3
P-value			0.000	0.000	0.724	0.010	0.021	0.039	0.962	0.701	0.514	0.006	0.013	0.470	0.256	0.295	0.007	0.00
Breast volume (cc)	≤ 400	97	3.1	-1.43	96.9	5.71	25.8	-0.14	54.6	-0.06	27.8	-0.52	8.2	-0.78	85.6	0.87	57.7	-1.0
	401-600	83	8.4	-0.85	100.0	6.68	15.7	-0.14	42.2	-0.52	32.5	-0.27	0.0	-0.91	78.3	1.03	59.0	1.9
	601-800	52	19.2	-0.64	100.0	6.79	25.0	-0.09	46.2	-0.28	40.4	-0.05	3.8	-0.83	90.4	1.49	73.1	4.1
	> 800	50	30.0	-0.37	100.0	6.56	36.0	-0.07	44.0	-0.31	50.0	0.00	6.0	-1.27	90.0	2.32	74.0	5.4
***P*-value**			0.000	0.000	0.123	0.108	0.066	0.188	0.360	0.448	0.047	0.010	0.065	0.136	0.163	0.000	0.088	0.00

$\Delta_{OAR} = D_{OAR}$ supine $- D_{OAR}$ prone. $\Delta_{PTV} = D_{PTV}$ supine $- D_{PTV}$ prone.

$\Delta_{Wsum} = (4\ \Delta_{Hrt}) + (\Delta_{Hrt}/6)^3 + \Delta_{Lips} + \Delta_{Lctl} + (2\ \Delta_{Tbed}) + \Delta_{PTV} + \Delta_{Bctl} + \Delta_{Body}$.

BMI： Body Mass Index; DiBH: deep inspiration breath-hold.

Table 4. Dosimetric studies of supine-prone breast radiotherapy reporting dual CT-planning with ≥ 40 patients.

Author, publication year	Patients N	Left breast N	Structure analyzed								Breast volume (ml)
			Breast PTV	Lung ipsilateral	Heart	LAD	Breast contralateral	Tumor bed	Lung contral lateral	Body	
Varga, 2009 [37]	61	34	S	P	≈	N/A	S	N/A	N/A	N/A	N/A
Kirby, 2010 [38]	65	30	N/A	P	≈	S	N/A	N/A	N/A	N/A	896
Lymberis, 2012 [41]	100	53	N/A	P	P	N/A	N/A	N/A	N/A	N/A	735
Krengli, 2013 [49]	41	17	S	P	≈	≈	N/A	N/A	N/A	N/A	525
Varga, 2014 [53]	138	138	≈	P	P	P	≈	N/A	N/A	N/A	962
Wurschmidt, 2014 [55]	46	13	N/A	P	≈	S	N/A	N/A	N/A	N/A	1718
Ours	282	138	S	P	S	N/A	S	S	S	P	553

P: favors prone. S: favors supine. ≈: no marked difference. N/A: not available. LAD: left anterior descending coronary.

Table 5. Relationship between breast cup size and breast volume.

	Breast volume (ml)					
Cup size	Min	1st Quartile	Median	Mean	3rd Quartile	Max
A	90	211	255	273	334	486
B	117	307	414	464	589	1433
C	218	469	572	617	765	1299
D	339	769	915	927	1178	1585
E	722	909	914	927	1002	1090
Missing	34	330	474	502	604	1580

Figures

Figure 1. DVHs of heart, lungs, tumor bed and breasts

Individual patients DVHs are plotted as thin lines. The pointwise average DVHs are plotted as thick lines. Red = supine. Blue = prone. Δ: prone dosimetric gain.

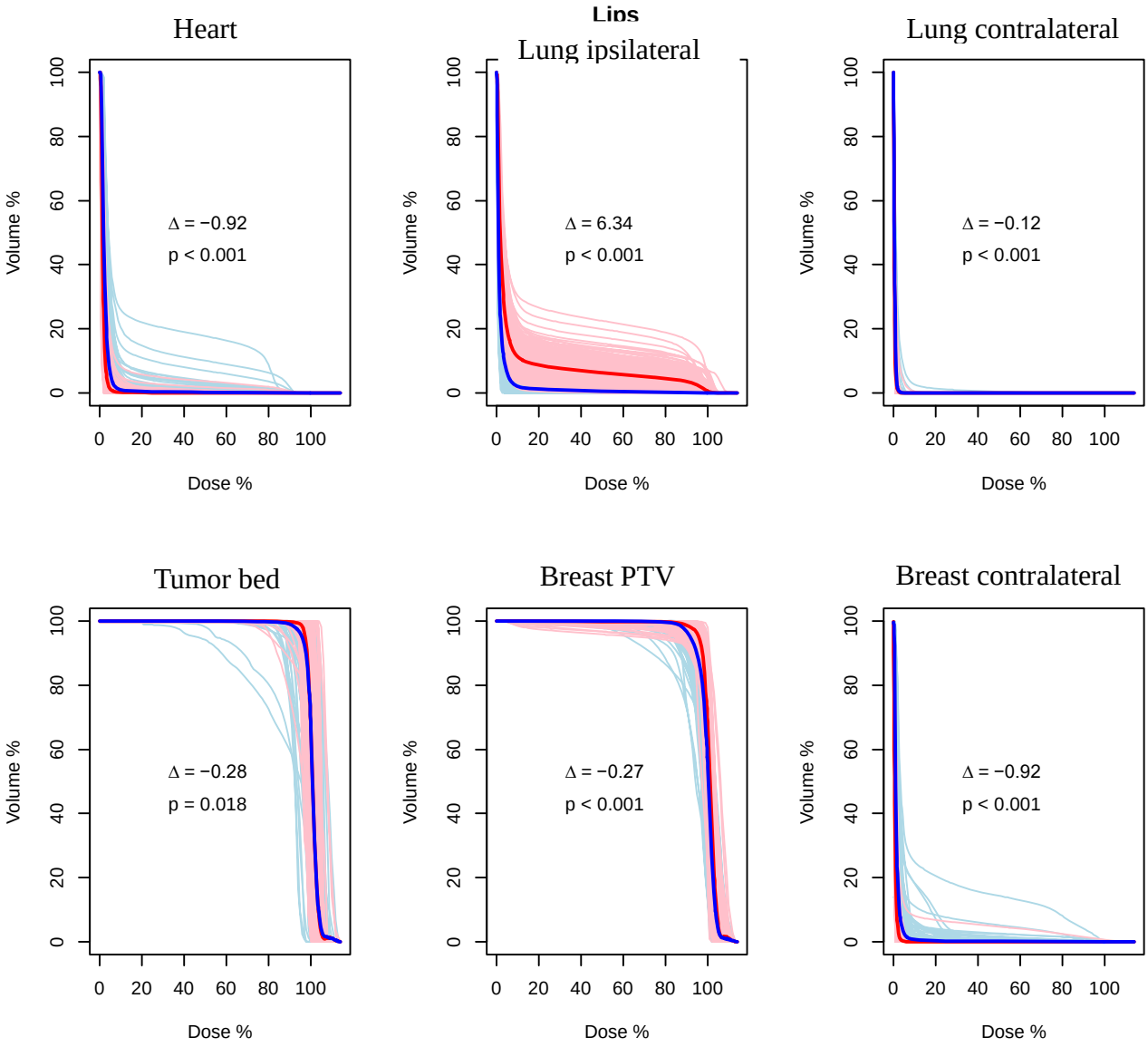

Figure 2. DVHs of body.

Red: supine. Blue: prone. Thin lines: random sampling of 20 cases. Thick lines: pointwise averages of all 282 cases. Shaded bands: 95% confidence intervals. Y-axis range 0-20,000 cc, truncated at 3,000 cc.

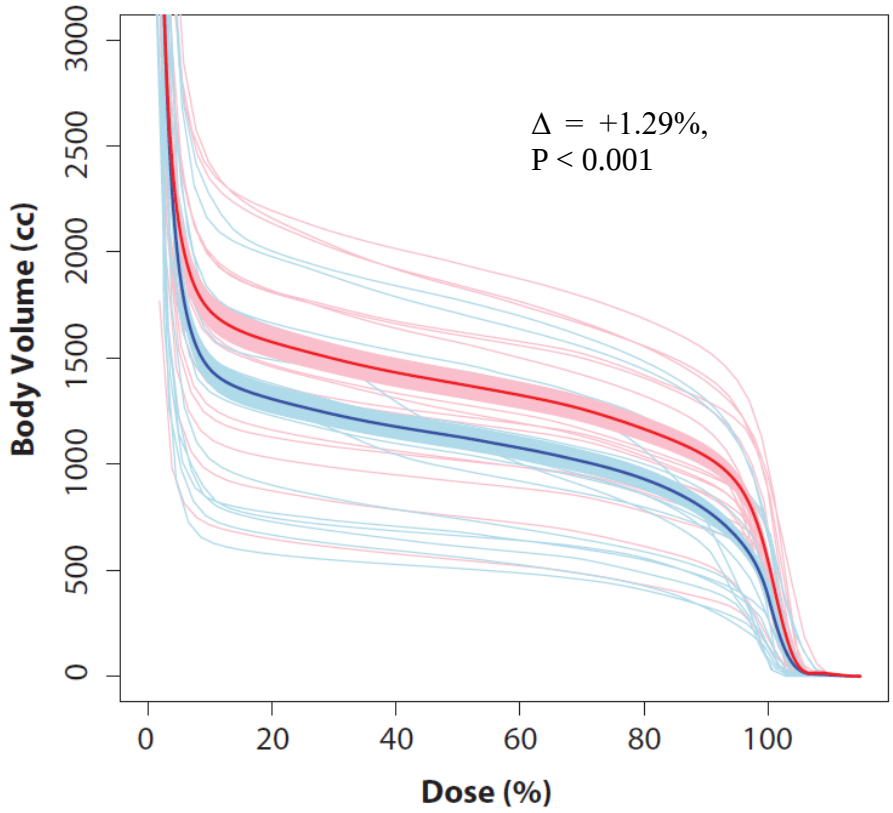

Figure 3. Recursive partitioning. Specific outcomes.

