Université de Strasbourg
Faculté de Médecine

Année : 2021 n°167

THÈSE

PRESENTEE POUR LE
DIPLOME DE
DOCTEUR EN
MÉDECINE

Diplôme
d'État

Mention D.E.S Oncologie
option Radiothérapie

par

Martin SCHMITT

né le
02/11/1991 à
Metz

Impact de la dose axillaire de « diffusion » dans le cancer du sein

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FACULTÉ DE MÉDECINE, MAÏEUTIQUE ET SCIENCES DE LA SANTÉ

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LA FACULTÉ A ARRETÉ QUE LES OPINIONS ÉMISES DANS LES DISSERTATIONS QUI LUI SONT PRÉSENTÉES DOIVENT ETRE CONSIDERÉES COMME PROPRES A LEURS AUTEURS ET QU'ELLE N'ENTEND NI LES APPROUVER, NI LES IMPROUVER

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En présence des maîtres de cette école, de mes chers condisciples, je promets et je jure au nom de l'Etre suprême d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine. Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.

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Table des matières

Introduction

Le cancer du sein est un problème de santé publique, c'est le cancer le plus fréquent chez la femme en France. Sa prise en charge a considérablement évolué au cours du temps que ce soit au niveau du traitement chirurgical ou de la radiothérapie. Plusieurs essais ont montré qu'il était possible de réduire la prise en charge au niveau axillaire tant en chirurgie qu'en radiothérapie dans l'optique de diminuer le risque de comorbidités. Dans le cas d'une irradiation mammaire ou de la paroi, plusieurs études ont mis en évidence qu'une dose non nulle et hétérogène dépendant de la technique d'irradiation était délivrée involontairement au creux axillaire.

Nous nous sommes intéressés au risque de récidive ganglionnaire axillaire. Dans un premier temps nous avons réalisé une revue systématique de la littérature selon les recommandations PRISMA et avec dépôt d'un protocole d'étude au sein de la base PROSPERO. Dans un deuxième temps nous avons réalisé un questionnaire national sur les pratiques dans le cadre de la radiothérapie des cancers du sein. Dans un troisième temps nous avons réalisé une étude rétrospective évaluant les facteurs de risque de récidive ganglionnaire axillaire. Enfin nous avons réalisé une analyse dosimétrique dans le cadre d'une irradiation des cancers du sein localisés évaluant la dose délivrée au creux axillaire et son impact clinique.

Irradiation axillaire prophylactique « de diffusion » dans le cancer du sein – revue de la littérature

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Résumé

Contexte : Dans le cancer du sein, la radiothérapie est un élément majeur de la prise en charge. Toutefois les indications de l'irradiation de la chaine mammaire interne et de l'aire axillaire sont débattues. L'évolution actuelle des pratiques est à une désescalade thérapeutique dans la prise en charge de l'aire axillaire dans le cancer du sein. L'irradiation mammaire permettrait de diminuer le taux de récidive axillaire en apportant une couverture des niveaux I, II et III.

Méthode : Une revue de la littérature a été réalisée grâce à PubMed et à la bibliothèque de données Cochrane pour identifier les articles réalisant une évaluation dosimétrique de la couverture des niveaux axillaires I, II et III avec différentes techniques lors de l'irradiation du sein afin de déterminer les implications thérapeutiques potentielles.

Résultats : Onze articles ont été retenus pour un total de 375 plans de traitement. Les résultats étaient très hétérogènes concernant la technique d'irradiation choisie, la dose initiale prescrite au sein, les volumes des niveaux axillaires délinéés et la dose reçue aux trois niveaux axillaires. En radiothérapie conformationnelle tridimensionnelle (RT3D) avec tangentiel standard la dose moyenne délivrée était comprise entre 24 Gy et 43,5 Gy, 3 Gy et 32,5 Gy et 1,0 Gy et 20,5 Gy pour le niveau I, II et III respectivement. En RT3D avec tangentiel haut la dose moyenne délivrée était comprise entre 38 Gy et 49,7 Gy pour le niveau I, entre 11 Gy et 47,1 Gy pour le niveau II et de 5 Gy pour le niveau III (résultat disponible dans une seule étude). Enfin la dose moyenne délivrée en radiothérapie conformationnelle avec modulation d'intensité (RCMI) était comprise entre 14,5 Gy et 42,6 Gy, 3,4 Gy et 35 Gy et entre 1,2 Gy et 25,5 Gy pour le niveau I, II et III respectivement.

Conclusion : La dose incidente délivrée à l'aire ganglionnaire axillaire est substantielle mais ne semble pas suffisante pour être thérapeutique quelle que soit la technique d'irradiation. Il existe des différences entre RCMI et RT3D.

Mots-clés : radiothérapie, creux axillaire, cancer du sein

Abstract

Background: In breast cancer, radiotherapy is an essential component of the treatment. However, indications of irradiation of the internal mammary chain and axillary area are debatables. Axillary recurrence in patients with invasive breast carcinoma remains an issue. Currently, the substitution of axillary lymph node dissection by sentinel node biopsy leads to revisit the role of axillary irradiation. Breast irradiation including level I,II and III might decrease the risk of axillary recurrence .

Patients and methods: A literature search was performed in PubMed and the Cochrane library to identify articles publishing data regarding dose-volume analysis of axillary levels in breast irradiation aiming to determine the potential therapeutic implications.

Results: Eleven articles were retained. A total of 375 treatment plans were analyzed. The results concerning the irradiation technique, initial dose prescribed to breast, delineated volumes and dose received at axillary levels were heterogeneous. The average dose delivered to axilla levels I-III with 3D-conformal radiotherapy using standard fields were between 24 Gy and 43,5 Gy, 3 Gy and 32,5 Gy and between 1,0 Gy and 20,5 Gy respectively. The average doses delivered to axilla levels I-III with 3D-conformal radiotherapy using high tangential fields were between 38 Gy and 49,7 Gy, 11 Gy and 47,1 Gy and 5 Gy 38,7 Gy, 32,1 Gy and 5 Gy (result available for only one study) respectively. Finally, the average doses delivered to axilla levels I-III with intensity modulated radiation therapy were between 14,5 Gy and 42,6 Gy, 3,4 Gy and 35 Gy and between 1,2 Gy and 25,5 Gy respectively.

Conclusions: Incidental axillary dose seems insufficient to be therapeutic regardless of the irradiation technique. There are meaningful differences between intensity modulated radiation therapy and 3D-conformal radiotherapy.

Key-words : radiotherapy, breast carcinoma, axillary lymph nodes

Revue de la littérature

Introduction :

Le traitement des cancers du sein s'appuie sur deux axes : i) le traitement locorégional avec la chirurgie, souvent associée à la radiothérapie complémentaire. Concernant la chirurgie, il faut distinguer la mastectomie et les traitements conservateurs (zonectomie, tumorectomie, …). La procédure du ganglion sentinelle est indiquée dans le cas d'un cancer infiltrant pT1 ou pT2. Le curage axillaire est indiqué d'emblée en cas de tumeur pT3, pT4 ou d'atteinte ganglionnaire prouvée par biopsie ou cytoponction ganglionnaire. Selon les résultats de l'exérèse du ganglion sentinelle un curage axillaire complémentaire sera nécessaire. Le traitement par irradiation exclusive n'est réalisé que dans de rares cas discutés en réunion de concertation pluridisciplinaire (RCP) (patiente très âgée, inopérable ou de maladie métastatique contrôlée); ii) le traitement systémique avec la chimiothérapie, le plus souvent séquentielle à base d'anthracyclines, associée à une thérapie ciblée *anti-human epidermal growth factor receptor-2* (HER2) en cas de statut HER2 - positif ou équivoque si l'hybridation in situ est positive. Une hormonothérapie seule ou adjuvante peut être proposée en cas de récepteurs hormonaux positifs. Les objectifs de ces traitements systémiques sont de réduire les risques de rechute à distance et d'augmenter le taux de survie (1–4).

L'irradiation du sein est un traitement de référence dans différentes situations, l'irradiation complémentaire après tumorectomie ou après mastectomie, l'irradiation partielle complémentaire du sein post tumorectomie ou l'irradiation de l'aire ganglionnaire sus claviculaire dans certaines conditions. Toutefois des questions restent en suspens, notamment l'indication de l'irradiation de la chaine mammaire interne qui est encore discutée (5–7) et actuellement la place de l'irradiation axillaire qui est le sujet de cette étude.

Indication de la radiothérapie mammaire :

Après tumorectomie :

L'irradiation postopératoire de la totalité de la glande mammaire est systématique après tumorectomie. Il a été démontré une amélioration de la survie spécifique à 15 ans et de la survie sans récidive à 10 ans après irradiation (8). Kevin *et al.* ont montré que toute les patientes avaient un bénéfice en terme de contrôle local après une radiothérapie 3D (RT3D) y compris celles à faible risque (cancer de stade pT1 N0, exérèse R0, récepteurs hormonaux exprimés, patientes de plus de 70 ans) (9).

Après mastectomie :

L'irradiation de la paroi thoracique est indiquée systématiquement sauf dans les cas de tumeurs classées T0 T1-T2 N0 (ou pT1 pT2) en marges saines et en l'absence de facteurs de mauvais pronostic (âge inférieur à 40 ans, grade 3 de Scarff-Bloom-Richardson (SBR), carcinome triple négatif, présence d'emboles vasculaires, surexpression de HER2, multifocalité) et dans le cas de carcinome in situ (10–16). Elle a montré un bénéfice en récidive locorégionale et en survie après mastectomie et curage axillaire (CA) chez les patientes ayant 1 à 3 ganglions axillaires atteints (8).

Après chimiothérapie néoadjuvante et mastectomie :

La radiothérapie est indiquée en cas de cytologie ganglionnaire initiale positive ou d'atteinte tumorale des ganglions axillaires observée à l'analyse du curage ganglionnaire ou en cas de tumeur localement avancée initialement (cT3-T4) (17–19).

Indication de l'irradiation des aires ganglionnaires :

Aires sus- et sous-claviculaires :

Une irradiation des aires sus- et sous-claviculaires est indiquée en cas d'atteinte des ganglions axillaires après curage ou d'un ganglion atteint lors de l'exérèse d'un ganglion sentinelle (GS) sans CA. Le bénéfice d'une irradiation des ganglions sus et sous-claviculaires

en termes de récidives locorégionale ou à distance et en termes de survie globale a été démontré dès l'envahissement d'un seul ganglion axillaire si la patiente a eu une mastectomie et un CA (8).

Chaine mammaire interne :

Les indications d'irradiation de la chaine mammaire interne (CMI) sont encore débattues (5–7). L'essai 22922-10925 de l'European Organisation for Research and Treatment of Cancer (EORTC) qui avait inclus 4004 patientes a mis en évidence un bénéfice en survie sans récidive et spécifique et une absence de bénéfice en survie globale de l'irradiation des aires ganglionnaires sus-claviculaires et de la CMI homolatérale chez des patientes atteintes d'un cancer du sein avec un envahissement ganglionnaire axillaire ou sans envahissement ganglionnaire mais avec une tumeur primitive centrale ou interne (5). Whelan et al. ont mis en évidence un bénéfice de l'irradiation des aires ganglionnaires sus-claviculaires, axillaires et de la CMI homolatérales en survie sans récidive mais pas en survie globale dans leur essai incluant 1832 patientes traitées pour un cancer du sein avec envahissement ganglionnaire ou à haut risque d'envahissement ganglionnaire (6). Dans ces deux essais il est difficile de dégager le rôle spécifique de l'irradiation de la CMI sur le bénéfice apporté vis-à-vis des autres aires ganglionnaires (5,6). La controverse porte également sur l'impact à long terme de cette irradiation et le risque d'induction de complications principalement cardiaques (20). Selon Hennequin *et al* les patientes qui bénéficieraient de l'irradiation de la CMI seraient celles présentant un envahissement ganglionnaire axillaire, une tumeur centrale avec des facteurs de mauvais pronostic (triple négatif, présence d'emboles vasculaires, grade SBR 3, âge jeune) (21). Les auteurs ont décrit quatre groupes prédictifs du bénéfice de l'irradiation de la CMI en fonction des résultats histologiques, de l'imagerie et de la localisation de la tumeur dans le sein (Tableau 1) (22). Récemment, Jellesmark *et al* ont analysé un ensemble de patientes ayant bénéficié ou non de l'irradiation de la CMI. L'impact positif sur la survie globale semblait être

plus important pour les patientes ayant une atteinte métastatique ganglionnaire (7). Si ces groupes peuvent être une base de discussion, l'indication définitive d'irradier la CMI doit être posée en RCP.

Concernant les risques cardiaques calculés dans l'étude de Hennequin et al. publiée en 2013, ils sont apparus significatifs principalement chez des patientes ayant été traitées plus de 12 à 15 ans auparavant et peuvent être actuellement discutés du fait des techniques d'irradiation dorénavant utilisées (23). Darby *et al* ont montré en 2013 que le risque cardiovasculaire débutait dès 5 ans après la radiothérapie et se poursuivait jusqu'à 30 ans après l'irradiation, ceci indépendamment des risques cardiovasculaires propres des patientes. Le risque augmentait d'environ 7% par Gy au-delà d'une dose moyenne d'environ 5 Gy dans l'ensemble du cœur (20). Toutefois des études récentes ont souligné le rôle important du nombre de faisceaux utilisés (24) et des techniques d'irradiation mises en place (25).

Aire axillaire :

L'indication d'irradiation de l'aire axillaire reste très débattue et doit donc être discutée en RCP. En l'absence de CA, il n'y a pas d'indication d'irradiation si le GS est négatif, en cas de cellules isolées ou de micrométastases ($\geq$ 0,2 mm et $\leq$ 2 mm) dans ce même ganglion (26,27). Si le GS est positif avec macrométastase et en l'absence de CA, il existe une incertitude quant aux sous-groupes de patientes GS positif qui bénéficieraient d'une irradiation axillaire plutôt que d'un CA. L'indication doit être discutée en RCP au cas par cas (22) sans toutefois que des référentiels puissent encore orienter la décision.

En cas de CA, les indications d'irradiation du creux axillaire sont limitées car l'irradiation axillaire majore le risque de lymphœdème (28–30). Dans l'optique d'une désescalade thérapeutique, Donker *et al*, dans l'étude prospective AMAROS qui a inclus 1425 femmes atteintes d'un cancer classé T1-2 avec un envahissement axillaire mis en évidence lors de la procédure du GS, ont montré qu'il était possible de substituer le CA complémentaire par une

irradiation axillaire. En effet, les auteurs n'ont pas mis en évidence de différence significative entre les deux groupes en ce qui concernait les récidives axillaires, les survies sans maladie et globale. La récidive axillaire à 5 ans était de 0,43% après CA versus 1,19% après irradiation axillaire, la différence n'était pas significative. A contrario, l'incidence et la sévérité du lymphœdème, à 1 an, 3 ans et 5 ans, étaient significativement inférieures dans le groupe irradiation axillaire comparativement à celles observées dans le groupe CA (29).

Indication de la radiothérapie conformationnelle par modulation d'intensité :

La radiothérapie conformationnelle 3D (RT3D) est la technique d'irradiation de référence dans le cancer du sein mais elle montre des limites notamment lors de l'irradiation des aires ganglionnaires du fait de la génération de volume plus complexe. Selon des accords d'expert, la radiothérapie conformationnelle avec modulation d'intensité (RCMI) serait indiquée en cas d'anatomie complexe, d'irradiation mammaire bilatérale, de prothèse mammaire et les situations dans lesquelles aucun compromis ne doit être fait dans le volume cible prévisionnel (31).

La RCMI permet d'améliorer l'homogénéité de la dose dans le volume traité et d'optimiser l'épargne des organes à risques notamment au cœur et au poumon homolatéral sans toutefois permettre un bénéfice en termes de survie (36–38), de plus dans ces études il n'y avait pas d'irradiation des aires ganglionnaires. Actuellement, il est difficile de savoir l'impact clinique de ces différences de doses en termes de contrôle local et de diminution de complications. A noter par ailleurs, que la distribution des faibles doses dans les tissus sains a été peu rapportée (39) mais semble plus importante que celle obtenue par la RT3D (34,35). Cela soulève la question du risque de second cancer radio-induit (40–43), chez des patientes dont l'espérance de vie peut être longue.

Impact de la radiothérapie mammaire sur le taux de récidive ganglionnaire axillaire :

Les résultats de l'essai Z0011 de l'*American College of Surgeons Oncology Group*

(ACOSOG) ont changé la prise en charge des patientes atteintes de cancer du sein stade T1-T2. L'essai ACOSOG Z0011 a inclus 891 patientes présentant des tumeurs T1 ou T2 avec un ou deux ganglions positifs à la procédure du GS. Toutes les patientes ont eu une mastectomie partielle suivie d'une irradiation mammaire. Les patientes étaient randomisées soit dans le groupe CA complémentaire soit dans le groupe surveillance. La RT3D adjuvante a consisté en deux champs tangentiels opposés de la totalité de la glande mammaire. Aucune des patientes n'a eu d'irradiation spécifique de l'aire ganglionnaire axillaire. Le délai de surveillance médian était de 6,3 ans. Les auteurs n'ont rapporté aucune différence significative entre les deux bras en termes de survies globale, sans progression ou en termes de taux de récidive locorégionale. L'incidence cumulée de récidive axillaire était de 1,5 % à 10 ans (5 patientes) dans le groupe surveillance et de 0,5 % à 10 ans (2 patientes) dans le groupe CA complémentaire. Il n'était pas précisé dans l'essai le pourcentage de faux-négatifs à la procédure du GS qui ont eu une récidive axillaire. Dans cette étude, 27% des patientes (115 patientes) qui ont eu un CA, avaient au moins une macrométastase (> 2 mm) ganglionnaire supplémentaire par rapport à la procédure du GS. Il est supposé que ce taux était comparable dans le bras observation. Le fait qu'il n'y avait pas de traduction en termes d'évolutivité de ces métastases suggérait que toutes ces métastases axillaires n'ont pas la même capacité évolutive. Il est à noter qu'une comparaison a été faite entre quatre groupes de patientes par rapport au statut hormonal (récepteurs hormonaux positifs et CA, récepteurs hormonaux positifs et GS seul, récepteurs hormonaux négatifs et CA et récepteurs hormonaux négatifs et GS seul). Il n'a pas été mis en évidence de différence significative en termes de survie globale entre les quatre groupes, mais il n'y a pas eu d'analyse sur le taux de récidive. Dans l'étude initiale la technique d'irradiation et notamment l'utilisation de tangentiels standards (TS) et tangentiels hauts (TH) n'était pas spécifiée (44).

Jagsi *et al.* en 2014 ont réalisés un recueil d'information en contactant directement les radiothérapeutes ayant participés à l'essai ACOSOG Z 0011 (45). Les caractéristiques de

l'irradiation n'ont pu être récoltées que chez 70,7 % des patientes, chez environ 19% d'entre elles, (43 patientes), l'aire axillaire a été traitée avec trois faisceaux d'irradiation bien que cette technique était un critère d'exclusion de l'essai. Le faisceau d'irradiation supplémentaire était plus fréquent chez les patientes dans le groupe GS seul, toutefois cette différence n'était pas significative (p = 0,067). Pour 142 patientes, les plans de traitement étaient assez précis pour évaluer si l'irradiation correspondait à des TS ou des TH. Les faisceaux TH étaient utilisés dans 50% des patientes randomisées dans le bras CA. Les faisceaux TS étaient utilisés dans 52,6% des patientes randomisées dans le bras GS.

L'essai B-32 du *National Surgical Adjuvant Breast and Bowel Project* (NSABP B-32) a corroboré ces résultats. Cet essai a comparé chez des patientes atteintes d'un cancer du sein sans atteinte clinique axillaire, les survies sans progression et globale, et le taux de récidive locale chez plus de 5600 patientes randomisées soit dans le bras GS suivi systématiquement d'un CA soit dans le bras CA seulement si le GS était positif. Le délai de surveillance médian était de huit ans (46). Le taux de faux négatif lors de la procédure du GS était de 9,8%, ce qui était similaire aux taux moyens de faux négatifs rapportés par deux méta-analyses (47,48). Dans cet essai, il n'y avait pas de différence significative entre les deux bras en termes de survies sans progression ou globale, ni en termes de taux de récidive locorégionale. Deux cas de récidive axillaire ont été observés dans le bras GS suivi systématiquement d'un CA et 8 cas dans le bras CA seulement si le GS était positif. Il n'était pas précisé le pourcentage de faux-négatifs à la procédure du GS qui ont eu une récidive axillaire (46).

En 2008, Van Wely *et al.* ont inclus 592 patientes pour évaluer le taux de récidive axillaire, le taux de faux négatifs lors de la procédure de GS et pour identifier les facteurs pronostiques de récidive après GS négatif. Le suivi médian était de 65 mois. Le taux de faux négatifs était de 6,9%. Onze patientes (2,8%) ont développé une récidive axillaire. Les auteurs ne précisaient pas si ces patientes faisaient partie des faux-négatifs. La majorité de ces patientes (10/11)

n'avait pas reçu de radiothérapie mammaire, c'était l'unique facteur pronostique mis en évidence par les auteurs (49).

Ces constatations ont incité ces mêmes auteurs à réaliser, en 2011, une revue systématique de la littérature avec pour hypothèse que la radiothérapie dans le cancer du sein pourrait réduire le risque de récidive axillaire après une procédure du GS négative. Quarante-cinq articles ont été étudiés pour un total de 23357 patientes. Le suivi médian était de 39 mois (15-102). Cette revue de la littérature a montré que la radiothérapie externe du sein était associée à un taux plus faible de récidive axillaire ($p < 0,001$) (50). L'hypothèse avancée alors par les auteurs était que lors de l'irradiation de la glande mammaire, une partie de l'aire axillaire étaient irradiée à des doses permettant le contrôle des cellules tumorales potentiellement présentes. Cette dose reçue au niveau axillaire variait en fonction de la technique d'irradiation.

La littérature sur ce sujet n'est pas importante et a rapporté des valeurs principalement avec les nouvelles techniques de radiothérapie. Nous proposons de réaliser une revue de la littérature pour préciser la dose délivrée et la couverture de l'aire ganglionnaire axillaire dans le cadre d'une irradiation adjuvante de la glande mammaire dans le cancer du sein en fonction de la technique d'irradiation. Une revue de la littérature a été réalisée en suivant les recommandations PRISMA (51). Le protocole de cette revue de la littérature a été enregistré sur PROSPERO. Onze articles ont été identifiés avec les moteurs de recherche PubMed et la bibliothèque de données Cochrane. (Figure 1).

Étude dosimétrique en RT3D

Huit articles concernant des patientes irradiées en technique RT-3D ont été identifiés. La majorité des études étaient rétrospectives avec un nombre de patientes variant de 15 à 50 (52–59). Ces études s'attachaient à réaliser une analyse comparative des histogrammes dose-volume entre une irradiation par des faisceaux TS et TH (Tableau 2).

En 2000, l'étude de Krasin *et al.* a porté sur l'analyse des histogrammes dose-volume chez

25 patientes irradiées au niveau du sein après mastectomie partielle. Une seule patiente avait 95% du volume du niveau axillaire I couvert par 95% de la dose prescrite (V95). Le V95 du niveau I n'était que de 50% chez 6 patientes. Aucune des patientes n'a eu une couverture adéquate des niveaux II et III. Les doses moyennes dans les niveaux I, II et III étaient respectivement, de 32 Gy (5,5 – 51,5), 26,5 Gy (4,8 – 47,7) et 18,2 Gy (4,7 – 38,1) (52).

En 2001, Aristei *et al.* ont réalisé une étude prospective chez 35 patientes traitées par chirurgie conservatrice et CA. Trois clips étaient mis en place pour délimiter les 3 niveaux axillaires. La radiothérapie adjuvante consistait en une irradiation de la totalité de la glande mammaire par deux faisceaux tangentiels opposés délivrant 50 Gy en 25 fractions ou 50,4 Gy en 28 fractions associé à un complément d'irradiation dans le lit tumoral de 10 Gy. Les doses moyennes délivrées dans les niveaux axillaires I, et II étaient, respectivement, de 38,6 Gy (3,5 – 47,1) et 20,6 Gy (0,95 – 38,9) (53).

En 2005, les résultats de Orechia *et al.* étaient similaires avec une dose moyenne délivrée dans le niveau I inférieure ou égale à 40 Gy pour toutes les patientes. Le volume médian du niveau I recevant au moins 80% de la dose prescrite était de 30,7% (0 – 70%) (54).

Reznik et al. ont été les premiers à avoir comparé l'impact dosimétrique de faisceaux TS et de faisceaux TH (55). L'analyse de 35 patientes a mis en évidence une meilleure couverture de l'aire axillaire par la technique des faisceaux TH. Les doses moyennes délivrées dans les niveaux I, II et III avec des TS et avec les TH étaient, respectivement, de 66% (35-91) et 86% (57-99), de 44% (10-96) et 71% (14-99) et de 31% (7-91) et 73% (27-96) de la dose prescrite.

En 2014, Belkacemi *et al.* ont étudié rétrospectivement, chez 25 patientes, la distribution de la dose dans la zone du prélèvement du GS visualisée par des clips. La dosimétrie a été calculée en RT3D avec des TS et des TH. Les doses moyennes délivrées dans les niveaux axillaires I, II, III et dans la zone du GS étaient significativement inférieures avec les TS qu'avec les TH, respectivement 22 Gy vs 38 Gy, ($p = 0,004$), 3 Gy vs 11 Gy, ($p = 0,019$), 2 Gy vs 5 Gy ($p =$

0,003) et 30 Gy vs 45 Gy (p = 0,02) (56).

Il est à noter que la définition des faisceaux d'irradiation TH variait entre les études. Pour deux études, ils étaient définis par une limite supérieure du faisceau à l'aplomb de la tête humérale (55,56) et pour une autre, lorsque la limite supérieure du faisceau était à moins de 2 cm de la tête humérale (44). Seules deux études (56,59) définissaient le volume axillaire délinéé par les recommandations du *Radiation Therapy Oncology Group* (RTOG) (60).

Étude dosimétrique en irradiation par modulation d'intensité (RCMI)

Trois études ont comparé la dose reçue au niveau axillaire entre une RT3D et une RCMI et ont regroupé peu de patientes (Tableau 2).

En 2013, Kataria *et al.* ont prospectivement comparé *in silico*, chez 50 patientes la dose reçue au niveau axillaire entre une irradiation par faisceaux TS, une RT3D et une RCMI. La dose était de 50 Gy en 25 fractions de 2 Gy. L'irradiation était délivrée après une chirurgie mammaire conservatrice et une procédure du GS négative. L'analyse des histogrammes dose-volume a montré que le pourcentage moyen de la dose prescrite délivrée au niveau axillaire I était supérieur avec les TS comparativement à la RT3D et la RCMI, respectivement, 87% [73-98], 80% [63-95], et 78% [67-90]), avec une différence significative entre les TS et la RMCI (p = 0,037). Pour les niveaux supérieurs, les valeurs étaient inférieures. Au niveau II et III, les valeurs pour les faisceaux TS, la RT3D et la RCMI étaient, respectivement, 65% [29-87], 72% [34-93], 70% [46-89] et 41% [6-72], 53% [19-86], 51% [28-76]). En termes de couverture de dose, aucune des trois techniques n'a permis une couverture optimale de l'aire axillaire. Le volume recevant 90% de la dose prescrite au niveau axillaire I était significativement supérieur avec les TS versus la RT3D (p = 0,029) et avec les TS versus la RCMI (p = 0,029). Au niveau II, seule la dose délivrée par RT3D était significativement supérieure à celle délivrée par les TS (p = 0,028). Au niveau III, la couverture par RCMI était significativement supérieure à celle délivrée par les TS (p = 0,039) (61).

Récemment, en 2016, Lee *et al.* ont décrit une dose délivrée dans l'aire axillaire significativement plus faible en RCMI par rapport à la RT3D-FIF (Field in Field) ($p = 0,001$ pour les trois niveaux) (62). Cependant, dans cette étude, les écarts de doses moyennes, entre la RT3D-FIF et la RCMI, reçues dans chaque niveau de l'aire axillaire étaient plus importants que dans les études de Kataria *et al.* et de Zhang e*t al.* (61,63) : niveau I : 42,6 Gy vs 14,5 Gy, niveau II : 26,2 Gy vs 3,4 Gy et niveau III : 6,3 Gy vs 1,2 Gy. Selon les auteurs, ces différences pourraient s'expliquer par le degré d'optimisation en RCMI et la limite supérieure du champ défini en RT3D-FIF (62).