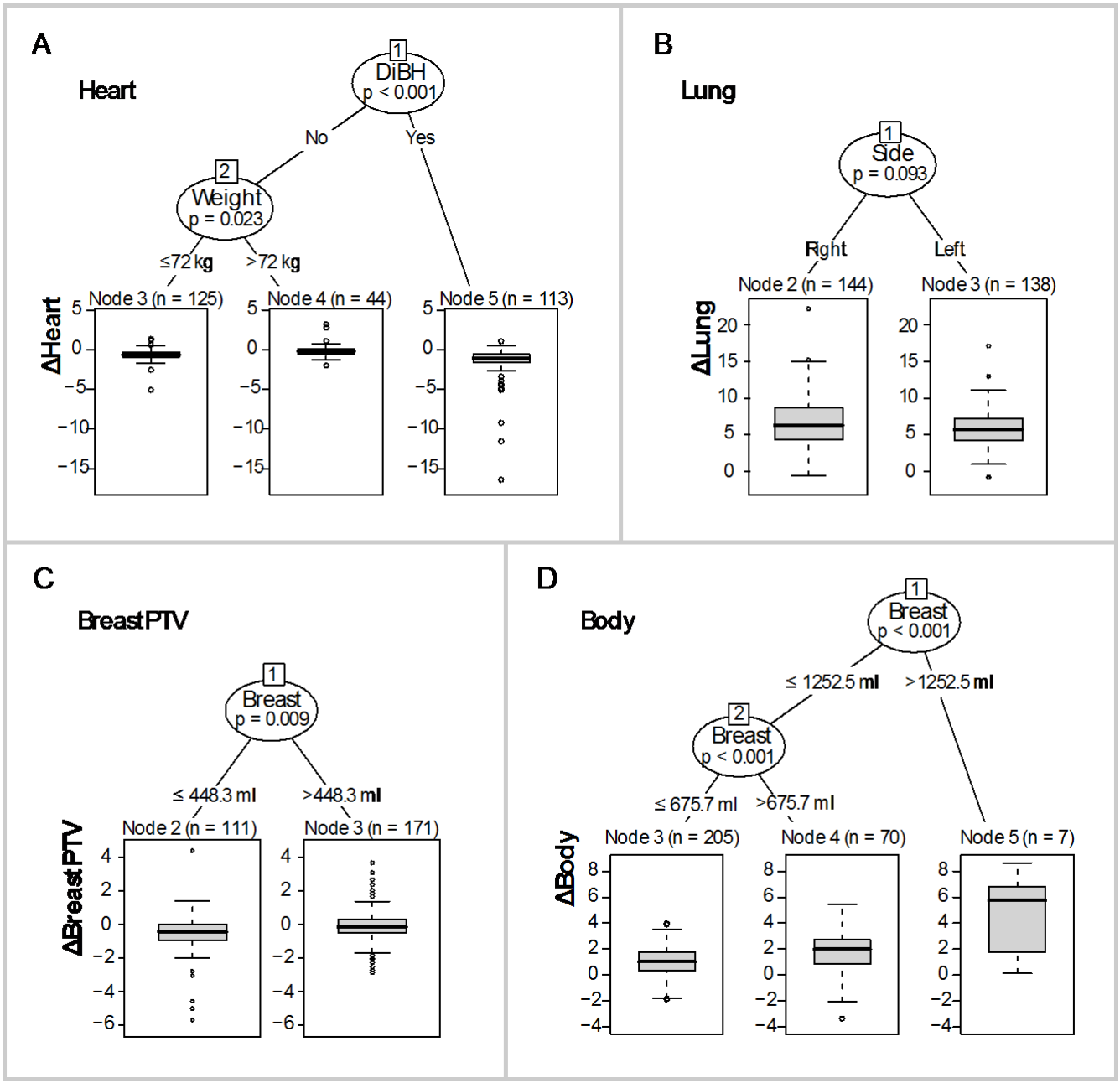

Figure 4. Recursive partitioning. Overall outcome.

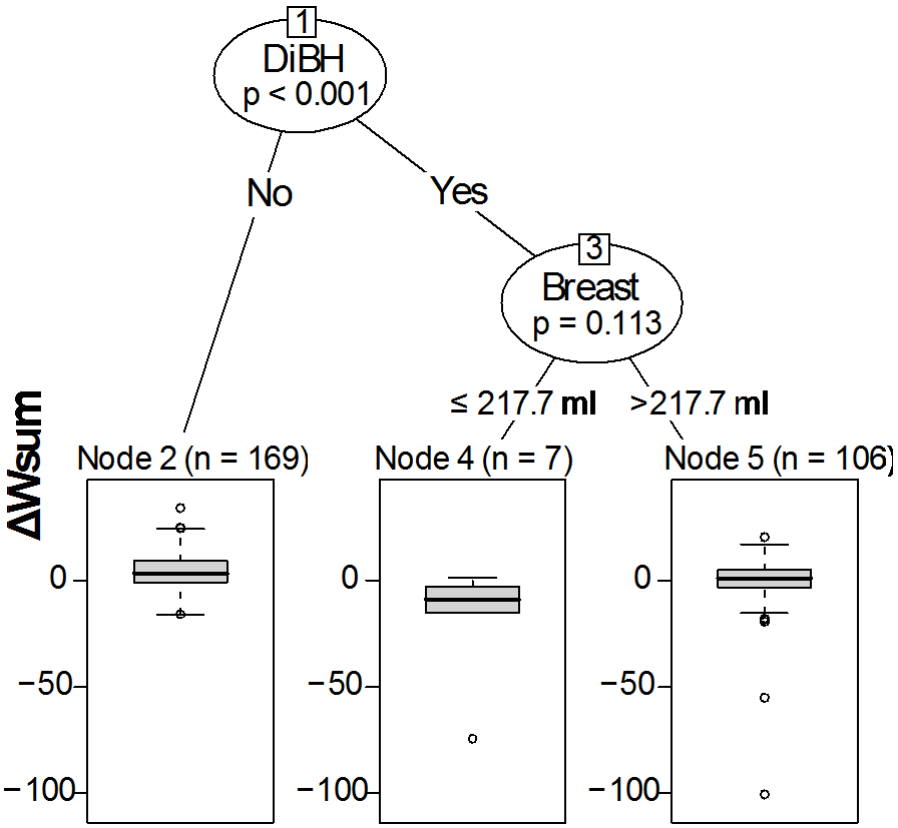

Figure 5. Excess irradiation of non-breast tissues in supine position.

Supine (left figure): area of dose exceeding 105% largely outside breast PTV (white arrows). Posteriorly, latissimus dorsi-teres major muscles and border of scapula are irradiated (red arrow).

Prone (right figure): tiny area > 105% (white arrow). Posteriorly, muscles and border of scapula are well out of fields (blue arrow). Adapted with permission from [48].

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III. Study 2: Automatic segmentation in prone position: the breast target volume and organs at risk (heart and coronary vessel)

Article 1: Automatic segmentation of the breast in prone position: relations between similarity indexes and breast pendulousness with dose/volume parameters

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Abstract

This study evaluates edited/reviewed automatically-segmented structures of the breast target in patients planned in prone position and their dose/volume effects. Contouring times were reduced using automatic-segmentation. Similarity-indexes and pendulousness showed that targets with *Dice* values over 0.965 and high pendulousness, presented the best dosimetric results.

Introduction

Contouring reproducibility is one of the most sensitive points in radiotherapy (RT) planning [1]. Expert panels were created to provide contouring guidelines in order to optimize reproducibility, reduce inter-observer differences, and improve the quality of the procedure [2, 3]. Automatic segmentation (*AS*) tools can help reduce contouring time and standardize target contours [4-6], including breast simulated in supine position [6, 7].

In this study, we have investigated the use of a commercial atlas-based *AS* tool, Smart Segmentation® Knowledge Based Contouring (Varian Medical Systems, Palo Alto, California), developed to contour the Clinical Target Volume (CTV) for breast cancer patients lying prone aiming to segment simultaneously the CTV, the heart, the left anterior descending coronary artery, and both lungs. We present the analysis on automatic CTV delineation and compare manual *vs*. automatic contouring methods using similarity indexes. Using edited/reviewed automatically-segmented CTVs for treatment planning, we correlated similarity indexes and patient's breast shapes with reference target dose coverage and normal tissue over-dosage.

Materials and methods

Forty breast cancer patients (17 left and 23 right) were enrolled and divided in 2 groups: a)

13 atlas-cases sampled by breast size (large >1100cc, medium 600-1100cc and small <600 cc) and laterality (left *vs.* right) to implement the *AS* atlas library; and b) 27 test cases selected to evaluate the reliability of the *AS* tool. All patients gave written informed consent. Patients' characteristics are presented in Table 1.

Computed tomography (CT) images of the thoracic region with 3 mm slices were acquired during free breathing with a slow acquisition mode (pitch 0.813 and rotation time 1.5 sec) and without IV contrast. Patients were lying prone on a dedicated breast board, kVue™ Access 360™ Prone Breast support (Qfix, Avondale, Pennsylvania), with both arms raised overhead and no radio-opaque wires placed to mark breast borders.

Prior to the *AS* tool testing, we created an atlas library with cases containing structures contoured by a seven-year experienced Radiation Oncologist (senior, *Sr*). Using this library, we manually selected the atlas case based on breast volume and shape similarity. A Dell Precision T5500 computer was used with 2 Intel processors (Intel (R) Xeon® CPU with a E560@ 2.4 and 3.9 GHz processor).

For each test case, contours were manually drawn by the *Sr* radiation oncologist (reference) and by a one-year experienced resident in training (Junior, *Jr*) (manual test structures), independently. Automatic segmentation was performed next. *Jr* and *AS*'s CTV contours were optimally adapted by the *Sr*, generating corrected structures (*Jr*+*Sr* and *AS*+*Sr*).

Whole breast contouring followed the consensus guidelines of the Radiation Therapy Oncology Group [3] and the Danish Breast cancer Cooperative group [8] (to define the lateral border limits of CTV using the vessels). All CTVs, drawn manually or automatically, were expanded out of the body and cropped at the skin, while interpolation was used for manual contouring.

Contours performed, by using VODCA (MSS GmbH, Hagendorn, Switzerland) version 5.4.0, were compared to the reference (*Vref*) drawn by the *Sr*. Parameters such as *Dice* (defined as $Dice=2\cdot Vref\cap Vi/Vref+Vi$ where *Vi* is the i_{th} group of structure investigated) [9], sensibility (*Se*) and inclusiveness (*incI*) indexes (defined as $Se=Vref\cap Vi/Vref$ *and* $IncI=Vref\cap Vi/Vi$, respectively) [10, 4], absolute center of mass (*COM*) displacements, and percentage of volume difference were assessed.

To measure pendulousness semi-automatic targets were defined using Eclipse™ version 11 (Varian Medical Systems, Palo Alto, California) by adjusting a Volume of Interest (*VOI*) around the breast, using the breast folds and the chest wall muscles as limits. These structures served to calculate the ratio between the surfaces of the target in contact with air over the total target surface (*RSA*). Figure 1, presents an example of *RSA* calculation. Times to edit/review the *Jr* and *AS* structures performed by the *Sr* in addition to the total contouring times for each procedure were recorded and compared. Contouring time needed by the *Sr* was used as reference. Finally, treatment plans were implemented with the (*AS*+*Sr*) defined CTVs, adding a 5-mm margin expansion from CTV to the Planning Target Volume (PTV). 3D conformal tangential fields were used. Dose-prescription to the PTV and constraints required 95% of the dose to cover at least 95% of PTV volume and no more than 2% volume exceeding 107% of the prescribed dose.

Calculations were performed using the analytical anisotropic algorithm [11] on Eclipse™. Overlaps between *Sr* PTVs (reference) and (*AS*+*Sr*) PTVs for each patient, allowed us to analyze the amount of *Sr* PTV volume being underdosed (i.e. receiving ≤ 95% of the prescription dose). The volume of normal tissue being overdosed, thus receiving a dose ≥95%, was calculated as the volume of (*AS*+*Sr*) PTV not overlapping with *Sr* PTV. Wilcoxon signed rank test was used to validate the comparison between different CTV groups and contouring-editing times. Mann–Whitney test and linear regression were also used for analysis.

Results

Mean *Dice* values were 0.93 and 0.91 for *Jr* and *AS*, respectively. Similarity indexes (*Jr*+*Sr* and *AS*+*Sr*) were all >0.95 and presented no statistical difference for all analyzed parameters (Table 2). The largest difference for the CTVs *COM* was in the cranio-caudal direction for both *Jr* and *AS* contours, with 75 % of the coordinates within 15 mm of the reference *COM*. This was due to *AS* and *Sr* CTVs contours ending cranially or caudally on different CT slices (Figure 2), with a median difference of 2 slices (range, -3 +10) in the cranial region and 0 slices (range, -10 +6) in the caudal region. The *Sr* CTV median length was 13.5cm (range, 9.6-17.5 cm) in the cranio-caudal direction. Center of mass shifts for both manual Jr and AS, were reduced with Sr editing, reaching values close to the pixel size resolution. Automatic segmented and corrected CTVs *Dices* significantly correlated with *RSA* ($p_{(AS)}$=0.03 and $p_{(AS+Sr)}$=0.01), increasing with pendulousness, but not with volume or laterality. Semi-automatically generated target volume (for *RSA* calculation) correlated with *Sr* CTV volumes (p=0.0001).

Senior's mean times to correct *Jr* (4.84 ±0.73 minutes) and *AS* (5.22 ±0.86 minutes) were not significantly different (*p*=0.064). All CTVs, including atlas case selection, were created within a mean time of 2.36±0.6 minutes. Manual contouring by the *Sr* required a mean time of 12.4 *vs.* 7.3 minutes by using the *AS* tool and editing/reviewing the structures.

Treatment planning using (*AS*+*Sr*) PTVs allowed a mean of 94.4% (SD ±1%) of the *Sr* PTV volume to be covered by 95% of the prescribed dose. *Dices* above 0.95 were associated with good reference target dose coverage, with dose prescriptions according to rules with less than 1% of volume under-dosed. For *Dices* of at least 0.96, differences were within ±1% of the volume (Figure 3). Furthermore, to reduce the outside target irradiation to less than 15cm^3 (approx. 1% the ref-target volume) *Dice* threshold was 0.965. Using this *Dice* threshold seven patients presented a "sum volume" (*Sr* PTV volume being under-dosed and volumes of normal

tissue being overdosed) ≤ 20cm3, corresponding to differences in percentage CTV *Sr* volume of 1 to 4% depending on the breast volume size. Using *RSA* threshold of 0.75, 5 patients, presenting good dose target coverage (within 1% of the volume) while non-target irradiation tissue <15cm3, were identified.

Discussion

Here we have reported for the first time, the results of auto-segmentation of CTVs for patients treated in prone position for breast RT. The time taken to draw the CTV was reduced by 40% when the Sr used the AS tool with manual editing, compared to manual contouring alone. This is similar to what has been reported in the literature for supine patient position [7]. The mean time for manual CTV contouring by the Sr (12.4 min) was comparable to the mean times reported by Reed et al. [7] for supine position (20.7 min, range 8.9–45.2 min), but might suggest that target delineation in the prone position could be easier.

Automatic segmentation required the same editing/correcting time as manual contours and resulted in structures of the same quality as for corrected manual contours (i.e. Jr + Sr). The mean Dice of 0.91 for AS was comparable to data reported in the literature for supine position [6]. However, these studies suggested an influence of breast size on AS contours that was not found in our study.

Explanations for this difference could be; (1) the division of the atlas database into three CTV volume groups, (2) the performance of the algorithms used by the AS tool, or (3) the prone position itself. It is of note that Dice values in the prone position increased with higher ASR values (more pendulous breasts).

Dice values of <0.93 in our study were linked to larger dosimetric differences than Dice values of >0.96, suggesting that inter-observer variability is an important factor in clinical practice [12]. The Sr-edited structures, from both Jr manual and AS contours, showed higher

mean (±SD) Dice values than the Jr structures, 0.96 (±0.01) and 0.93 (±0.03) respectively. It could be attributed to inter-observer variability (i.e., Jr vs. Sr) [7,13] or, since the atlas case contours and the contouring corrections were made by the same observer (Sr), it might also be possible that this biased the results of the present study, and represents a possible pitfall. Furthermore, since there are no delineation guidelines/recommendations for prone breast radiotherapy, we extrapolated supine guidelines [3,8] to prone position. This might represent a limitation due to deformations, rotations and translations of the breast due to gravity, and patient positioning on the breast support. Data from the literature suggest that target definition for prone breast radiotherapy is variable. For example Formenti et al. used the anterior extent of the latissimus dorsi muscle to delimit the lateral breast boundary [14] while Bartlett et al. [15] and Krengli et al. [16] used the glandular breast tissue, skin folds, and radio-opaque wires to visually encircle the breast to be treated. It is evident that prone guidelines should be developed, not only to allow for plan comparison between centers, but also to reduce inter-observer variability, as shown in a supine breast contouring RTOG study [1].

Regarding the dosimetric results, we would like to point out that they are dependent on the treatment technique employed (tangential fields). Tangential fields are less influenced by small in-field left–right border contour differences, while cranial-caudal differences may be more important as these limits are used to define jaw apertures.