Discussion :

La RCMI et la RT3D-FIF délivrent une dose moins importante à la partie inférieure de l'aire axillaire comparée à celle de la RT3D avec faisceaux TS. Cette différence tend à s'inverser aux niveaux II et III mais les doses délivrées peuvent être très faibles (62). En ce qui concerne la RCMI, la couverture et la dose délivrée dans toute l'aire axillaire semblaient supérieures à celles obtenues avec des faisceaux TS en RT3D (61,62).

Les conclusions de cette analyse de la littérature sont limitées par de nombreuses faiblesses des études. Aucune comparaison n'a été faite entre les faisceaux TH et la modulation d'intensité. La définition de la limite supérieure des faisceaux TH variait en fonction des études rendant difficile la comparaison des résultats. La définition des volumes ganglionnaires axillaires variait en fonction des études avec l'utilisation de recommandations internationales dans une minorité d'études. Enfin, la plupart de ces études présentaient une population très hétérogène notamment concernant le volume de la glande mammaire. Toutes ces hétérogénéités pourraient expliquer les variations de dose et de couverture de l'aire axillaire.

Aucune méthode d'irradiation mammaire n'a permis une couverture adéquate ni de délivrer une dose thérapeutique au niveau axillaire. Toutefois, les résultats des essais ont démontré que le taux de récidive axillaire diminuait avec l'irradiation mammaire. La méta-analyse de Van

Wely et *al.* en 2011 a montré au travers de 45 articles et de 23357 patientes, un taux de récidive axillaire de 0,4% pour les patientes qui avaient reçu de la radiothérapie et de 1,2% pour les patientes qui n'en avaient pas eu, se traduisant par une diminution du risque relatif (RR) de récidive axillaire (RR= 0,32 [0,23-0,46] ; $p < 0,001$) mais aucune comparaison des techniques d'irradiation ni de dose n'avait pu être faite à cause du manque d'information adéquate dans les études (50). L'un des arguments qui pouvait expliquer ces résultats était basé sur la dose incidente axillaire reçue lors de l'irradiation mammaire.

Toutefois celle-ci reste faible et une première hypothèse propose qu'une dose tumoricide de 45-50 Gy n'est peut-être pas nécessaire pour obtenir le contrôle axillaire. L'administration de doses plus faibles ont montré leur efficacité pour éradiquer des cellules métastatiques de différentes tumeurs primitives (64–66). La radiosensibilité des cellules tumorales pourrait être inversement proportionnelle à la densité cellulaire tumorale.

La deuxième hypothèse est que la radiothérapie par faisceaux tangentiels permettrait d'éliminer les métastases en transit encore présentes après la chirurgie (67).

La troisième hypothèse est le rôle d'un mécanisme immunitaire indépendant de la dose et déclenchée par l'irradiation mammaire apportant un bénéfice pour le contrôle local (68).

De plus Berg et al. en 1955 ont montré que le premier ganglion axillaire envahi est majoritairement situé dans le niveau I avec un envahissement dans 95% des cas séquentiel du niveau I puis II et enfin III. Dans seulement 5% des cas il peut survenir des skips métastases retrouvaient dans le niveau II ou III sans atteinte du niveau précédent (69). A la lumière de ces données on peut relever l'importance relative du niveau axillaire I vis-à-vis des niveaux axillaires II et III.

Conclusion :

La dose incidente délivrée à l'aire ganglionnaire axillaire ne semble pas suffisante par elle-même pour être thérapeutique quelle que soit la technique d'irradiation. Il existe des différences

significatives de dose délivrée et de couverture du volume entre la RCMI et la RT3D. À notre connaissance, aucun essai n'a étudié l'impact des différentes techniques d'irradiation sur le taux de récidive axillaire. Ces résultats sont à corréler à des essais de plus grande ampleur comprenant plus de patientes ainsi qu'une comparaison du taux de récidive axillaire chez les patientes entre les différentes techniques d'irradiation.

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Tableau 1 : Groupes prédictifs du bénéfice de l'irradiation de la CMI (Adapté de Hennequin et al 2016)

Groupe	Définition	Population
1	Sous-groupe bénéficiant avec une forte probabilité de l'irradiation de la chaîne mammaire interne	Atteinte prouvée (biopsie positive) ou fortement suspecte (tomographie par émission de positons (TEP)–scanographie positive) Atteinte ganglionnaire axillaire importante (≥ 4 ganglions atteints), d'autant que la tumeur est centrale ou interne avec des critères d'agressivité (femme jeune, grade 3, récepteurs hormonaux non exprimés, etc.)
2	Sous-groupe dont le bénéfice de l'irradiation de la chaîne mammaire interne est probable	Tumeur interne avec atteinte axillaire modérée (1–3 ganglions atteints)
3	Sous-groupe dont le bénéfice de l'irradiation de la chaîne mammaire interne est possible	Tumeur externe avec atteinte axillaire modérée (1–3 ganglions atteints) Tumeur des quadrants internes pN0
4	Sous-groupe ne bénéficiant probablement pas de l'irradiation de la Chaîne mammaire interne	Tumeur externe et pas de ganglion histologiquement atteint

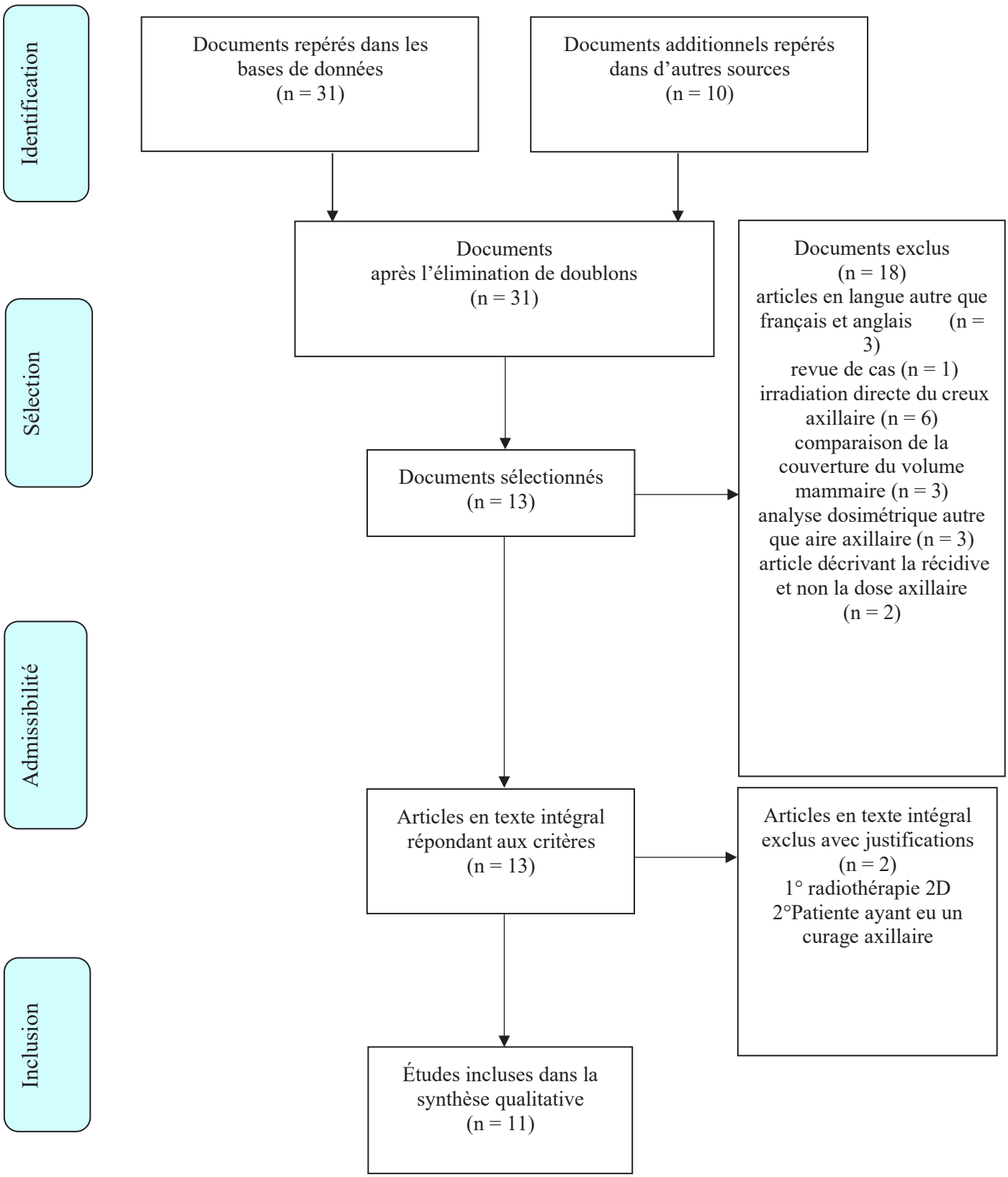
Tableau 2 : résultats des études incluses dans la revue de la littérature.

Auteurs	Nombre de patients	Technique	chirurgie axillaire	Volumes axillaires (mL)	Dose moyenne axillaire (% de la dose prescrite ou Gy)	Dose axillaire dans les niveaux axillaires (% de la dose prescrite ou Gy)
Krasin *et al.*	25	TS	CA	N I : 50 (22-173) N II : 23 (10-60) N III : 6 (3-14)	N I : 32 Gy N II : 26 Gy N III : 18 Gy	ND
Aristei *et al.*	35	TS	CA	ND	N I : 38,6 Gy NII : 20,6 Gy	N I : D90% : 6,7 Gy N II : D90% 1,7 Gy
Orecchia *et al.*	15	TS	GS	N I : 29 (15-59)	N I : 24 Gy	non documentée
Reed *et al.*	50	TS	CA	N I+II : 146 (83-313)	ND	N I+II : V95% : 55%
Reznik *et al.*	35	TS	GS	N I : 85 (24-232) N II : 17 (4-40) N III : 5 (1-24)	N I : 66% N II : 44% N III : 31%	N I : V95% : 51% N II : V95% : 26% N III : V95% : 15%
		TH	GS	N I : 85 (24-232) N II : 17 (4-40) N III : 5 (1-24)	N I : 86% N II : 71% N III : 73%	N I : V95% : 79% N II : V95% : 51% N III : V95% : 49%
Alco *et al.*	30	TH	GS	N I : 62 (24-135) N II : 12 (4-36)	N I : 39,4Gy N II : 26,6 Gy	ND
		TH-CML	GS	N I : 62 (24-135) N II : 12 (4-36)	N I : 49,7 Gy N II : 47,1 Gy	ND
Belkacemi *et al.*	25	TS	GS	ND	N I : 22 Gy N II : 3 Gy N III : 2 Gy PTV*GS* : 30 Gy	ND
		TH	GS	ND	N I : 38 Gy N II : 11 Gy N III : 5 Gy PTVGS : 45 Gy	ND

Kataria *et al.*	50	TS	GS	N I : 68 (29-151) N II : 25 (14-56) N III : 9 (5-16)	N I : 43,5 Gy N II : 32,5 Gy N III : 20,5 Gy	N I : V95% : 51% N II : V95% : 8% N III : V95% : 3%
		RTC3D	GS	N I : 68 (29-151) N II : 25 (14-56) N III : 9 (5-16)	N I : 40 Gy N II : 36 Gy N III : 26,5 Gy	N I : V95% : 44% N II : V95% : 19% N III : V95% : 11%
		RCMI	GS	N I : 68 (29-151) N II : 25 (14-56) N III : 9 (5-16)	N I : 39 Gy N II : 35 Gy N III : 25,5 Gy	N I : V95% : 39% N II : V95% : 17% N III : V95% : 8%
Zhang *et al.*	40	RCMI-s	GS	ND	N I : 27,7 Gy N II : 10,6 Gy N III : 2,5 Gy	N I : V95% : 16,9% N II : V95% : 1,7% N III : V95% : 0%
		RCMI-FIF	GS	ND	N I : 29,1 Gy N II : 10,9 Gy N III : 2,8 Gy	N I : V95% : 27,6% N II : V95% : 1,8% N III : V95% : 0%
Jacobson *et al.*	50	TS	GS et/ou curage	ND	N I : 29,03 Gy N II : 6,09 Gy N III : 1,04 Gy	N I : V95% : 30,80% N II : V95% : 0,65% N III : V95% : 0%
Lee *et al.*	20	RT3D-FIF	ND	ND	N I : 42,58 Gy N II : 26,25 Gy N III : 6,26 Gy	N I : V95% : 36,44% N II : V95% : 0,67% N III : V95% : 0%
		RCMI	ND	ND	N I : 14,49 Gy N II : 3,41 Gy N III : 1,16 Gy	N I : V95% : 0,99% N II : V95% : 0% N III : V95% : 0%

CA : curage axillaire ; D90% : dose médiane délivrée à 90% du volume ; GS : ganglion sentinelle ; ND : non documentée ; PTVGS : volume cible comprenant le lit du ganglion sentinelle biopsié ; TH : Tangentiel haut ; TH-CML : Tangentiel haut-collimateur multi-lame ; TS : Tangentiel standard ; RCMI-s : radiothérapie par modulation d'intensité simplifiée ; RT3D-FIF : Radiothérapie par modulation d'intensité field in field ; V95% : volume recevant 95% de la dose prescrite.

Figure 1 : Diagramme de flux selon PRISMA 2009



1

Incidental axillary dose delivering to axillary lymph node level I-III by different techniques of whole breast irradiation: a systematic literature review

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Abstract

In breast cancer treatment, the indications of irradiation of the axillary area are debatable. Axillary recurrence in patients with invasive breast carcinoma remains an issue. Currently, the standard use of sentinel lymph node biopsy (SLNB) for the evaluation of the axilla in early-stage breast cancer in lieu of complete axillary lymph node dissection (ALND) and the omission of ALND in certain SLNB-positive patients has resulted in renewed interest in axillary irradiation for the management of the axilla. The questions of whether breast irradiation may unintentionally include levels I, II, and III and may decrease the risk of axillary recurrence remain topics of discussion. A literature search was performed to identify articles that have published data regarding dose–volume analysis of axilla levels in breast irradiation, aiming to determine the potential therapeutic implications.