Furthermore, it is difficult to evaluate the influence of the AS performance on the structures that were subsequently edited, because intra-observer variability is introduced in this process. Nevertheless, even if the automatic segmentation performance wasn’t as good as manual contouring by an expert observer, it did not degrade the final edited contours, which were similar to expert manually delineated ones. In this study, we aimed to investigate which *Dice* values could be considered clinically acceptable from a plan quality (dosimetry) point of view, and to establish whether or not we could predict for which patients contouring

variability would be the smallest. Our reasoning being that, if it is important to correlate Dice values to dose/volume effects, it is even more important to find a parameter predicting the Dice value before planning [12]. The ASR parameter could help in selecting patients for whom extra care is required when reviewing structures. If Dice values higher than 0.965 (high pendulousness, associated with good dose target coverage and less than 15 cm^3 of normal tissue outside the target volume receiving the prescribed dose) can be achieved by automatic segmentation in the future, then we could argue that not editing the structures would not worsen the plan quality results for some patients, for this treatment technique. Hurkmans et al. [13] have shown that intra-observer contouring variability is smaller than inter-observer variability for supine breast treatment, and this is also likely to be true for prone breast treatment. It is a clinical objective to reduce contouring variability.

To summarize, auto-segmentation tools look promising for prone breast contouring and could help to reduce inter and intra-observer contouring variability with a gain in contouring time. Nevertheless, multicenter studies with several experienced radiation oncologists following a prone consensus contouring guideline and using an independent expert-contoured atlas database are needed. Such studies could further asses if contouring reproducibility of CTVs in prone position can be predicted by ASR, which could be a surrogate of *Dice* in predicting dose/volume effects when planning.

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Tables

Table 1. Patients' characteristics (n=40).

	Atlas cases	Test cases
# pts (Left/ Right)	7/6	11/16
Median age (range)	53 (39-82)	61 (40-87)
Breast cup size (range)	75B-105C	75A-105D
Median Breast CTV volume cc (range)	746 (257-1825)	738 (298-1911)
# Small CTV < 600 cc	5	8
# Medium CTV 600-1100 cc	4	12
# Large CTV > 1100 cc	4	7
# pts Tumor Stage Tis-1	7	23
# pts Tumor Stage T2	6	4

Abbreviations: Patients =pts, CTV = Clinical Target Volume.

Table 2: Mean values and standard deviation (SD) of parameters that evaluate the contouring generated by Jr, AS, Jr+Sr, AS+Sr for Clinical Target Volume (CTV) for breast of all the patients.

Abbreviations: ABS= Absolute; R-L=Right-Left; A-P=Anterior-Posterior; C-C=Cranial-Caudal.

Groups	Jr	AS	Jr+Sr	AS+Sr	Jr vs. AS	(Jr+Sr) vs. (AS+Sr)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*P*-value	*P*- value
DICE	0.93 (0.03)	0.91 (0.04)	0.96 (0.02)	0.96 (0.01)	0.0014	0.8286
Sensibility	0.95 (0.04)	0.90 (0.06)	0.96 (0.03)	0.96 (0.02)	0.0011	0.4236
Inclusiveness	0.92 (0.05)	0.92 (0.04)	0.95 (0.03)	0.95 (0.02)	0.8382	0.4350
ABS Center of mass Shifts						
X=R-L [mm]	3.5 (4.6)	4.8 (4.5)	2.6 (3.4)	2.0 (1.5)	0.0179	0.4117
Y=A-P [mm]	3.7 (3.3)	2.5 (1.8)	2.3 (2.7)	1.7 (1.2)	0.1067	0.7637
Z=C-C [mm]	8.9 (6.5)	8.6 (6.9)	4.7 (4.1)	4.5 (4.0)	0.8636	0.8630
Volume Difference [%]	2.0 (8.6)	-4.0 (7.0)	0.9 (4.4)	0.5 (2.8)	0.0325	0.7639

Figures

Figure 1. Procedure to obtain the Ratio-Surface-Air (approximated to the ratio of the volume of a target shell in contact with air over the volume of the entire target shell), from left to right: selection of the region of interest via a box, for the semi-automatic creation of the target; creation of a target shell of 3mm; creation of a skin shell of 3mm; creation of the overlap volume of the target shell with the skin shell approximating the target surface in contact with air.

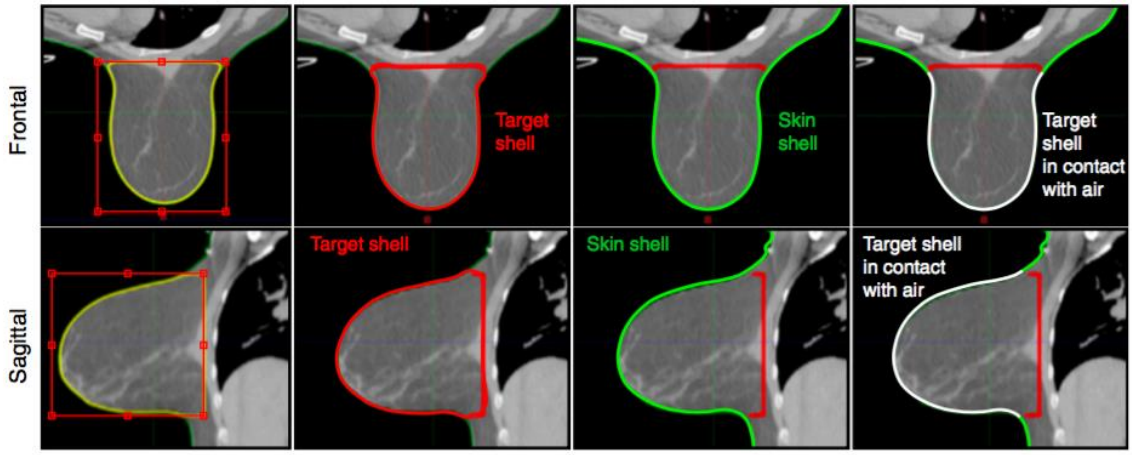


Figure 2. Examples of AS and manual contours by Jr and Sr for two test patients.

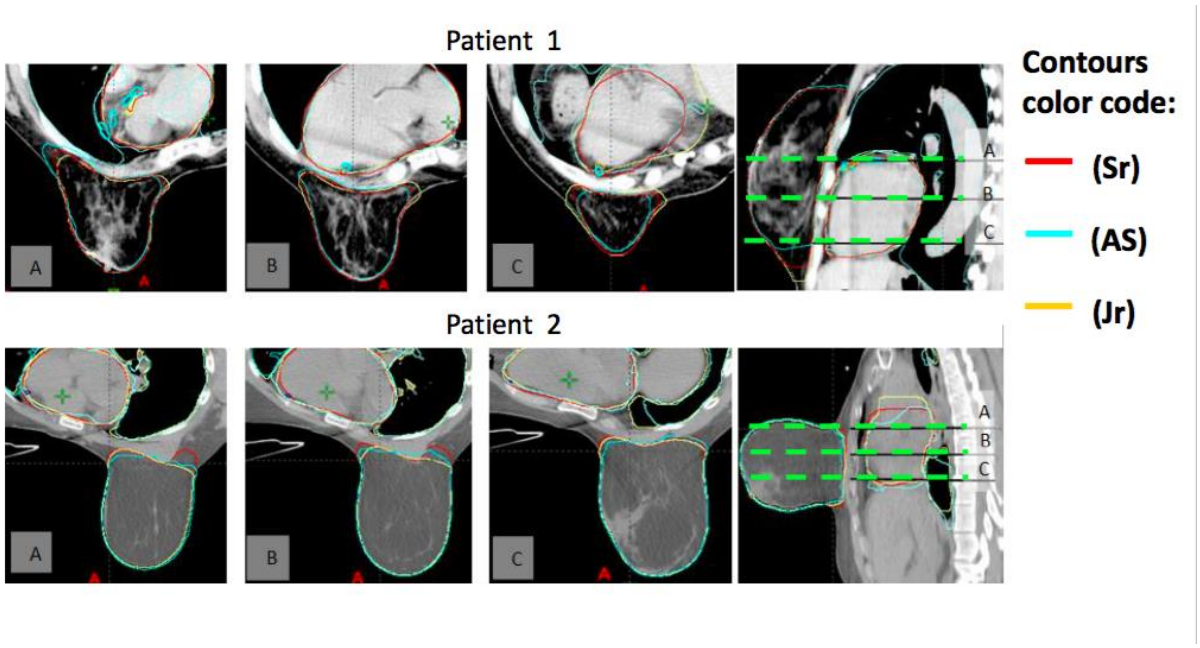
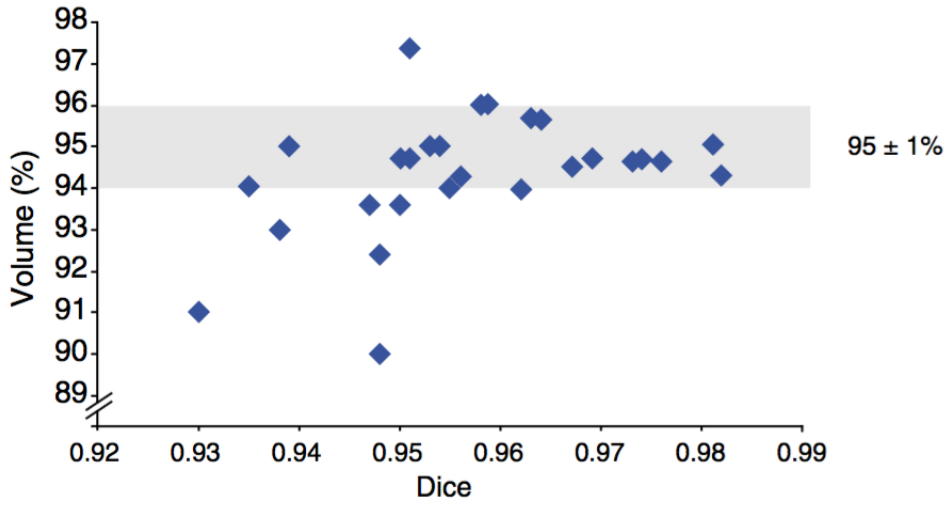


Figure 3. The volume (%) of the reference PTV (drawn by the Senior radiation oncologist) receiving 95% of the prescribed dose, as a function of *Dice*, for plans generated using PTVs automatically segmented and reviewed by the Senior.