Keywords: radiotherapy, breast carcinoma, axillary lymph nodes, three dimensional radiotherapy, intensity-modulated radiotherapy

Abbreviations:

SLNB: sentinel lymph node biopsy

ALND: axillary lymph node dissection

MTM: multidisciplinary team meeting

IMN: internal mammary lymph node

ACOSOG: American College of Surgeons Oncology Group

3DRT: three dimensional radiotherapy

ST: standard tangential

HT: High tangential

NSABP 32: National Surgical Adjuvant Breast and Bowel Project B-32

PBI: partial breast irradiation

PRISMA: preferred reporting items for systematic reviews and meta-analyses

V95: volume covered by 95% of the prescribed dose

RTOG: Radiation Therapy Oncology Group

IMRT: Intensity-modulated radiotherapy

DVH: dosimetric volume histogram

FIF-3DRT: field-in-field 3D radiotherapy

RR: relative risk

WBI: whole breast irradiation

1. Introduction:

a. Indication of whole breast irradiation:

Locoregional treatment of the breast combines surgery and often radiotherapy. Postoperative irradiation of the whole breast is systematic after lumpectomy [1, 2]. An improvement in specific survival and recurrence-free survival after irradiation has been demonstrated [3, 4].

b. After neoadjuvant treatment and surgery:

The radiation oncologist has historically relied on ALND findings in the design of the radiation treatment fields [5], however, the increasing use of neoadjuvant chemotherapies or immunotherapies is challenging the indications for locoregional treatments. The role of adjuvant radiotherapy based on treatment response after neoadjuvant chemotherapy is not well defined [6]. Several trials have been focused on the place of adjuvant radiotherapy with neoadjuvant chemotherapies or immunotherapies [7, 8]. Alliance A11202 trial evaluate whether radiation to the undissected axilla and regional lymph nodes is not inferior to axillary lymph node dissection with radiation to the regional lymph nodes but not to the dissected axilla in terms of invasive breast cancer recurrence-free interval in patients with positive sentinel lymph node after completion of neoadjuvant chemotherapy, results will be available in 2024 [7].

c. Indication of regional node irradiation:

Regional node irradiation showed a benefit in several studies [9–11]. However, the irradiation of internal mammary lymph nodes (IMN) remains debated, particularly irradiation of the left breast because of the risk of induced cardiac complications [12]. In case of isolated cells or micrometastases at sentinel lymph node biopsy (SLNB) there is no indication of axillary irradiation [13, 14]. In the case of positive SLNB and in the absence of axillary lymph node dissection (ALND), the indication of axillary irradiation is debated. The Z0011 trial, which we will detail later, showed that ALND and axillary irradiation is not required after positive SLNB in T1-2 breast cancer with 1-2 sentinel lymph nodes receiving WBI and adjuvant systemic

therapy [15]. The AMAROS trial showed that axillary irradiation is not inferior to ALND for localized SLNB positive breast cancer and causes significantly less lymphoedema [16].

1.1 Impact of breast radiotherapy on the rate of axillary lymph node recurrence:

The results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial changed the management of patients with T1-T2 breast cancer. The Z0011 trial included patients with T1 or T2 breast cancer with one or two positive SLNBs and treated by lumpectomy followed by whole breast irradiation, randomized to either the complementary ALND group or the surveillance group. The authors report a non-inferior overall survival with no ALND and even an overall survival at 10 years worse with ALND despite 27% of the patients (115 patients) had additional undissected positive nodes. These axillary metastatic nodes that did not receive specific treatment did not, however, lead to axillary recurrence [15]. However, the Z0011 trial had been criticized for its design and data collection by several publications [17, 18]. The trial did not complete accrual, the authors used a 2-sided 90% confidence interval, Latosinsky et al reported that several of the patients included did not meet the inclusion criteria and twenty-one percent of patients in the ALND arm and 17% in the SLNB arm were lost to follow-up [17].

In 2014, Jagsi et al. conducted an informal study by directly contacting radiation oncologists who participated in the Z0011 trial. Irradiation characteristics could only be collected in 27% of patients. In approximately 50% of them received a treatment to regional lymph nodes, either with HT fields or separate fields to the supraclavicular or axillary area. Of the 27% of patients with records reviewed, 19% received directed regional nodal irradiation using at least three irradiation fields, although this technique was an exclusion criterion in the trial. The additional irradiation field was more frequent in the SLNB only group; however, the difference was not significant ($p=0.067$). For 142 patients, treatment plans were specific enough to assess whether the irradiation was consistent with ST or HT fields. HT fields were used in approximately 50% of patients randomized to the ALND arm and SLNB arm [19].

With the publication of Z0011 trial, the optimal design of radiation fields for patients with positive sentinel lymph node who do not undergo ALND is uncertain, Haffty et al. proposed an approach to assess the risk of microscopic involvement in the regional nodes. They suggested consideration of tumor size, grade, histology, receptor status, lymphovascular invasion, number of positive sentinel lymph nodes in combination with clinical judgment to target nodes that are at significant risk in the radiation treatment plan [20].

The National Surgical Adjuvant Breast and Bowel Project B-32 (NSABP B-32) trial randomized patients with breast cancer without axillary clinical involvement in either the SLNB arm systematically followed by ALND or the ALND arm, only if the SLNB was positive [21]. No significant differences were observed in progression-free survival, overall survival, or locoregional recurrence rates between the trial arms [21].

In 2008, Van Wely et al. included 592 patients to assess the axillary recurrence rate and the false negative rate during SLNB and to identify prognostic factors for recurrence after negative SLNB. The median follow-up was 65 months. The false negative rate was 6.9%. Eleven patients (2.8%) developed axillary recurrence. The majority of these patients (10/11) had not received breast radiotherapy, which was the only prognostic factor identified by the authors [22].
These findings encouraged these same authors to conduct a systematic literature review with the hypothesis that radiotherapy in breast cancer could reduce the risk of axillary recurrence after a negative SLNB (15–102). This literature review showed that external breast radiotherapy was associated with a lower rate of axillary recurrence ($p<0.001$) [23]. The hypothesis suggested by the authors was that when the breast was irradiated, part of the axillary area was irradiated at doses that allowed for the control of potential tumour cells. This dose received at the axillary area varied according to the irradiation technique. The subject of this article is to evaluate the incidental axillary dose delivered at axillary levels according to the irradiation technique.

1. Methods and materials:

The literature review was conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) recommendations [24]. A research protocol was published in the PROSPERO database (registration number: CRD42020131898). Eligibility criteria were prospective or retrospective studies analysing dose or coverage of the axillary lymph node area in the context of adjuvant whole breast irradiation without specific axillary field. The exclusion criteria were as follows: case report, bi-dimensional irradiation, studies not specifying the modalities of irradiation and articles not written in English or French. References were retrieved from two database: MEDLINE via Pubmed and the Cochrane data library. The following MESH terms were used: “breast cancer / lymph nodes” AND “radiotherapy dosage”. The titles and abstract of studies retrieved using the search strategy were screened to identify studies that potentially met the inclusion criteria. We did not define a starting date and stopped searching on September 1st, 2020. The titles and abstracts of the studies retrieved through the search strategy were independently reviewed by two reviewers to identify studies likely to meet the inclusion criteria described above. The full text of these potentially eligible studies was then retrieved and independently evaluated by the same reviewers. Any disagreement between the two reviewers about the eligibility of a particular study was resolved through discussion with a third reviewer. By checking the references of this articles, other studies were considered eligible for our review. Thirteen articles were identified (**Figure 1**).

3. Results

3.1 3D radiotherapy dosimetric study:

Nine articles concerning patients irradiated with 3DRT were identified. The majority of the studies were retrospective, with a number of patients ranging from 15 to 50 [25–33]. These studies focused on a comparative analysis of dose–volume histograms between ST and HT irradiation fields (**Table 1**).

In 2000, the study by Krasin et al. focused on the analysis of dose–volume histograms in 25 patients irradiated at the breast after lumpectomy. Only one patient had 95% of the volume of axillary level I covered by 95% of the prescribed dose (V95). The level I V95 was only 50% in six patients. None of the patients had adequate coverage of levels II and III. The average doses in levels I, II, and III were 32 Gy (5.5–51.5), 26.5 Gy (4.8–47.7), and 18.2 Gy (4.7–38.1), respectively [27].

In 2001, Aristei et al. conducted a prospective study in 35 patients treated with conservative breast surgery and ALND. Three clips were implanted to delimit the three axillary levels. Adjuvant radiotherapy consisted of irradiating the whole breast with two opposite tangential fields delivering 50 Gy in 25 fractions or 50.4 Gy in 28 fractions, combined with additional irradiation (10 Gy) in the tumour bed. The average doses delivered in axillary levels I and II were 38.6 Gy (3.5–47.1) and 20.6 Gy (0.95–38.9), respectively [28].

In 2005, Orechia et al. presented similar results, with an average dose less than or equal to 40 Gy delivered in level I for all patients. The median volume of level I receiving at least 80% of the prescribed dose was 30.7% (0–70%) [29].

Reznik et al. were the first to compare the dosimetric impact of ST and HT fields. The analysis of 35 patients showed better coverage of the axillary area by the HT field technique. The average doses delivered in levels I, II, and III with ST and HT fields in the following percentages of the prescribed dose were 66% (SD = 13%) and 44% (SD = 18%), 31% (SD = 20%) and 86% (SD = 9%), and 71% (SD = 19%) and 73% (SD = 17%), respectively, [31].

In 2014, Belkacemi et al. retrospectively studied the dose distribution in the SLNB area visualized in 25 patients by clips. Dosimetry was calculated in 3DRT with ST and HT fields. The mean doses delivered in axillary levels I, II, and III and in the SLNB area were significantly lower with ST fields than with HT fields and were 22 Gy vs 38 Gy ($p=0.004$), 3 Gy vs 11 Gy ($p=0.019$), 2 Gy vs 5 Gy ($p=0.003$), and 30 Gy vs 45 Gy ($p=0.02$), respectively [26].

In 2020, Borm et al. studied the dose distribution from randomized trials on lymph node irradiation for assessment of the dose distribution in actual lymph node metastases and in the CTV according to the ESTRO guidelines. Three templates, standard, obese and slender patients were chosen for treatment planning based on weight, body mass index and breast shape. Treatment plans were designed for all patients based on the study protocols of MA-20, EORTC, AMAROS and Z0011 trial. Treatment of the axillary levels I and II was intended in the AMAROS and in the observation arm of the MA-20 trial but neither the Z0011 nor the EORTC purposedly included the axillary levels I and II in the target volumes [9, 10, 15, 16]. The mean doses delivered in axillary levels I, II, and III in Z0011 trial in the standard patient with ST fields and with HT fields were 42.2 Gy vs 48.4 Gy, 35.6 Gy vs 47.5 Gy, 12.0 Gy vs 44.7 Gy, respectively. In EORTC trial the means doses delivered in axillary levels I, II and III in the standard patient were 36.5 Gy, 20.3 Gy and 36.3 Gy. The authors showed that the incidental irradiation in the axillary nodes depended on the patient's body shape with the lowest values for the slender patient [33].

It should be noted that the definition of HT radiation fields varied among the studies. For two studies, they were defined by an upper limit of the field plumbing the humeral head [26, 31], and for another, they were defined as when the upper limit of the field was less than 2 cm from the humeral head [15]. Only two studies [26, 32] defined the axillary volume delineated by the Radiation Therapy Oncology Group (RTOG) recommendations [34].

3.2 Intensity-modulated radiotherapy (IMRT) dosimetry study:

Five studies compared the dose received at the axillary level between 3DRT and IMRT and included a small number of patients (**Table 1**).

In 2013, Kataria et al. prospectively compared *in silico* the dose received at the axillary level among ST field irradiation, 3DRT, and IMRT in 50 patients. The dose was 50 Gy in 25 fractions of 2 Gy. The irradiation was delivered after conservative breast surgery and a negative SLNB.

Analysis of the DVH showed that the mean percentage of the prescribed dose delivered at the axillary I level was higher with ST fields than 3DRT and IMRT [87% (73–98), 80% (63–95), and 78% (67–90), respectively], with a significant difference between ST and IMRT (p=0.037). For the higher levels of axillary nodes, the values were lower. At levels II and III, the values for the ST, 3DRT, and IMRT fields were 65% (29–87) and 72% (34–93), 70% (46–89) and 41% (6–72), and 53% (19–86) and 51% (28–76), respectively. In terms of dose coverage, none of the three techniques provided optimal coverage of the axillary area. The volume receiving 90% of the prescribed dose at axillary level I was significantly higher with ST fields than with 3DRT (p=0.029) or IMRT (p=0.029). At level II, only the dose delivered by 3DRT was significantly higher than that delivered by ST fields (p=0.028). At level III, coverage by IMRT was significantly higher than that provided by ST fields (p=0.039) [35].

Recently, in 2016, Lee et al. described a significantly lower dose delivered in the axillary area with IMRT compared to field-in-field 3D radiotherapy (FIF-3DRT) (p=0.001 for all three levels) [36]. However, in this study, the mean dose differences between FIF-3DRT and IMRT received in each level of the axillary area were greater than those in the studies by Kataria et al. and Zhang et al. [35, 37]: level I: 42.6 Gy vs 14.5 Gy; level II: 26.2 Gy vs 3.4 Gy; and level III: 6.3 Gy vs 1.2 Gy. According to the authors, these differences could be explained by the degree of optimization in IMRT and the field's upper limit defined in FIF-3DRT [36].

4. Discussion:

IMRT and FIF-3DRT deliver a lower dose to the lower part of the axillary area compared to 3DRT with ST fields. This difference tends to be reversed at levels II and III, but the doses delivered can be very low [36]. For IMRT, the coverage and dose delivered over the entire axillary area appeared to be lower than those obtained with 3DRT ST fields [35, 36].

The conclusions of this literature review are limited by many study weaknesses. No comparison was made between the HT fields and the intensity modulation. The definition of

the upper limit of the HT fields varied according to the studies, making it difficult to compare the results. The definition of axillary node volumes varied according to the studies, with the use of international recommendations in a minority of studies. Finally, most of these studies presented a very heterogeneous population, particularly with regard to the volume of the breast and it has been shown that the axillary incidental dose varies with the body shape of the patients [33]. All these heterogeneities could explain the variations in the dose and coverage of the axillary area.

The incidental dose delivered to the axilla during WBI is heterogenous and dependent on the irradiation technique utilized. The clinical translation of this axillary dose is not clearly demonstrated however the meta-analysis by Van Wely et al. in 2011 showed an axillary recurrence rate of 0.4% for patients who had received radiotherapy and 1.2% for patients who had not, resulting in a decrease in the relative risk (RR) of axillary recurrence [RR=0.32 (0.23–0.46), $p<0.001$], but no comparison of irradiation and dose techniques could be made due to the lack of adequate information in the studies [23]. One of the arguments that could explain these results was based on the incident axillary dose received during breast irradiation.

Moreover, some axillary metastases are not necessarily revealed by surgical lymph node staging. In the NSABP B32 trial, the false negative rate for SLNB was 9.8% [21] and the probability of occult axillary metastases was estimated at 15,9% in Weaver et al. study. They found that occult metastases in sentinel nodes are an independent predictor of overall survival, disease-free survival, and distant-disease–free interval. Radiation therapy, among other factors, appears to attenuate the adverse clinical effect of these metastases [38].

The risk of axillary recurrence is also a concern with partial breast irradiation (PBI). Two randomized phase III trials compared postoperative external PBI with WBI [39, 40]. Livi et al. showed a noninferiority of PBI with IMRT compared to WBI with a 5-year recurrence rate in the homolateral breast [39]. Coles et al. showed that PBI was not inferior to WBI, with 5-year

local recurrence rates [40]. However, the authors of both trials did not report the axillary recurrence rate [39, 40]. In a retrospective study Gentilini et al. showed that WBI lowered the risk of axillary recurrence by two thirds as compared to PBI [41]. This concern should be highlighted also in the light of sentinel micrometastases without ALND [42].

However, this incidental dose remained low, and an initial hypothesis suggested that a tumoricidal dose of 45–50 Gy may not be necessary to achieve axillary control. Lower doses have been shown to be effective in eradicating metastatic cells from different primary tumours [43, 43, 44]. The radiosensitivity of tumour cells may be inversely proportional to the tumour cell density.

The second hypothesis was that tangential field radiotherapy would eliminate the transit metastases still present after surgery [45].

The third hypothesis was the role of a dose-independent immune mechanism triggered by breast irradiation that provides a benefit for local control [46].

Moreover, in 1955, Berg et al. showed that the first invaded axillary node was mainly located in level I, with invasion in 95% of sequential cases of level I, then II, and finally III. In only 5% of cases, skips metastases can occur, which were found in level II or III without reaching the previous level [47]. In light of these data, we can note the importance of axillary level I compared to axillary levels II and III.

5. Conclusion:

Our literature review suggests that the incidental dose delivered to the axilla during WBI is heterogenous and dependent on the irradiation technique utilized. However, if this observation can be translated into a therapeutical effect is still a matter of debate. This debate could be resolved by larger prospective trials.

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Table 1. Results from the literature review.

Authors	Number of patients	Technique	Axillary surgery	Mean (min-max) axillary volumes (ml)	Mean axillary dose (Gy) or % of the prescribed dose	Axillary dose (Gy) as D 90% or % for V95%
Krasin et al.	25	ST	ALND	N I: 50 (22-173) N II: 23 (10-60) N III: 6 (3-14)	N I: 32 Gy N II: 26 Gy N III: 18 Gy	ND
Aristei et al.	35	ST	ALND	ND	N I: 38,6 Gy NII: 20,6 Gy	N I: D90%: 6,7 Gy N II: D90% 1,7 Gy
Orecchia et al.	15	ST	SLND	N I: 29 (15-59)	N I: 24 Gy	ND
Reed et al.	50	ST	ALND	N I+II: 146 (83-313)	ND	N I+II: V95%: 55%
Reznik et al.	35	ST	SLND	N I: 85 (24-232) N II: 17 (4-40) N III: 5 (1-24)	N I: 66% N II: 44% N III: 31%	N I: V95%: 51% N II: V95%: 26% N III: V95%: 15%
		HT	SLND	N I: 85 (24-232) N II: 17 (4-40) N III: 5 (1-24)	N I: 86% N II: 71% N III: 73%	N I: V95%: 79% N II: V95%: 51% N III: V95%: 49%

Alco et al.	30	HT	SLND	N I: 62 (24-135)	N I: 39,4Gy	ND
				N II: 12 (4-36)	N II: 26,6 Gy	
		MLC-HT	SLND	N I: 62 (24-135)	N I: 49,7 Gy	ND
				N II: 12 (4-36)	N II: 47,1 Gy	
Belkacemi et al.	25	ST	SLND	ND	N I: 22 Gy	ND
					N II: 3 Gy	
					N III: 2 Gy	
					PTV*GS:* 30 Gy	
		HT	SLND	ND	N I: 38 Gy	ND
					N II: 11 Gy	
					N III: 5 Gy	
					PTVGS: 45 Gy	
Kataria et al.	50	ST	SLND	N I: 68 (29-151)	N I: 43,5 Gy	N I: V95%: 51%
				N II: 25 (14-56)	N II: 32,5 Gy	N II: V95%: 8%
				N III: 9 (5-16)	N III: 20,5 Gy	N III: V95%: 3%

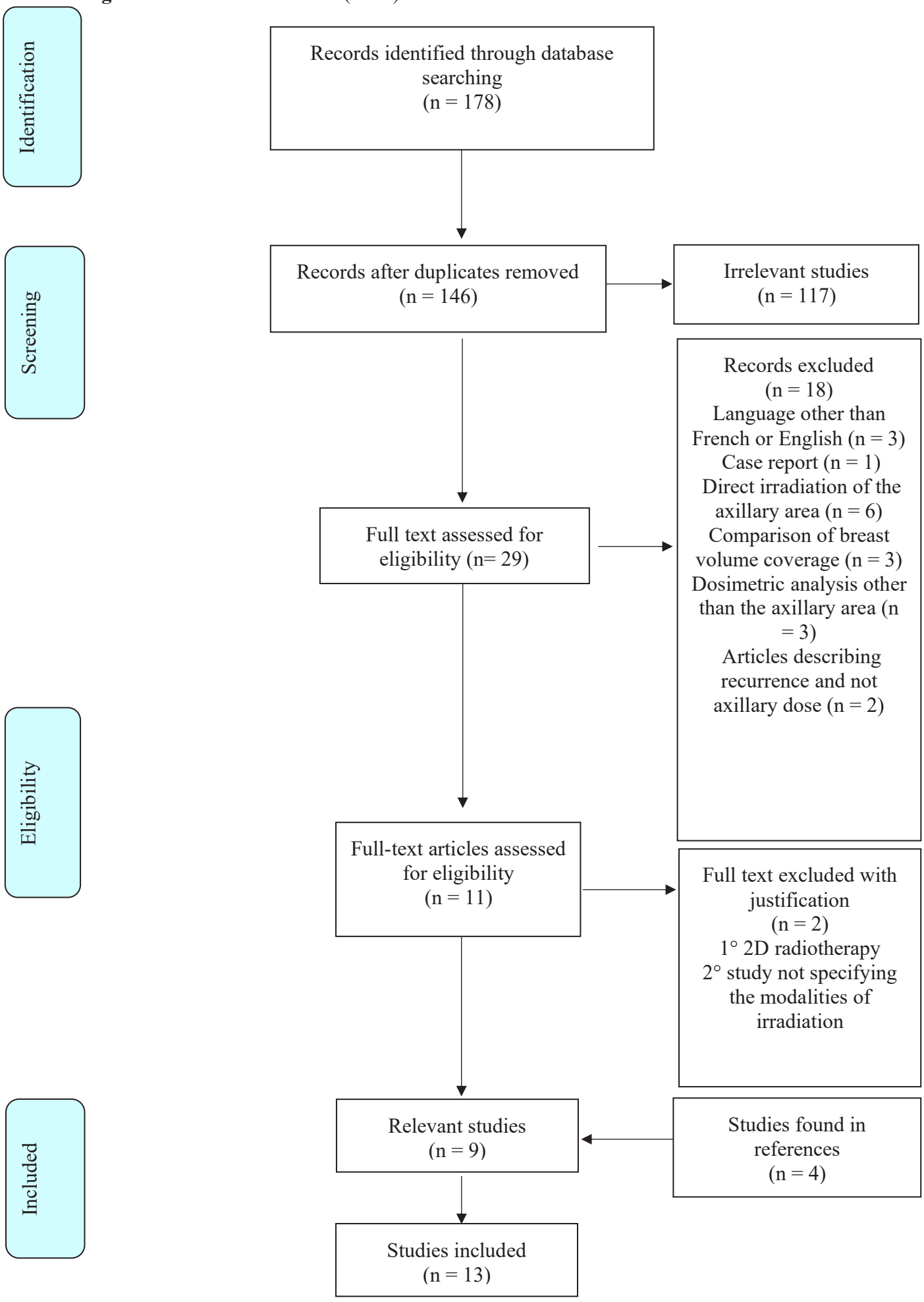
		3DCRT	SLND	N I: 68 (29-151)	N I: 40 Gy	N I: V95%: 44%
				N II: 25 (14-56)	N II: 36 Gy	N II: V95%: 19%
				N III: 9 (5-16)	N III: 26,5 Gy	N III: V95%: 11%
		IMRT	SLND	N I: 68 (29-151)	N I: 39 Gy	N I: V95%: 39%
				N II: 25 (14-56)	N II: 35 Gy	N II: V95%: 17%
				N III: 9 (5-16)	N III: 25,5 Gy	N III: V95%: 8%
Zhang et al.	40	s-IMRT	SLND	ND	N I: 27,7 Gy	N I: V95%: 16,9%
					N II: 10,6 Gy	N II: V95%: 1,7%
					N III: 2,5 Gy	N III: V95%: 0%
		IMRT-FIF	SLND	ND	N I: 29,1 Gy	N I: V95%: 27,6%
					N II: 10,9 Gy	N II: V95%: 1,8%
					N III: 2,8 Gy	N III: V95%: 0%
Jacobson et al.	50	ST	SLND and/or ALND	ND	N I: 29,03 Gy	N I: V95%: 30,80%
					N II: 6,09 Gy	N II: V95%: 0,65%
					N III: 1,04 Gy	N III: V95%: 0%

Lee et al.	20	3DCRT-FIF	ND	ND	N I: 42,58 Gy N II: 26,25 Gy N III: 6,26 Gy	N I: V95%: 36,44% N II: V95%: 0,67% N III: V95%: 0%
		IMRT	ND	ND	N I: 14,49 Gy N II: 3,41 Gy N III: 1,16 Gy	N I: V95%: 0,99% N II: V95%: 0% N III: V95%: 0%
Mayinger et al.	90	TT	ND	ND	N I: 31,6 Gy N II: 8,43 Gy N III: 2,38 Gy	ND
		3DCRT	ND	ND	N I: 24 Gy N II: 11,2 Gy N III: 3,97 Gy	ND
		3DCRT-DIBH	ND	ND	N I: 24,7 Gy N II: 13,3 Gy N III: 5,59 Gy	ND

De Santis et al.	10	3DCRT	SLND	N I: 31,9 (SD ± 10.8)	N I: 31,15%	N I: V95%: 26,4%
				N II: 17,3 (SD ± 7.6)	N II: 22,93%	N II: V95%: 5,4%
				N III: 17,9 (SD ± 3.9)	N III: 4,7%	N III: V95%: ND
		Static	SLND	N I: 31,9 (SD ± 10.8)	N I: 27,58%	N I: V95%: 8,6%
		IMRT		N II: 17,3 (SD ± 7.6)	N II: 17,71%	N II: V95%: 1,9%
				N III: 17,9 (SD ± 3.9)	N III: 5,74%	N III: V95%: ND
		Volumetric	SLND	N I: 31,9 (SD ± 10.8)	N I: 26,66%	N I: V95%: 2,6%
		IMRT		N II: 17,3 (SD ± 7.6)	N II: 17,83%	N II: V95%: 2,6%
				N III: 17,9 (SD ± 3.9)	N III: 5,96%	N III: V95%: ND

3DCRT-FIF: tridimensional conformational radiotherapy field-in-field; ALND: axillary lymph node dissection; DIBH: deep inspiration breath hold; IMRT: intensity modulated radiation therapy; IMRT-FIF: intensity modulated radiation therapy field-in-field; HT: high tangential field; MLC-HT: multilane collimator high tangential field; ND: not documented; s-IMRT: simplified intensity modulated radiation therapy; SLND: sentinel lymph node dissection; ST: standard tangential field; TT: tomotherapy.

Figure 1. PRISMA flow chart (2009).



Should the management of radiation therapy for breast cancer be standardized?

Results of a survey on current French practices in breast radiotherapy

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Abstract

Purposes: Breast cancer is the most frequent cancer in women in France. Its management has evolved considerably in recent years with a focus on reducing iatrogenic toxicity. The radiotherapy indications are validated in multidisciplinary consultation meetings; however, questions remain outstanding, particularly regarding hypofractionated radiotherapy, partial breast irradiation, and irradiation of the internal mammary chain and axillary lymph node area.

Materials and methods: An online survey was sent to 47 heads of radiotherapy departments in France. The survey consisted of 22 questions concerning indications for irradiation of the supraclavicular, internal mammary and axillary lymph node areas; irradiation techniques and modalities; prescribed doses; and fractionation.

Results: Twenty-four out of 47 centers responded (response rate of 51%). This survey demonstrated a wide variation in the prescribed dose regimen, monoisocentric radiotherapy, and indications of irradiation of the lymph node areas.

Conclusion: This survey provides insight into the current radiotherapy practice for breast cancer in France. It shows the need to standardize practices.

Key words: breast cancer; clinical practice; radiotherapy; survey

Abbreviations:

3DRT: three-dimensional radiotherapy

ACOSOG:American College of Surgeons Oncology Group

ALND: axillary lymph node dissection

ASTRO: American Society for Radiotherapy and Oncology

DFS: disease free survival

EORTC: European Organisation for Research and Treatment of Cancer

ESTRO: European Society for Radiotherapy and Oncology

GEC ESTRO: Groupe Europeen de Curietherapie and European Society for Radiotherapy and Oncology

HF-RT: hypofractionated radiotherapy

IBCSG: international Breast Cancer Study Group

IMN: internal mammary lymph node

IMRT: intensity-modulated radiotherapy

MTM: multidisciplinary team meeting

NCCN: National Comprehensive Cancer Network

NORA: nodal radiotherapy survey

OR: odd ratio

OS: overall survival

PBI: partial breast irradiation

PFS: progression-free survival

PTV: planning target volume

RFS: recurrence free survival

SBR: Scarff Bloom Richardson

SIB: simultaneously integrated boost

SLND: sentinel lymph node dissection

SN: sentinel node

UK: United Kingdom

WBI: whole breast irradiation

Introduction:

Breast cancer is the most frequent cancer in women in France (1). Management has considerably evolved in recent years with the introduction of advanced irradiation techniques and schedules such as intensity modulated radiotherapy (IMRT), hypofractionated radiotherapy (HF-RT) and partial irradiation (2,3). On the surgical side, the sentinel node (SN) procedure has become increasingly important to the detriment of systematic axillary lymph node dissection (ALND), and recently, the AMAROS trial showed that in patients with stage T1-2 breast cancer with one to two lymph node metastases, radiotherapy could substitute for ALND (4). However, if the indication of radiotherapy is validated in a multidisciplinary consultation meeting (MTM), the technique and the definition of target volumes are frequently at the discretion of the radiation oncologist or depend on department protocols. A guide to external radiotherapy procedures, published in 2007 in its first version and in 2016 in its second version, aimed to optimize, harmonize and homogenize national practices. In 2021, one hundred and seventy-five centers were performing radiotherapy in France, and thirty-four were authorized to perform brachytherapy. There are 25 Comprehensive cancer centers and 25 University centers. Currently, each radiotherapy center treats at least 600 patients per year. The purpose of this national survey sent to French Comprehensive cancer centers and university centers aimed to look for and describe potential heterogeneities in current practices.