98
97
96
95
94
93
92
91
90
89
Volume (%)
0.92
0.93
0.94
0.95
0.96
0.97
0.98
0.99
Dice
95 ± 1%

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III. **Article 2:** Atlas sampling for prone breast automatic segmentation of organs at risk: the importance of patients' body-mass-index and breast cup-size for an optimized contouring of the heart and the coronary vessels

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Abstract

Background: Organs at risk (OaR) contour delineation is a time-consuming task. This study evaluates the benefits of using atlas-based automatic segmentation (AS) of OaR in breast cancer patients treated prone. Two different atlases were tested. Together with laterality (left/right), one atlas sampled for breast volume, while the other sampled for body-mass-index (BMI) and breast-cup-size (BCS).

Methods and Materials: Two different AS atlases were created to sample the OaR for breast radiotherapy, with a special focus on the heart, the left-anterior-descending-artery (LADA), and the right coronary artery (RCA). Manual and AS contours of the heart, the LADA, the LADA+1cm, the RCA, the RCA+1cm, the lungs, the contra-lateral breast, and breast-CTV (Clinical Target Volume) were created for 27 additional "non-atlas" patients. The contouring times were recorded and the reliability of AS was clinically assessed in the context of 3D-planning.

Results: Accounting for BMI and BCS improved AS results compared to breast volume. Using BMI and BCS, an optimal segmentation of the heart was achieved with mean similarity-indexes >0.9 for AS-edited OaR and CTV. Furthermore, the mean similarity-indexes for the LADA+1cm and the RCA+1cm was ≥0.8 after editing the AS derived contours. A 40% reduction in contouring time was observed for manually edited BMI and BCS atlas generated structures, compared to manual contouring alone. A mean dose difference <1.5% was estimated for manually edited versus automatically generated contours. The mean heart dose was reliable for the unedited heart segmentation, and - for right-sided treatments – the unedited heart structures were adequate for treatment planning with 3D-conformal tangential fields.

Conclusions: For AS in prone breast radiotherapy, atlas definition based on samples stratified by BMI and BCS improved segmentation accuracy for the heart and coronary vessels compared to samples stratified by breast volume only. A significant reduction in contouring time can be achieved by using AS.

Keywords: Breast cancer, heart and coronary arteries, left-anterior-descending-artery, automatic segmentation

Introduction

Treatment planning for breast radiotherapy requires contouring of several organs at risk (OaR) in order to optimize the dose distribution and prevent potential treatment related complications. Manual organ contouring is a complex and time-consuming task. Several automatic segmentation (AS) algorithms have been developed and used to reduce contouring time and improve inter- and intra-observer reproducibility [1-6]. In a previous study using an atlas based automatic segmentation (ABAS) tool (Smart Segmentation® Knowledge Based Contouring, Varian Medical Systems, Palo Alto, California), we showed that AS was useful for contouring the Clinical Target Volume (CTV) [2]. For auto-segmentation of the CTV to work well, breast volume was used to sample the atlas library. It is not clear, however, whether organs with dimensions unrelated to the breast volume-such as the heart – could be automatically contoured to satisfaction without introducing other anatomic parameters to the atlas algorithm. Ideally, AS should be able to contour both the breast CTV and the heart, and give results for the similarity index of the heart of > 0.9.

The purpose of this study was to test the hypothesis that using body mass index (BMI) and breast cup size (BCS) could improve the performance of AS of OaR for breast radiotherapy with treatment in prone position. We were particularly interested in AS results for the heart and main coronary vessels.

Materials and Methods

A group of 27 patients representing a population of different breast size and shapes was used to test the atlas-based Smart Segmentation® Knowledge Based Contouring tool for concomitant OaR and CTV contouring. We investigated the effect of sampling either stratifying by (1) breast volume (AS_1), AS_1or by (2) BMI and BCS (AS_2). Published data

correlating BMI to heart volume [7] for a group of female patients receiving BREAST RADIOTHERAPY helped to build-up our own atlas stratified in three BMI levels: < 24 kg/m2, 24 kg/m2 to 28 kg/m2, and >28 kg/m2.

The target and OaR of the atlas library were manually drawn (MS) on non-contrast CT axial slices by a senior radiation oncologist. The contouring of the heart and coronary arteries was reviewed and validated by an experienced cardio-vascular radiologist. The contouring of the heart, the left anterior descending artery (LADA), and the right coronary artery (RCA) was performed according to the recommendations of Feng *et al.* [8]. In particular, the heart delineation included the heart muscles, chambers, and the outermost fibrous layer of the pericardium. The coronary arteries crossing the epicardial fat were included in the heart contour. A 1 cm margin was added around the LADA and RCA, manually drawn or automatically segmented (LADA+1cm and RCA+1cm) as described by Kirby *et al.* [9]. As in clinical practice, lung contouring was done automatically with an Eclipse™ version 11 treatment planning system with manual correction of the trachea and bronchus.

Manual derived contours were compared to AS with or without editing in order to evaluate the reliability of the AS algorithm and atlas database under test. For CTVs and each OaR similarity indexes (Dice, sensibility and inclusiveness indexes, percentage of volume difference, and absolute center of mass shifts) were calculated using the VODCA software. Figure 1, shows a diagram describing the study workflow.

3D treatment plans using conformal tangential fields were generated on hand contoured CTVs and dose-volume parameters on automatically-segmented OaR with and without editing. Treatment plans were done using Eclipse™ and calculated using the Analytical Anisotropic Algorithm [10]. The planning target volume PTV was obtained by expanding the CTV with a 5-mm margin while cropping 5 mm inside the breast skin surface. Dose prescription to the PTV required 95% of the dose to cover at least 95% of the PTV volume

with no more than 2% of the PTV volume exceeding 107% of the prescribed dose. Dose volume histograms (DVH) were used to get dose-volume information such as the mean dose, the dose to 2%, 5%, and 10% of the organ volume (D2%, D5%, and D10%, respectively) for every OaR and segmentation type. Finally, we measured contouring times to determine whether AS in addition to editing can be faster than contouring by hand. The Wilcoxon signed rank test was used to evaluate the similarity indexes, dosimetric parameters, and contouring times for the different contouring methods and OaR.

Results

An atlas of breast samples based on BMI and BCS gave the best AS results for the heart and coronary arteries. Figure 2, presents three patients with left breast targets in which the heart and the LADA, in addition to be manually contoured, were automatically segmented either by selecting atlas samples stratified by breast volume only (AS_1) or by selecting atlas samples stratified by BMI and BCS (AS_2). Manual segmentation was the reference for comparison of both AS algorithms.

Table 1, presents mean Dice and sensibility values for the heart increasing from 0.89 and 0.88 for AS_1 to 0.91 and 0.92 for AS_2, respectively ($p<0.05$) and an optimal inclusiveness index of 0.91. Unlike the heart, similarity index mean values were low for the LADA and the RCA (i.e., 0.1-0.2), regardless of the used AS atlas. Nevertheless, when expanding by 1cm the LADA and the RCA the similarity index improved with both AS algorithms, approaching values of 0.5 for the RCA+1cm and 0.7 for the LADA+1cm. These Dice values represent a moderate (Dice=0.5) and a good (Dice >0.7) agreement between reference and test structures [11]. For the LADA such an improvement was more marked for AS_2 compared to AS_1. The minimum Dice of LADA+1cm after AS_1 increased compared to AS_2 from 0.25 to 0.55. A significant improvement in Dice mean value after AS_2 compared to AS_1 was not observed

though after editing the AS_2 LADA+1cm and RCA+1cm contours Dice values increased from 0.5 and 0.7 to ≥ 0.8. Concerning centre of mass shifts, the largest difference was in the LADA's latero-lateral coordinate and in the RCA's cranio-caudal one with shifts remaining after editing.

To complete AS, mean (±SD) times of 2.1 (±1.3) and 1.5 (±1.5) minutes were needed with AS_1 and with AS_2, respectively. Figure 3, displays the average times required for hand contouring and for AS with editing/reviewing. The segmentation/review/editing of all structures contoured with AS_2 was faster than the segmentation/review/editing with AS_1. Indeed, a mean (±SD) gain in time of 8.5 (±3.3) min and 11.4 (±2.4) minutes, respectively was observed when contouring the CTV and all OaR with AS_1 and AS_2 compared with manual contouring, respectively ($p<0.01$).

A mean dose difference of <1.5% was estimated after editing the OaR contours with AS compared to manual segmentation.