Methods:

All French Comprehensive cancer centers as well as university radiotherapy centers were surveyed except 3 because of a refusal to communicate their email addresses. The survey was carried out on the www.survio.com website, and a link was provided to each of the 47 heads of radiotherapy departments in France (Appendix A). Anonymous responses were recorded from April 2020 to July 2020. The survey included 22 questions concerning irradiation indications of the supraclavicular, internal mammary and axillary lymph node areas; irradiation techniques

and modalities; prescription doses; and fractionation.

Results and Discussion:

Question 1: *Seventy-one percent (17/24) of respondents considered themselves to be an expert in breast cancers.*

Questions 2 and 3: *Of the 47 centers, 23 responded to the survey. The number of cases treated per year in each center is shown in Figure 1. Cases were systematically presented at radiotherapy technical committees in ten centers, only for cases considered difficult in seven centers and never in six others.*

In comparison, in the Nodal Radiotherapy (NORA) survey, 82% of the centers validated the volumes and modalities of irradiation at technical meetings (5). This decrease in the requirement for technical meetings could be partly explained by the publication of recent recommendations, such as the ESTRO (European Society for Radiotherapy and Oncology) recommendations for the delineation of target volumes and the ASTRO (American Society for Radiotherapy and Oncology) guidelines that have made breast irradiation a well-supervised practice (6,7).

Questions 4 and 5: *Concerning irradiation techniques, all of the questioned centers carry out breast and* chest wall *irradiation in three-dimensional radiotherapy (3DRT). In the case of mammary or* chest wall *irradiation in three-dimensional radiotherapy, 30% of the centers systematically used a monoisocentric technique. However, the majority of the centers reserved this technique for particular cases or never used it (Figure 2).*

Monoisocentric 3DRT was first described for breast cancer in 1984 (8). Better dose homogeneity in the junction zones, better sparing of organs at risk and better reproducibility

compared to a technique with two isocenters have been demonstrated (9–11). Despite these advantages, its use seems low in France. Regarding this observation, we hypothesize that the following reasons may account for its low use: i) difficulty in finding an appropriate dose calculation reference point (10), ii) tangential field length limited to 20 cm due to half-beam blocking (12), iii) lack of randomized trials or iv) technical limitations due to the treatment machines in place.

Question 6: *After total mastectomy, the majority of participants (56.5%) did not have treatment with electron beams, and none had systematic irradiation of the chest wall with electron beams.*

Theoretically, electron-beam chest wall irradiation has an advantage over photon-beam chest wall irradiation because of the rapidly decreased depth-dose curve. In the case of adjuvant irradiation after total mastectomy, several studies have shown the possibility of carrying out irradiation with an electron beam of variable energy according to the thickness of the thoracic wall to be treated (13–15). It has already been shown that this technique yields locoregional control, disease-free survival, and overall survival rates similar to those of standard photon beam radiotherapy (13,14,16). However, because of variations in patients' chest wall thickness, CT-based planning is necessary for accurate electron beam energy selection to ensure optimal target coverage while minimizing normal tissue dose (17); plus, the source–surface distance would vary dramatically across the field, which would lead to excessive dose heterogeneity in the target tissues, a situation that would be enhanced in selected patients with greater chest wall curvature.

Question 7: *Concerning IMRT, 74% of the centers used this technique in cases of pectus excavatum and 61% used bilateral whole breast irradiation (WBI) or bilateral wall chest irradiation associated with regional nodal areas. Five centers never treated breast cancer with IMRT, and only one center systematically treated breast cancer with IMRT (Figure 3).*

While 3DRT remains the standard in adjuvant breast cancer, several studies showed the increase in the use of IMRT (18,19). According to expert agreement, IMRT would be indicated in cases of complex anatomy, bilateral breast irradiation, breast prosthesis and situations where no compromise should be made in the predicted target volume (20). Several dosimetric studies have shown a significant difference in the homogeneity of the delivered dose and in the sparing of organs at risk in favor of IMRT (21–23). However, these indications of IMRT are discussed, and the distribution of low doses in healthy tissues has been scarcely documented (24) but seems to be more important than that delivered by 3DRT (21,25). This raises the question of the risk of potential radiation-induced second cancer in patients whose life expectancy may be long (26–28).

Questions 8 and 9: *None of the centers performed brachytherapy boost. Boost by external irradiation with photons is performed by 91% of the centers, and the use of electrons is less frequent and was used in only 61% of the centers. Sequential boost was performed by 96% of the centers.*

The lack of use of brachytherapy for boost may be due to the lack of access to the technique. Only 56 centers were practicing brachytherapy in France in 2013, a number that has been declining since 2008. This is probably due to the disappearance of iridium-192 wires and inadequate funding. Bartelink et al. showed a significant decrease in the local recurrence rate ($p < 0.0001$) when the boost was irradiated either by electrons or photons with tangential beams or by brachytherapy with an iridium-192 implant. However, the authors showed a significantly higher rate of severe skin fibrosis at 10 years in the group that received a boost ($p < 0.0001$) (29).

The EORTC trial number NCT02295033 showed a significant reduction in the 20-year cumulative incidence of homolateral intramammary recurrence from 31% (95% CI 22%-39%)

to 15% (95% CI 8%-21%) when a boost was performed in high-risk patients (30).

A retrospective analysis was conducted to assess whether the choice of boost technique could influence the local recurrence rate. The authors showed that at 13.1 years of median follow-up, there were no significant differences difference in the local recurrence rate between electron beam, brachytherapy or photon beam (31). A randomized trial showed that at 36 months of follow-up, there were no significant differences in the overall global cosmetic scores between the implant boost group and the photon/electron boost group; telangiectasia was more severe, and the breast retraction assessment value was greater in the implant group (32).

Since the development of IMRT, simultaneously integrated boost (SIB) is technically easy to perform. Renoult et al. demonstrated in a retrospective study that the 5-year overall, no recurrence and local no recurrence survival rates were 98.2%, 100% and 100%, respectively, in patients treated for stage T1-T2N0 breast cancer by conservative surgery and IMRT at a dose of 50 Gy with a concomitant boost of 10 Gy in 10 fractions of 1 Gy (33). The SIB allows for a reduction in the treatment time (34). There was no evidence of increased long-term toxicity with increasing dose per fraction (35,36). The IMRT-MC2 trial (NCT01322854) is a prospective phase III, multicenter, randomized trial comparing IMRT with SIB and 3DRT irradiation with sequential boost. The main objective is the evaluation of cosmetic results at 6 weeks and 2 years and the local recurrence rate at 2 and 5 years after the end of irradiation.

Questions 10 and 11: *Except for inclusions in clinical trials, three centers (13%) performed partial breast irradiation (PBI) according to indications. External beam irradiation was the technique used in the majority of cases; two centers used it, while one center also used brachytherapy, and another performed intraoperative irradiation.*

The survey published by Dundas et al. showed similar results, with 11% of the radiotherapy centers proposing partial radiotherapy (37). The justification for postoperative PBI is based on

the low recurrence rate in the remaining gland after external irradiation and the reduction in irradiated volumes with a consequent reduction in side effects. Indeed, Bartelink et al. noted 5 to 7% grade 3 mammary fibrosis after total breast irradiation by opposite tangential beams, of which the two main risk factors were the breast volume irradiated and the total irradiation dose (29). In addition, it should be noted that 80 to 90% of local relapses occurred at the lumpectomy site (38). Two recent randomized phase III trials compared postoperative external PBI with WBI (39,40). Livi et al. showed a noninferiority of PBI with IMRT compared to WBI with a 5-year recurrence rate in the homolateral breast of less than or equal to 1.5% in both groups (39). Coles et al. randomized 2018 patients into three groups (two groups receiving external WBI at a dose of 40 Gy in 15 fractions and 36 Gy in 15 fractions and one group receiving PBI at a dose of 40 Gy in 15 fractions). Patients in both groups were treated with IMRT. It was shown that PBI was not inferior to WBI, with 5-year local recurrence rates equal to 1% in both arms (40). Indications for PBI are currently reserved for selected patients with a very low risk of tumor recurrence (41). The randomized trial of the Groupe Européen de Curiethérapie and European Society for Radiotherapy and Oncology (GEC ESTRO) showed that interstitial brachytherapy was noninferior to WBI, with 5-year local recurrence rates of less than 1.5% in both arms (42).

Irradiation can be performed intraoperatively. To date, two randomized trials have been published: ELIOT and TARGIT-A. The authors of both trials showed a significant increase in local recurrences in the arms with intraoperative radiotherapy (2,3). Partial irradiation therefore remains marginal in France and is carried out only with well-selected patients.

Question 12: *In the case of isolated cells after sentinel lymph node dissection (SLND) followed by ALND, 20 centers (77%) did not irradiate the ganglion areas. One center irradiated only the supraclavicular area, and two centers treated the internal mammary lymph node (IMN) and*

supraclavicular area.

The NORA survey reported comparable results. For the vast majority of respondents in both surveys, there was no indication to irradiate the node areas in this situation. The supraclavicular area, axillary area and IMN area were treated with 4%, 4%, and 0%, respectively (5). The French guidelines do not recommend systematic irradiation for tumors located in the external quadrants and in the case of isolated cells. In tumors located in the internal and central quadrants, the indication should be modulated "according to the tumor size, patient's age and associated comorbidities as well as consideration of the risk/benefit ratio" (43,44). The National Comprehensive Cancer Network (NCCN) guidelines do not provide specific recommendations in the case of isolated cells (45).

Question 13: *In the case of microscopic cells after SLND followed by ALND, 54% of respondents did not irradiate any lymph node areas. Nineteen percent irradiated only the supraclavicular area. Eight percent of respondents irradiated the whole regional node area (IMN, supraclavicular and axillary areas).*

In the NORA survey, 2%, 24% and 7% of the centers retained the indication for treatment of the IMN and the supraclavicular and axillary areas, respectively, in the same situation. We can note that irradiation of the IMN and the supraclavicular area is more frequent in our survey but less frequent for the axillary area in comparison with Belkacémi et al. (5). In tumors located in the internal and central quadrants, the indication should be modulated "according to the tumor size, patient's age and associated comorbidities as well as consideration of the risk/benefit ratio" (43,44). The National Comprehensive Cancer Network (NCCN) guidelines do not provide specific recommendations on the appropriate conduct in the case of micrometastases (45).

Question 14: *In cases of macroscopic disease after the SLND procedure followed by ALND, less than 5 out of 10 affected lymph nodes were found. All of the centers irradiated the supraclavicular area. The IMN was irradiated by 69% of the surveyed centers, and the axillary area was irradiated by 15% of them.*

In a similar clinical situation, the indication of irradiation of each lymph node area was retained more in our investigation than in the previous study. In the study by Belkacémi et al., the number of affected lymph nodes and the number of lymph nodes sampled were not specified (5). The NCCN recommends "irradiation of supraclavicular areas, IMN, and any part of the axillary bed that may be suspicious" (45). The French recommendations systematically retain the irradiation of the supraclavicular and IMN areas in this situation. These guidelines recommend that the indication for axillary radiation therapy after ALND be discussed at the MTM. They retain the indication in cases of massive invasion (with consideration of the nodal ratio) (43).

Question 15: *In the case of isolated cells in the SLND procedure, without ALND, 74% of the centers did not irradiate any lymph node area, and 12% treated either the supraclavicular, IMN and axillary areas or only the supraclavicular area.*

The NORA survey found a comparable 14% of centers performing axillary area irradiation, but only 1.2% irradiated the IMN and 8% irradiated the supraclavicular area (5). In the meta-analysis of Van Deurzen et al., which included 29 publications, the overall risk of macroscopic lymph node invasion in cases of SLND involvement by isolated cells was 12.3%. The authors concluded that there was an indication for axillary dissection in the case of positive SLND with isolated cells if patients did not receive any adjuvant systemic therapy (46). Two retrospective studies reported divergent results (47,48). De Boer et al. showed a lower 5-year progression-free survival (PFS) in patients with axillary involvement by isolated cells (47), although Hansen

et al. found no significant difference in 8-year PFS and OS for patients with SLND-isolated cells compared to those with SLND-negative cells (48). The prospective NSABPB-32, IBCSG23-01 and ACOSOG Z0011 trials included breast cancer patients with isolated SLND cells. These trials were not performed to show a specific difference in this subpopulation, but the subgroup analysis did not show any benefit in OR or in recurrence-free survival (RFS) in the groups that received local axillary treatment (49–51).

Question 16: *In the case of axillary microscopic involvement after the SLND procedure without ALND, 50% of the centers did not treat the lymph node areas; 15% treated the supraclavicular area; another 15% treated the supraclavicular, IMN and axillary areas; and 4% treated the supraclavicular and axillary* areas.