Dose-volume parameters for the heart, the LADA, and the RCA after AS_2 and edited AS_2 are plotted against values obtained for manually contoured structures in Figure 4. The plots show good agreement between AS_2 and manual contouring regarding dose-distribution to the heart. Furthermore, no differences were observed between mean values of the dose parameters analyzed comparing unedited and edited AS_2. For right-sided treatments, unedited AS_2 heart structures could reliably be used when planning 3D-conformal tangential fields. For left-sided treatments, however, the heart $D_{2\%}$ was different for unedited AS_2 compared to manual contouring with a mean (±SD) dose difference of 3.2% (±7.3%). Editing the heart after AS_2 for left-sided treatments resulted in a heart D2% similar to that calculated after manual segmentation with a mean (±SD) dose difference of -0.5% (±0.8%) though better than values obtained with unedited AS_2 ($p=0.02$).

Regarding the LADA and the RCA, dose-volume parameters after AS_1 and AS_2 were

different from the reference. Nonetheless, after AS, editing the LADA, and the RCA did not succeed to improve the dose distribution parameters compared to the reference.

Lungs' AS performed to satisfaction in terms of overlap and dose parameters except for the lungs near the diaphragm for which AS was less reliable. However, in the context of prone position this limitation contributed weakly to the variation in the estimated mean doses to the lungs.

Contralateral, non-target, breast contouring was not optimal neither after AS_1 nor after AS_2 segmentation.

Discussion

To optimally plan breast cancer treatments with radiotherapy it is important to reliably contour the CTV and OaR, especially the heart, the LADA, and eventually the RCA. In this study, including BMI and BCS in the AS atlas database helped to sample optimal atlas patients for a reliable contouring of the heart and coronary vessels, much better than by sampling patients stratified by breast volume as usually performed for AS of the breast-CTV.

Automatic segmentation of the heart in prone position may be as reliable as data reported in literature for supine planned and treated patients [12]. Indeed, in the present study, after heart editing (AS_2), mean Dice (SD) values improved from 0.91 (0.02) to 0.94 (0.01) which compares favorably with data from Lorenzen *et al.* with patients treated supine [13]. The later reported a mean (range) inter-observer Dice value of 0.93 (0.91-0.95). In another study Lorenzen *et al.* tested an atlas-based AS algorithm for heart contouring on the same group of patients and analyzed the result in terms of dose and clinical significance [3]. To obtain good results they needed 8-9 atlas cases to reach an acceptable mean dose compared to manual, but with a heart AS time of approximately 30 minutes. Their mean heart dose difference between "unedited" automatic- and manual segmentation was -0.1%, which is similar to our prone AS_2,

(i.e., 0.1%) notwithstanding the anatomical differences of the heart in relation to the anterior chest wall when lying either prone or supine.

For left-sided breast cancers, unlike right-sided ones, the heart, in contact with the chest wall and exposed to high doses, needed further editing considering that the heart D2% differed significantly from manual contouring doses after unedited AS_2.

The LADA and the RCA contours drawn with either AS_1 or AS_2 overlapped poorly with the manually drawn structures though with some improvements after editing. The poor spatial overlap was partly due to the LADA and the RCA anatomical characteristics is small volume, slender and twisted, with motion artifacts, and a challenging identification on CT images. Furthermore, the RCA was found even more difficult to contour compared to the LADA (lower conformity index), as also observed by Feng *et al.*, when analyzing supine breath hold images from breast treatments [8]. LADA contouring has always been challenging even among experienced observers [13] though the use of dynamic CT imaging may not improve LADA's identification [14].

Contouring the contralateral, non-target, breast with the prone technique presented in this report, may have not been optimal neither after AS_1 nor after AS_2. Editing, however, improved Dice values to 0.9 and above in both cases. So far, the prone breast irradiation technique has focused mostly to improve the target-breast repositioning reliability being much less strict with the repositioning reproducibility of the contralateral non-target breast, often randomly compressed against the treatment board. This is not a major constraint when 3D conformal treatment techniques with tangential fields are planned but may not be so if volumetric modulated arc techniques are used to treat patients lying prone. In this case, the contralateral breast may receive a fraction of low-intermediate-dose that has to be accounted for if the contralateral breast has already been irradiated or accounting for future radiotherapy if needed.

Editing after AS in order to contour the CTV and OaR in patients treated in prone position was 30%-40% faster than hand-contouring (time reduction to <15 minutes). This achievement has been possible as a result of enlarging the data base with additional atlas cases. Sampling patients according to breast cup-sizes A to F and three distinct BMI levels translated in two sets of 18 atlas-patients (right and left). This number may look large but we have to underline that it includes almost all breast-cup sizes. To optimize AS results, it may be capital to feed the algorithm with the right parameters that better describe the atlas. Furthermore, a multi-atlas approach containing multiple images available for co-registration with the test image may further help to obtain the best segmentation result for each organ [15].

In conclusion, selecting samples stratified by BMI and BCS helped to improve an AS atlas in order to optimally define the heart, the LADA, and the RCA when planning breast radiotherapy in prone position. A significant contouring time reduction was observed between AS vs. manual segmentation.

Tables

Table 1. Mean values and standard deviations (SD) of contouring parameters with automatic segmentation (AS1, AS2) and manual editing (Edit AS1 and Edit AS2) for all OaR considered.

	Dice	**Sensibility**	**Inclusiveness**	**Volume difference %**	**Absolute center of mass shifts**		
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*X = R-L (mm)*	*Y = A-P (mm)*	*Z = C-C (mm)*
Heart (27patients)							
AS1	0.89 (0.03)	0.88 (0.05)	0.91 (0.02)	-3.2 (6.48)	1.79 (1.47)	2.04 (1.34)	4.94 (3.69)
AS2	0.91 (0.02)*	0.92 (0.04) *	0.91 (0.04)	3.4 (6.97)*	1.66 (1.48)	1.94 (1.92)	3.39 (2.68)
Edit AS1	0.95 (0.01)	0.95 (0.03)	0.94 (0.03)	1.47 (4.85)	1.08 (1.08)	1.06 (0.74)	2.39 (2.64)
Edit AS2	0.94 (0.01)	0.96 (0.02)	0.93 (0.02)	-1.08 (4.34)	0.70 (0.56)	1.10 (0.70)	2.28 (1.78)
LADA (11 left-side patients)							
AS1	0.13 (0.09)	0.15 (0.11)	0.13 (0.09)	-6.38 (34.41)	7.25 (5.70)	2.73 (2.30)	6.27 (7.67)
AS2	0.18 (0.11)	0.17 (0.11)	0.19 (0.13)	9.76 (36.55)	6.28 (4.05)	2.69 (1.57)	3.41 (2.52)
Edit AS1	0.59 (0.11)	0.61 (0.12)	0.58 (0.13)	-6.87 (18.04)	3.63 (3.33)	1.31 (1.20)	2.05 (2.04)
Edit AS2	0.51 (0.10)	0.50 (0.11)+	0.53 (0.11)	-11.75 (15.03)	5.45 (3.46)	2.18 (2.45)	2.59 (3.36)
LADA1cm (11 left-side patients)							
AS1	0.61 (0.15)	0.63 (0.16)	0.61 (0.16)	-1.95 (16.30)	6.65 (5.30)	3.32 (2.45)	6.82 (7.51)
AS2	0.66 (0.07)	0.68 (0.06)	0.65 (0.07)	4.94 (5.72)	3.44 (3.38)	3.16 (2.03)	4.09 (2.77)
Edit AS1	0.86 (0.06)	0.87 (0.07)	0.85 (0.07)	-2.53 (6.63)	4.69 (3.57)	1.34 (1.17)	1.64 (1.25)
Edit AS2	0.82 (0.07)	0.84 (0.06)	0.80 (0.08)	-5.38 (7.19)	6.78 (4.62)	2.66 (2.58)	2.05 (1.21)
RCA (16 right-side patients)							
AS1	0.10 (0.10)	0.09 (0.09)	0.12 (0.12)	-29.69 (24.59)	4.49 (3.64)	2.86 (2.46)	14.63 (10.56)
AS2	0.12 (0.10)	0.15 (0.11)	0.10 (0.09)	-36.39 (29.19)	6.00 (3.93)	3.74 (2.84)	11.25 (12.10)
Edit AS1	0.49 (0.15)	0.48 (0.17)	0.52 (0.17)	-5.64 (29.63)	2.30 (1.94)	2.26 (2.14)	6.19 (4.61)
Edit AS2	0.46 (0.19)	0.47 (0.20)	0.45 (0.19)	-1.39 (28.61)	2.23 (2.15)	2.00 (1.92)	6.09 (6.85)