The supraclavicular result compared favorably with those of the NORA survey with a value of 34% for supraclavicular and axillary irradiation. For IMN, only 5% of the centers retained the indication. The prospective IBCSG 23-01 and AATRM 048/13/2000 trials did not show any significant benefit in OS and RFS for patients with breast cancer and micrometastatic SLND who underwent local axillary irradiation (49,52). The IMN irradiation indication is more important in our survey than in Belkacémi et al.'s results (5). The indications for irradiation of the IMN are still debated (53–55). Two trials demonstrated a RFS and specific survival benefit but no OS benefit after lymph node irradiation in cases of axillary lymph node invasion or high-risk node-positive breast cancer, but in these two trials, identifying the specific role of IMN irradiation on the benefit to other lymph node areas was not possible (53,54). The debate also concerned the long-term impact of this irradiation and radiation-induced cardiac complications (56). According to Hennequin et al., patients with axillary lymph node invasion with a central tumor with poor prognostic factors (triple negative, vascular invasion, SBR grade 3, young age) could benefit from IMN irradiation (57). The authors described four predictive groups that

benefit from IMN irradiation. The groups were based on histological findings, imaging and tumor location in the breast (Table 1) (44). Recently, Jellesmark et al. analyzed a set of patients with and without IMN irradiation. The positive impact on OS appeared to be greater for patients with metastatic lymph node involvement (55). If these groups according to Hennequin can represent a putative irradiation reference, the final decision to irradiate IMN should be made in an MTM (57).

Concerning the cardiac risks calculated in the study by Hennequin et al. published in 2013, they appeared to be significant mainly in patients who had been treated more than 12 to 15 years previously and can currently be discussed because of the irradiation techniques now used (58). Darby et al. showed in 2013 that cardiovascular risk began 5 years after radiotherapy and continued up to 30 years after irradiation, independent of the patient's own cardiovascular risks. The risk increased by approximately 7% per Gy above an average dose of approximately 5 Gy in the whole heart (56). However, recent studies have highlighted the important role of the number of beams used (59) and the irradiation techniques used (60,61). The systematic review of Drost et al. showed that breathing control significantly reduced the mean dose delivered to the heart. They also showed that the mean dose steadily decreased over the years (between 2014 and 2017) (61).

Question 17: *In the case of pT2 tumors with macroscopic axillary involvement after the SLND procedure without ALND, none of the centers omitted lymph node irradiation. The supraclavicular, IMN and axillary areas were irradiated together by 42% of the centers; 12% of the centers irradiated the supraclavicular and axillary areas; 8% irradiated only the supraclavicular area; and 4% irradiated the IMN and axillary areas.*

The NORA survey showed a lower frequency of axillary irradiation for this same indication (57%) (5). Since the publication of the ACOSOG Z0011 trial in 2017 and AMAROS in 2015,

the place of ALND and axillary irradiation has been questioned for patients with stage T1-T2 breast cancer (4,51). The prospective ACOSOG Z0011 trial included 891 patients with T1 or T2 tumors with one or two nodes positive for the SLND procedure. All patients underwent partial mastectomy followed by WBI. With a median follow-up of 6.3 years, there was no difference in OS and LRS between patients with and without ALND. It should be noted that this study was the subject of several criticisms because the number of included patients was much lower than initially planned and the irradiation carried out was heterogeneous (51). The prospective AMAROS trial, which included 1425 women with cancer classified as T1-2 with axillary invasion diagnosed after the SLND procedure, showed that it was equivalent to substituting complementary ALND with axillary irradiation. Indeed, the authors found no significant difference between the two groups in terms of axillary RFS, DFS and OS (4). Table 3 summarizes the indications for lymph node irradiation according to French, European and American guidelines (44,45,62) and the regional lymph node irradiation rates according to axillary involvement in our survey and the NORA survey (5) (Table 3).

Question 18: *Technically, axillary irradiation was carried out by enlarged tangential mammary beams, enlarged supraclavicular beams or specific beams in 4%, 13% and 22% of the centers, respectively. In this situation, 48% of the centers treated patients with IMRT.*

Concerning the axillary area, Berg level I was generally included in the opposite tangential beams, but levels II and III have limited coverage by tangential beams despite the use of widened tangential beams (63–68) (CANRAD-D-19-00135R1). In 2004, Jephcott et al. showed that the addition of an anterior and posterior beam provided better coverage of the predicted target volume (PTV) but increased the areas of overdose above 120% of the prescribed dose (69). In 2013, Hernandez et al. demonstrated a significant difference in coverage of axillary levels in favor of irradiation combining a modified anterior and posterior beam (70). The

axillary area irradiation technique was heterogeneous, as our investigation reports.

Question 19: *The relevant criteria for axillary irradiation were that at least 50% of the lymph nodes were invaded in 74% of the centers. In terms of the number of removed lymph nodes in total, less than four, seven or ten were relevant criteria for 57%, 13% and 4% of the centers. Other criteria were specified: the presence of capsular rupture, macroscopic remnants, involvement of 100% of the harvested nodes, invasion of fat and PET-CT data.*

The indications for axillary irradiation are heterogeneous and vary according to the recommendations (Table 2). Rivera et al. retained the indication of axillary irradiation in cases of axillary lymph node involvement and incomplete ALND, massive axillary involvement and axillary fat invasion (71). In 2016, Hennequin et al. identified unspecified massive axillary involvement and insufficient clearance, defined by less than ten lymph nodes removed as criteria to irradiate the axillary area (44). Axillary irradiation, because of the risk of side effects, should require validation in a MTM.

Question 20: *Except in cases of trial inclusion, HF-RT was retained by 96% of the centers for WBI with or without boost and by 48%, 13% and 9% of the centers in cases of irradiation of the chest wall, breast and lymph node areas and chest wall and lymph node areas, respectively.*

The survey by Van der Laan et al. described the use of HF-RT in only 28% of the surveyed centers. HF-RT was not performed in any of the four German centers, while four out of five UK centers prescribed 15-fraction treatment of 2.67 Gy. This greater use of HF-RT in the UK is probably related to the publication of the START-B trial (72,73). Another explanation could be the lower ease of access to radiotherapy facilities, the cost of treatment based on the number of fractions and the long distance to reach a radiotherapy center (74–77). The survey by Ratosa et al. confirms the previous results. The use of HF-RT is heterogeneous on a

European scale. HF-RT was chosen as the preferred schedule for WBI and for WBI and lymph node area irradiation by 54.7% and 28.7% of the responding radiation oncologists, respectively (78). Park et al. showed that 36% of the surveyed radiation oncologists used HF-RT, and among them, 26% performed both breast and lymph node HF-RT (79). Wang et al. published a randomized trial showing that postmastectomy hypofractionated radiotherapy, including regional node irradiation, is noninferior and has similar toxicities compared to conventionally fractionated radiotherapy; however, late toxicity data are insufficient to recommend HT-RT for all patients (80). The results of the HYPOG01 (NCT03127995) trial will provide answers to late toxicity. The St. Gallen 2019 guidelines indicated that HF-RT can be used for most patients as a care standard (52% for all patients and 19% following breast conservation only) (81). The Covid-19 pandemic was also an argument for the publication of recommendations on HF-RT in an effort to mitigate risk to patients and optimize resource utilization (82,83). Coles et al. proposed in their guidelines HF-RT for all breast or chest wall and nodal irradiation in a moderately hypofractionated scheme (82). Braunstein et al. published similar recommendations proposing hypofractionated radiotherapy for all breast or chest wall and nodal irradiation (83).

Question 21 and 22: *In the context of adjuvant HF-RT, the total dose and fractionation retained by 74% of the centers was 40 Gy in 15 fractions. Specifically, 42.5 Gy in 16 fractions, 5 fractions per week, 41.6 Gy in 13 fractions, 5 fractions per week and 39 Gy in 13 fractions, 3 fractions per week were retained by 35%, 9% and 9% of the centers, respectively. Three centers used one of the three following schedules: 40.5 Gy in 15 fractions of 2.7 Gy, 5 fractions per week, 45 Gy in 15 fractions, 3 fractions per week, and 28.5 Gy in 5 fractions, 1 fraction per week.*

For the boost during HF-RT, the total dose and fractionation were 10 Gy in 4 fractions, 16 Gy

in 8 fractions and 10 Gy in 5 fractions for 48%, 26% and 22% of the centers, respectively. The schedule with a total dose of 12.5 Gy in 5 fractions was retained by only one center. One center did not perform any hypofractionated boost outside therapeutic trials.

The dose and fractionation in the case of breast irradiation and boost are heterogeneous. This heterogeneity is also reported in several articles (19,37,79). The most commonly used scheme is 40 Gy in 15 fractions according to the START-B trial (73). For the boost, the most commonly used scheme is the Lyon schedule delivering 10 Gy in 4 fractions (84). Four phase III trials compared mammary HF-RT to normofractionated irradiation (50 Gy in 25 fractions) in terms of local control, side effects and cosmetic results. The trial by Yarnold et al. randomized 1410 patients with stage T1-T3/N0-N1 breast cancer into three groups: 50 Gy in 25 fractions, 39 Gy in 13 fractions and 42.9 Gy in 13 fractions. In this study, 75% of the patients received a tumor bed boost of 14 Gy in 7 fractions by a direct electron beam (85). The START A trial randomized 2236 pT1-3a pN0-1 patients into three groups: normofractionated (50 Gy/25 fractions) and hypofractionated (41.6 Gy/13 fractions and 39 Gy/13 fractions) irradiation. In this trial, 60.6% of patients received a boost with an electron beam at a dose of 10 Gy in 5 fractions (86). The START B trial included 2215 patients with the same criteria as the START A trial. It compared normofractionated irradiation (50 Gy/25 fractions) to HF-RT (40 Gy/15 fractions). Only 42.6% of patients received a boost, as in the START A trial, at a dose of 10 Gy in 5 fractions by a direct electron beam (73). The Canadian trial included 1234 randomized pT1-2 N0 patients in the standard arm (50 Gy/25 fractions) or in the experimental arm (42.5 Gy/16 fractions). There was no boost in this trial (87). Consequently, it is difficult to conclude whether a hypofractionated boost should be used simultaneously or sequentially. However, from a financial point of view, in France, payment by the number of sessions and not by the treatment protocol as such cannot help to achieve the boost concomitantly.

Conclusion:

This survey showed that French practices remained heterogeneous despite the publication of national and international references, particularly concerning irradiation techniques, prescribed doses and indications of irradiation of lymph node areas. This may be due to the different technology parks in the different centers but also to the more or less precise application of these guidelines. These results imply that there is a need to standardize practices with additional clinical studies being conducted, including radiation therapy for lymphatic drainage, to support existing guidelines. These studies should establish a more standardized treatment of lymph node regions in clinical practice. Finally, quality assurance should impose a broad application of consensus recommendations.

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1	Subgroup benefiting (with a high probability) from the irradiation of the internal mammary lymph node chain	Proven disease (positive biopsy) or highly suspect [positron emission tomography (PET), positive computerized tomography (CT)]. Significant axillary lymph node involvement (≥ 4 affected lymph nodes), especially if the tumor is central or internal with aggressive criteria (young woman, grade 3, unexpressed hormone receptors, etc.).
2	Subgroup whose benefit from irradiation of the internal mammary node chain is probable.	Internal tumor with moderate axillary involvement (1–3 lymph nodes affected).
3	Subgroup whose benefit of irradiation of the internal mammary node chain is possible.	External tumor with moderate axillary involvement (1–3 lymph nodes affected). Tumor of the internal quadrants pN0.
4	Subgroup probably not benefiting from irradiation of the internal mammary node chain.	External tumor and no histologically affected lymph node.

Table 1: Internal mammary lymph node irradiation benefit prediction groups (adapted from Hennequin et al., 2016).

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Reference	Recommendations
	Massive invasion of ALND with at least seven lymph nodes
Saint Paul de Vence, 2011 (43)	In cases of insufficient ALND (less than seven lymph nodes)
	Ratio of metastatic nodes to nodes > 50% at ALND
	In cases of insufficient ALND (< 6 nodes)
Remagus, 2019-2020 (88)	To be validated by MTM
	Unspecified node involvement with < 4 nodes on ALND
NHS MCCN, 2018 (89)	Metastatic lymph node with < 4 nodes on ALND
ASCO, 2001 (90)	Not systematic; insufficient level of evidence to make a recommendation
Saint-Gallen, 2013 (91)	Not systematic; no vote on the indications for axillary irradiation after ALND
NCCN, 2020 (45)	Indication for unspecified axillary irradiation
Inca, 2008 (92)	After ALND to be discussed in MTM according to the number of lymph nodes examined, affected and extranodal extension
RECORAD, 2016 (44)	≥ 10 lymph nodes affected and/or removal of < 10 lymph nodes but half or more affected

Table 2: Recommendations concerning axillary irradiation after ALND (adapted from Rivera et al. (71)).

ALND: axillary lymph node dissection; ASCO: American Society of Clinical Oncology; INCA: National Institute of Cancer; MTM:

multidisciplinary team meeting; NHS MCCN: National Health Services Merseyside and Cheshire Cancer Network; NCCN: National Comprehensive Cancer Network

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Appendix:

Appendix A: Survey

1. Do you consider yourself as a referent in senology? Yes/No
2. How many breast cancer cases are treated per year in your institution?
3. In your institution, the senology files are presented to a technical committee of radiotherapy:
    a. Systematically
    b. Only for specific cases
    c. Never
4. Do you perform whole breast/chest wall irradiation in three-dimensional radiotherapy (3DRT)? Yes/No
5. Do you use a monoisocentric technique for 3DRT?
    a. Yes, systematically
    b. According to particular cases
    c. No, never
6. Do you perform chest wall irradiations with electron beams?
    a. a. Yes, systematically
    b. b. Yes, sometimes
    c. c. No
7. When do you use intensity modulated radiation therapy (IMRT)?
    a. Systematically
    b. Pectus excavatum
    c. Bilateral whole breast/chest wall irradiation
    d. Bilateral whole breast/chest wall and lymph node area irradiation
    e. Left whole breast/chest wall irradiation

f. Whole breast/chest wall and lymph node area irradiation

g. Left whole breast/chest wall and lymph node area irradiation

h. Never

8. When necessary, do you perform a tumor bed boost:

    a. Simultaneously

    b. Sequentially

9. What are the two most common techniques used in your department to perform a tumor bed boost:

    a. Brachytherapy

    b. External photon irradiation

    c. External electron irradiation

10. Do you perform partial breast irradiation (excluding trial)? Yes/No

11. If yes, what technique(s) do you use?

    a. Brachytherapy

    b. External radiotherapy

    c. Intraoperative irradiation

12. If isolated pNi+ cells are involved after the sentinel node procedure followed by axillary lymph node dissection, you would irradiate:

    a. The internal mammary chain

    b. The supraclavicular area

    c. The axillary area

    d. No lymph node irradiation

13. In the case of microscopic pNmi involvement after the sentinel node procedure followed by axillary lymph node dissection, you would irradiate:

    a. The internal mammary chain

b. The supraclavicular area

c. The axillary area

d. No lymph node irradiation

14. In the case of macroscopic pN+ involvement after the sentinel node procedure followed by axillary lymph node dissection with less than 5 out of 10 affected lymph nodes removed, you would irradiate:

    a. The internal mammary chain

    b. The supraclavicular area

    c. The axillary area

    d. No lymph node irradiation

15. If isolated pNi+ cells are affected after sentinel node procedures without axillary lymph node dissection, you would irradiate:

    a. The internal mammary chain

    b. The supraclavicular area

    c. The axillary area

    d. No lymph node irradiation

16. In the case of microscopic pNmi involvement after the sentinel node procedure without axillary lymph node dissection, you would irradiate:

    a. The internal mammary chain

    b. The supraclavicular area

    c. The axillary area

    d. No lymph node irradiation

17. In the case of a pT2 tumor with macroscopic axillary pN+ involvement after the sentinel node procedure without axillary lymph node dissection, you would irradiate:

a. The internal mammary chain
b. The supraclavicular area
c. The axillary area
d. No lymph node irradiation
e. Need additional information