RCA1cm (16 right-side patients)							
AS	0.47 (0.17)	0.42 (0.16)	0.54 (0.20)	-19.68 (13.59)	4.51 (3.57)	2.99 (2.63)	14.72 (10.68)
AS2	0.52 (0.19)	0.58 (0.22)	0.47 (0.19)	-32.89 (30.50)	6.06 (3.97)	3.78 (2.83)	11.44 (12.09)
Edit AS1	0.76 (0.10)	0.75 (0.14)	0.79 (0.13)	-3.20 (20.78)	2.79 (3.41)	2.30 (2.20)	5.44 (3.28)
Edit AS2	0.76 (0.13)	0.75 (0.16)	0.78 (0.14)	-3.80 (16.73)	2.24 (2.15)	1.99 (1.95)	6.19 (6.77)
Ipsilateral lung (27patients)							
AS1	0.94 (0.03)	0.97 (0.02) *	0.91 (0.06)	6.90 (8.89)	2.61 (2.27)	2.41 (4.18)	4.50 (4.58)
AS2	0.94 (0.02)	0.95 (0.03)	0.94 (0.04)*	3.84 (6.37)*	3.11 (3.77)	1.63 (2.05)	4.00 (4.71)
Edit AS1	0.95 (0.02)	0.97 (0.02)	0.93 (0.03)	4.66 (6.00)	2.25 (1.82)	1.59 (2.50)	3.06 (3.18)
Edit AS2	0.95 (0.01)	0.96 (0.02)	0.95 (0.03)	-1.49 (4.95)+	2.57 (3.16)	1.37 (1.48)	2.89 (2.82)
Contra lateral lung (27patients)							
AS1	0.93 (0.04)	0.96 (0.03) *	0.90 (0.06)	7.58 (9.04)	1.86 (2.07)	1.52 (1.43)	7.39 (8.85)
AS2	0.94 (0.04)	0.95 (0.03)	0.91 (0.09)*	5.42 (11.40)	2.25 (2.23)	1.63 (1.60)	6.50 (9.74)
Edit AS1	0.95 (0.02)	0.97 (0.02)	0.93 (0.04)	4.91 (5.88)	1.28 (1.41)	1.21 (1.20)	4.44 (5.24)
Edit AS2	0.95 (0.01)	0.96 (0.03)	0.94 (0.03)	2.39 (5.68)	1.73 (1.68)	1.54 (1.26)	3.56 (3.38)
Contra lateral breast (27patients)							
AS1	0.86 (0.04)	0.88 (0.06)	0.84 (0.08)	5.89 (13.00)	4.62 (4.13)	4.72 (4.51)	9.56 (7.75)
AS2	0.84 (0.06)	0.84 (0.09)	0.85 (0.09)	2.56 (15.64)	7.21 (6.57)	4.31 (4.23)	14.39 (12.26)
Edit AS1	0.90 (0.03)	0.92 (0.04)	0.89 (0.05)	2.92 (8.28)	3.56 (2.71)	3.44 (2.32)	7.06 (4.55)
Edit AS2	0.91 (0.04)	0.95 (0.05)+	0.87 (0.06)	-4.83 (11.42)+	3.92 (3.68)	2.02 (2.05)+	7.83 (8.33)

Abbreviation: SD = standard deviation; Automatic segmentation (AS); left anterior descending coronary artery (LADA); LADA + 1cm margin (LADA1cm); Right coronary artery (RCA); RCA + 1cm margin (RCA1cm); R-L = right-left; A-P = anterior-posterior; C-C = cranial-caudal; * AS1 vs. AS2 $p < 0.05$; + Edit AS1vs. Edit AS2 $p < 0.05$.

Figures

Figure 1. Study workflow.

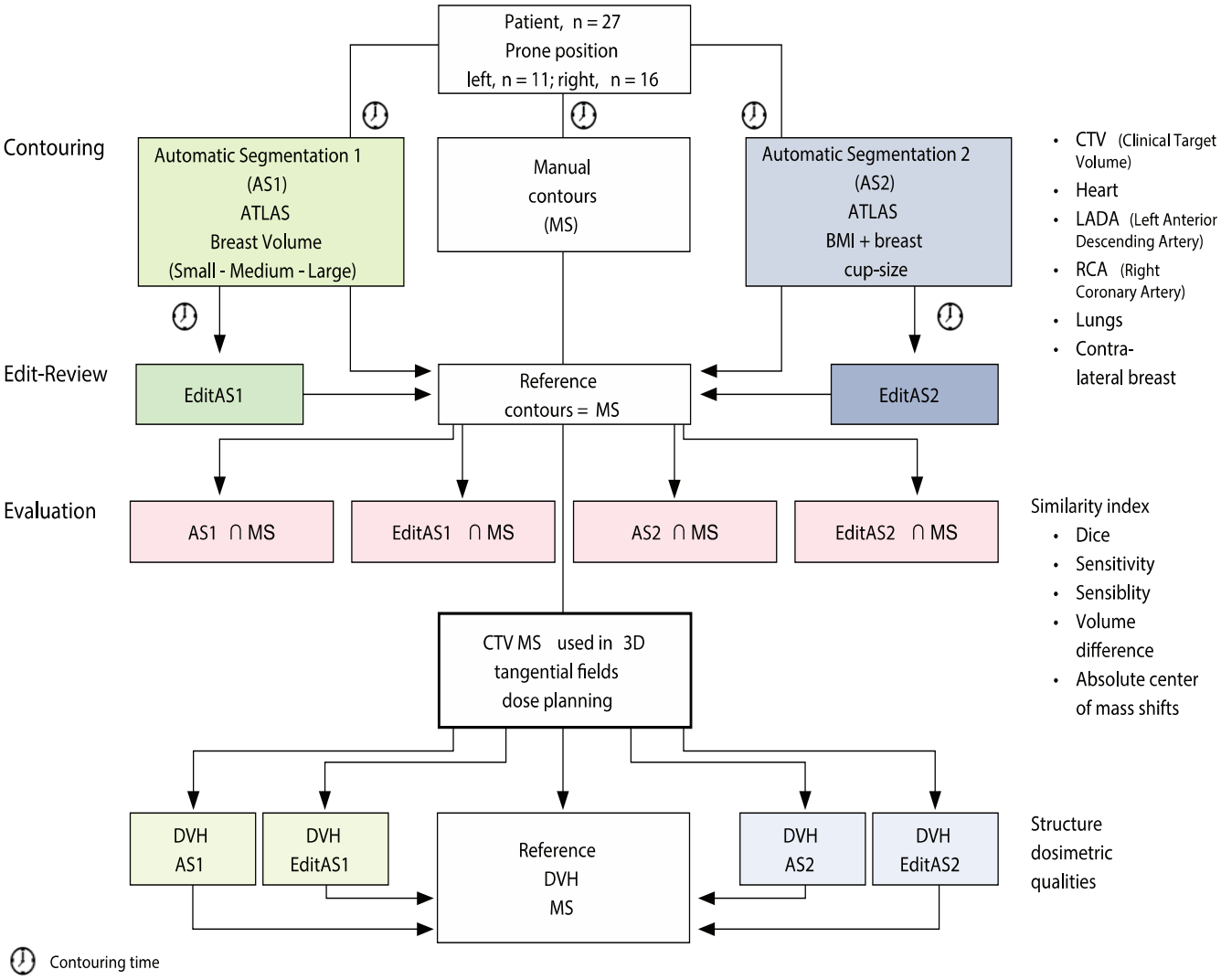


Figure 2. Heart (dark blue) and left anterior descending artery LADA (cyan) contours after non-optimized AS1 (top) and after optimized-AS2 (bottom) and manually segmented organs (pink for the heart and red for the LADA).

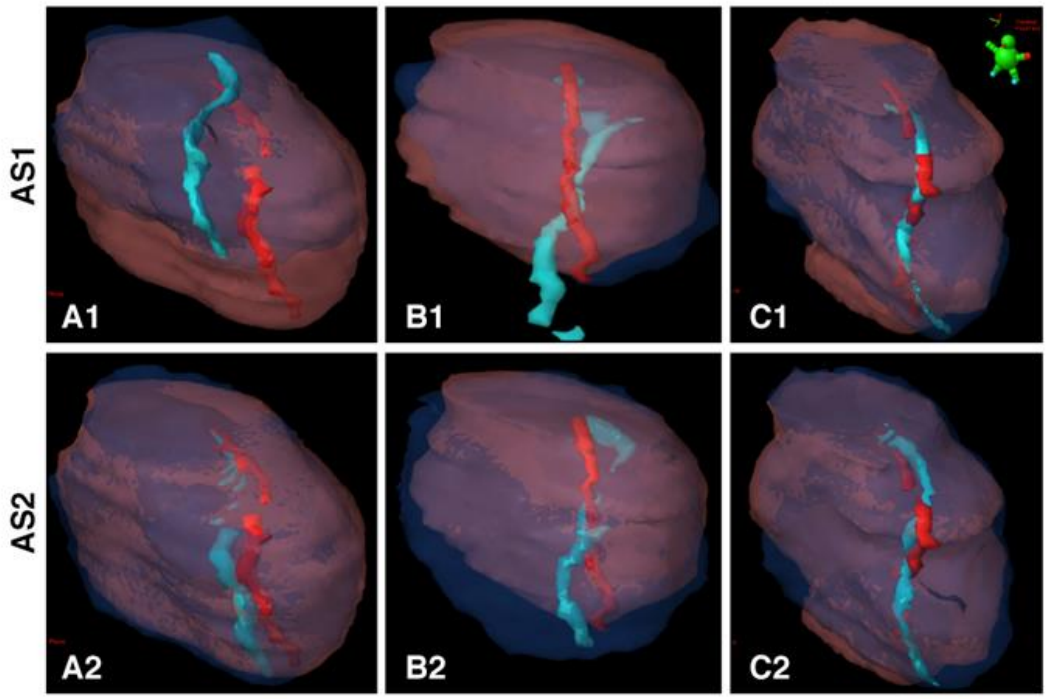
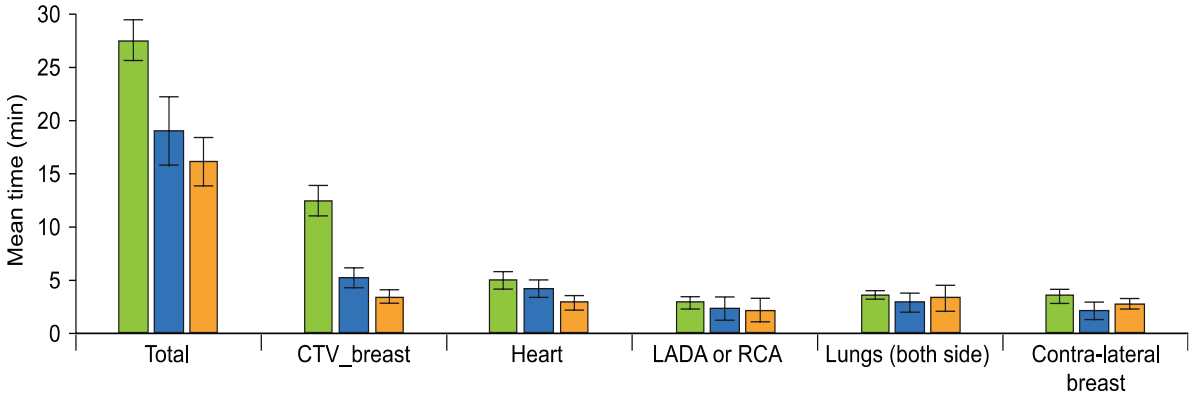
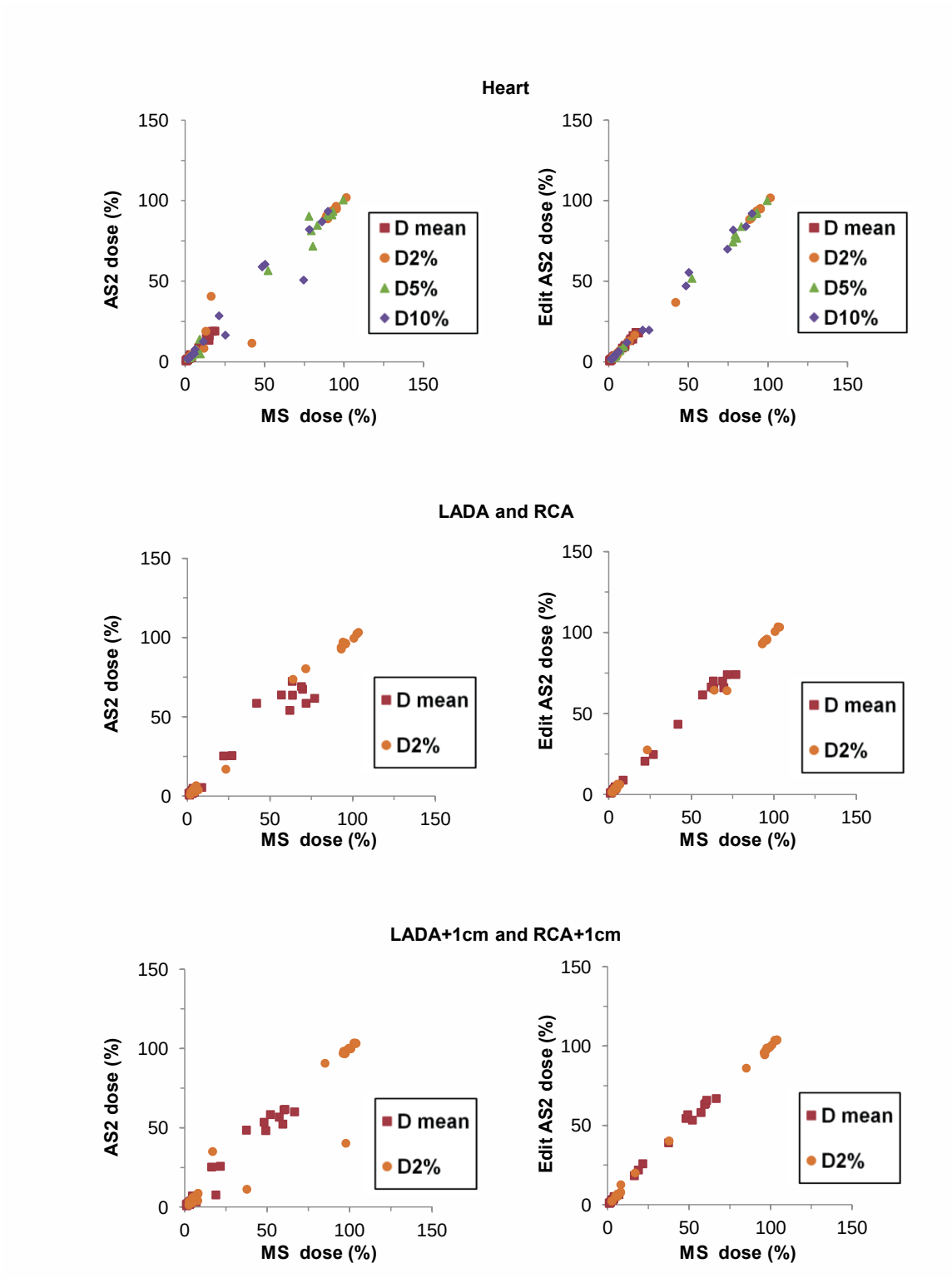


Figure 3. Contouring times of manual vs. automatic segmentation after editing.



MS	27.5 ± 1.9	12.4 ± 1.4	5.0 ± 0.8	2.9 ± 0.6	3.7 ± 0.3	3.5 ± 0.7
Edit AS1	19.0 ± 3.2	5.2 ± 0.9	4.2 ± 0.8	2.4 ± 1.1	2.9 ± 0.9	2.1 ± 0.8
Edit AS2	16.1 ± 2.3	3.4 ± 0.6	2.9 ± 0.7	2.2 ± 1.1	3.3 ± 1.2	2.8 ± 0.5

Figure 4. Dose-volume parameters for the heart, the LADA, the LADA +1cm, the RCA, and the RCA +1cm after AS2 and edited (Edit AS2) plotted against the same values obtained for manually contoured structures (MS)



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IV. Conclusion

Whole breast radiotherapy plays an important role in conservative treatment of patients with early-stage breast cancer. Radiotherapy reduces the risk of local recurrence and specific mortality rate but can induce acute and/or chronic injury to the skin, the heart, the lungs, and the contralateral breast. New radiotherapy techniques allow for an individualized treatment planning and delivery. Prone positioning and respiratory control techniques may be used to optimize dose distribution while sparing healthy tissue thus reducing radiotherapy toxicity. Automatic segmentation (AS) of target volumes and involved organs at risk can improve the quality and reproducibility of contouring while sparing time to implement this task.

In the first part of the study, we aimed to assess the dosimetric optimization potential for 282 patients simulated and planned both supine *vs.* prone. A global penalty score was computed as a weighted sum of supine *vs.* prone differences of the mean doses to organs at risks and the mean absolute dose deviation from prescription to target volumes. The results showed that the dose distribution to the heart, the contralateral lung, the breasts, and the tumor bed slightly benefitted from supine, while the ipsilateral lung and the body integral dose largely benefitted from prone treatment. Prone correlated with a dosimetric gain in the majority of patients, while supine appeared advisable mostly for left-sided breast patients treated under deep inspiration breath hold conditions.

In the second part of the study, we compared manual *vs.* automatic contouring using an atlas-based automatic segmentation tool of patients lying prone. After the creation of a dedicated atlas library stratified by breast volumes, we tested the system on the CT scans of 27 breast cancer patients lying prone aiming to contour simultaneously the CTV, the heart, the left anterior descending coronary artery, the right coronary artery, the contralateral breast, and both lungs. Similarity indexes as well as dosimetric parameters were used while time for

contouring was registered. Similarity index values (Dice) were investigated aiming to asses which values could be considered acceptable from a treatment plan quality point of view and establish whether or not one could predict for which patients contouring variability would be smallest. A quantitative index, Air-to Surface Ratio, was created to describe the breast pendulous shape and correlate it with the quality of the treatment plan.

The dosimetric results showed that most target volumes created with the help of the atlas-based AS method approximated well the dose coverage of manually contoured targets. Dice values higher than 0.965 were linked to small clinically acceptable dosimetric differences. Breasts with high Air-to Surface Ratio correlated with good contouring results with AS, with a good dose target coverage, and with small volumes of normal tissue outside the target receiving the prescribed dose.

The third part of the study showed that stratifying by body mass index and by breast cup-size the AS atlas library helped to sample optimal atlas patients for a reliable contouring of the heart and coronary vessels. Using this AS tool, including manual editing of all structures, reduced the overall contouring time by 40% compared to manual segmentation alone.

Future dosimetric studies should introduce respiratory control techniques for patients treated in prone position, specially for left-sided cancer breast patients. This may allow, both, a dose reduction to the lungs compared to the supine position and a dose reduction to the heart (displacing the heart away from the chest wall under deep inspiration breath hold conditions).