18. If axillary irradiation is necessary, you would irradiate using:
    a. Breast high tangential beams
    b. Enlarged supraclavicular beams
    c. Specific beams
    d. Intensity modulated radiotherapy
    e. Other
19. What criteria do you consider relevant for irradiation of the axillary lymph node area:
    a. Axillary lymph node dissection with < 4 lymph nodes removed in total
    b. Axillary lymph node dissection with < 7 lymph nodes removed in total
    c. Axillary lymph node dissection with < 10 lymph nodes removed in total
    d. At least 7 lymph nodes affected
    e. At least 10 lymph nodes affected
    f. At least 50% of affected lymph nodes
    g. Other
20. Indicate in the context of infiltrating breast cancer in which situation you would practice hypofractionated irradiation (excluding therapeutic trials):
    a. Chest wall only
    b. Whole breast +/- boost
    c. Chest wall and regional node areas

d. Whole breast and regional node areas

21. Concerning the boost in the context of hypofractionated irradiation, you prescribe:

a. 10 Gy/5 fractions of 2 Gy

b. 10 Gy/4 fractions of 2.5 Gy

c. 16 Gy/8 fractions of 2 Gy

d. Other

22. Concerning the prescription in the case of hypofractionated irradiation after surgical treatment, which regimen(s) do you use?

a. 42.5 Gy/16 fractions in 22 days, 2.66 Gy per fraction

b. 41.6 Gy/13 fractions in 5 weeks, 3.2 Gy per fraction

c. 40 Gy/15 fractions in 3 weeks, 2.66 Gy per fraction

d. 39 Gy/13 fractions in 3 weeks, 3 fractions per week, 3 Gy per fraction

e. Other

A retrospective analysis of survival and prognostic factors of axillary recurrence of breast cancer.

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Abstract:

Purpose:

This was a retrospective study of risk factors for axillary recurrence of invasive breast cancer treated with surgery, selective sentinel lymphadenectomy and radiotherapy.

Methods:

We performed a retrospective analysis including 1,645 patients with localized breast carcinoma who underwent surgery and were irradiated between January 2006 and December 2017. To be included, patients had to have a histological confirmation of breast cancer diagnosis, surgical treatment without axillary lymph node dissection (ALND), and whole breast irradiation without axillary irradiation by a specific field.

Results:

The rate of axillary lymph node recurrence is 0.38%. Hormonotherapy (99.7% [range 99.3%; 100.0%] versus 72.3% [range 40.9%; 100.0%], $p < 0.01$) and oestrogen receptor (ER) positivity (99.7% [range 99.3%; 100.0%] versus 72.1% [range 40.9%; 100.0%], $p < 0.012$) had a positive impact on regional node-free survival. Ki67 was significantly higher in cases of axillary lymph node recurrence (median: 12% [7.5–22] vs. 55% [37.5–72.4] $p < 0.01$). The presence of a local relapse negatively influenced regional node-free survival (99.5% [range 99.0%; 100.0%] versus 40.0% [range 9.35%; 100.0%], $p < 0.001$).

Conclusion:

The irradiation technique used was not identified as a risk factor for axillary lymph node recurrence; however, there seems to be a trend according to the height of the tangential beams. Future studies may compare the unintentional dose delivered in axillary areas I to III, the irradiation technique and the axillary recurrence rate.

Keywords:

Breast carcinoma, radiotherapy, three-dimensional radiotherapy, intensity-modulated radiotherapy, axillary lymph node

Abbreviations:

3DRT: Three-Dimensional Radiation Therapy

ACOSOG: American College of Surgeons Oncology Group

ALND: Axillary Lymph Node Dissection

CTCAE: Common Terminology Criteria for Adverse Events

DFS: Distant free survival

ESTRO: European Society for Radiation Therapy and Oncology

ER: Oestrogen Receptor

HT: High Tangential

IMN: Internal mammary lymph nodes

IMRT: Intensity Modulated Radiation Therapy

OS: Overall survival

PET-CT: Positron Emission Tomography-Computed Tomography

PRV: Planning Risk Volume

RFS: Recurrence free survival

RR: Relative Risk

SEER: Surveillance, Epidemiology and End Results

SNLB: Sentinel Lymph Node Biopsy

ST: Standard Tangential

WBI: Whole Breast Irradiation

Introduction:

Breast carcinoma is the most identified carcinoma in the world. In 2012, 1.7 million women were diagnosed, and 522,000 died from this tumour (1). According to data from the SEER program, 93% of breast cancer cases are diagnosed at an early stage (62% localized to the breast and 31% localized to the breast and regional lymph nodes) (2).

Radiotherapy is part of the therapeutic arsenal in localized breast cancer. Its impact has been demonstrated in several meta-analyses (3,4), in adjuvant schedules after conservative treatment (4) and nonconservative treatment in the case of pT3-T4 tumours and regardless of the lymph node status (3). Therapeutic de-escalation is ongoing in localized breast cancer for surgical procedures, from mastectomy (5) to the introduction of conservative treatment (6–11), SLNB (12,13) and axillary surgery indications (14–16). Radiotherapy de-escalation is also ongoing with the development of hypofractionation (17–20), partial breast irradiation (21–23), and IMRT development, allowing better conformation of target volumes and organs at risk avoidance (24). The results of the EORTC 22922/10925 trial led to a scarcity of internal mammary lymph node (IMN) irradiation (25). Moreover, since the results of the ACOSOG Z0011 trial in 2017 and AMAROS in 2015, the place of ALND and axillary irradiation has been questioned for patients with stage T1-T2 breast cancer (14,15). The prospective AMAROS trial, which included 1425 women with cancer classified as T1-2 with axillary invasion diagnosed after the SLND procedure, showed that it was equivalent to substituting complementary ALND with axillary irradiation. Indeed, the authors found no significant difference between the two groups in terms of axillary RFS, DFS or OS (15). The prospective ACOSOG Z0011 trial included 891 patients with T1 or T2 tumours with one or two positive nodes after the SLND procedure. All patients underwent partial mastectomy followed by WBI. With a median follow-up of 6.3 years, there was no difference in OS and LRS between patients with and without ALND. It should be noted that in this trial, the

patients received 3DRT with tangential beams (26). The hypothesis is that involuntary axillary irradiation induced by WBI explains the lack of a significant difference in locoregional control. The review by Van Wely et al. supported this hypothesis. They conducted a literature review of 45 articles and 23,357 patients. They found an axillary recurrence rate of 0.4% for patients with localized breast cancer after negative SLNB and whole breast irradiation and 1.2% for patients without radiotherapy, resulting in a decreased relative risk (RR) of axillary recurrence (RR = 0.32 [0.23–0.46]; $p < 0.001$). However, no comparison of irradiation techniques or doses could be made due to the lack of adequate information in the studies. The hypothesis advanced by the authors was that during irradiation of the whole breast, part of the axillary area was irradiated at doses allowing the control of tumour cells potentially present in the axillary area (27). Therefore, the purpose of this study was to investigate prognostic factors that comprehensively predict breast cancer axillary recurrence.

Methods:

Patients:

This monocentric retrospective analysis involved 1645 patients (1672 irradiated breasts) with localized breast carcinoma treated from 01/01/2007 to 31/12/2017 in one radiation oncology department of a comprehensive cancer centre in France who met the selection criteria. The inclusion criteria were i) histologic diagnosis of breast neoplasm, ii) lumpectomy or mastectomy, and iii) whole breast irradiation with or without irradiation of the internal mammary and/or supraclavicular areas. The exclusion criteria were i) ALND, ii) irradiation by electron beam, and iii) axillary irradiation by a specific field.

Treatment was delivered by 3DRT or IMRT using a normofractionated or moderately hypofractionated regimen. In the case of 3DRT, radiation beams were defined as standard tangential (ST) if beam limits were located at least 2 cm below the inferior border of the humeral

head. Radiation beams less than 2 cm from the inferior border of the humeral head were defined as high tangential (HT). This study follows the mandatory French laws required by the CNIL (*Commission Nationale de l'Informatique et des Libertés*) and was declared to this French institution by the MR004 form and was recorded in the HDH (Heath Data Hub).

Statistical analysis:

Categorical data were analysed as frequency counts and percentages, whereas measured data were evaluated using medians and ranges. Fisher's exact test was used for the comparison of categorical variables. Student's t test was used for comparison of two means. Tests were significant if $p \leq 0.05$. Local-free survival was defined as the time between diagnosis and the date of recurrence in homolateral breast or chest wall diagnosed histologically. Regional node-free survival was defined as the time between diagnosis and the date of recurrence in the internal mammary chain, supraclavicular or axillary lymph node diagnosed histologically. Metastasis-free survival was defined as the time between diagnosis and the date of distant recurrence diagnosed on CT or positron emission tomography-computed tomography (PET-CT). The statistical analysis was carried out with R v3.6.0 software.

Results:

Treatment was delivered on Saturne® (General Electric, Boston, USA), Primus® (Siemens, Munich, Germany), Clinac® (Varian, Palo Alto, USA), Novalis® (Varian, Palo Alto, USA), and Tomotherapy® (Accuray, Sunnyvale, USA).

The median age of the patients was 61 years (53.0–70.0). Eighteen patients had lymph node involvement at the SLNB. The median follow-up was 51.0 months (1.0–174.0). The median prescribed dose at the International Commission on Radiation Units and Measurements reference point was 66.0 Gy (50.0–66.0). The median prescribed fractionation was 33 fractions (25–33). Ninety-eight percent of the patients were treated with three-dimensional radiotherapy (3DRT), and among them, 81% (1332 patients) were treated with ST. The patients and

treatment characteristics are summarized in Tables 1 and 2.

The five-year local-free survival rate was 99.4% (95% CI: 98.8–99.9%), with a median interval from radiotherapy to recurrence of 40 months (range 22.0–118.0). The five-year regional node-free survival rate was 99.6% (95% CI: 99.2–100.0%), with a median interval from radiotherapy to recurrence of 38.5 months (range 11.0–52.0) (Figure 1). The rate of axillary lymph node recurrence was 0.38% (6 patients). The five-year metastasis-free survival rate was 97.7% (95% CI: 96.7–98.7%), with a median interval from radiotherapy to recurrence of 36 months (range 2.0–52.0). Among the six patients with lymph node recurrence, one patient had simultaneous locoregional recurrence, four had simultaneous regional and distant recurrence, and one patient had simultaneous local and distant recurrence.

In univariate analysis, several factors influence node control. Positivity for oestrogen receptor (ER) positively impacted regional node-free survival by 99.7% (95% CI 99.3%–100.0) compared to 72.1% (95% CI: 40.9–100.0) ($p < 0.012$) for patients with ER-negative tumours. Triple-negative histology impacted regional node-free survival 99.7% (95% CI: 99.4%–100.0%) compared to 71.8% (40.7%–100.0%) for patients with no triple-negative tumour ($p < 0.01$). The presence of a local relapse negatively influenced regional node-free survival by 40.0% [95% CI: 9.35%– 100.0%] compared to 99.5% [95%: CI 99.0%– 100.0%] for patients with locally controlled tumours ($p < 0.001$). The initial Ki67 immunohistochemical staining was significantly higher in cases of axillary lymph node recurrence than in cases where it was absent (median: 55% (37.5–72.4) vs. 12% (7.5–22); $p < 0.01$).

Neither fractionation nor the irradiation technique statistically influenced axillary recurrence rates ($p = 0.53$ and $p = 0.95$); however, for patients treated with 3DRT, there was a trend towards axillary lymph node recurrence depending on the distance between the field and the humeral head ($p = 0.079$), and 6 recurrences were in the ST group. Due to the small number of events, it was not possible to perform a multivariate analysis.

Discussion:

First, in this current study, the local control and node control were high. IMRT was used less than 3DRT (2% vs. 98%). This is consistent with the literature, as 3DRT remains the standard in adjuvant breast cancer treatment (28). According to expert agreement, IMRT would be indicated in cases of complex anatomy, bilateral breast irradiation, breast prosthesis and situations where no compromise should be made in the predicted target volume (29). A series similar to ours did not specify the modalities of irradiation (30–33). Only Sanli et al. specified that 100% of patients received adjuvant irradiation by 3DRT (30).

The use of HT in 3DRT is also low (19% vs. 81%). The definition is equivocal to an irradiation beam at a variable distance from the humeral head. High tangential fields have been proposed to ensure coverage of the level I and II lymph nodes (34,35). Some studies have defined HT by an upper limit of the field plumbing the humeral head (36,37), while others have defined HT when the upper limit of the field was less than 2 cm from the humeral head (14). We therefore defined HT when the distance between the humeral head and the radiation beam was less than 2 cm. Most of the series studying the same topic did not specify the radiation fields (27,31,33,38).

Treatment regimens were predominantly normofractionated (76% vs. 24%) and had no influence on axillary recurrence. The low use of hypofractionated regimens can be explained by the treatment period in our study, 2007 to 2017. Pivotal trials on hypofractionation, such as START A and START B, were published only in 2008 (17,18). However, in our study, 1613 patients (98%) were irradiated after the publication of these trials. Another hypothesis that may explain the low use of hypofractionation is that these trials did not propose hypofractionation for regional node irradiation. Patients included in the START A and B trials had hypofractionated regional node irradiation in 14% and 7% of cases, respectively (17,18). In our study, 9.9% of patients with associated regional node irradiation (7/71) received a

hypofractionated regimen. For patients who had breast or wall irradiation without regional node irradiation, 24.5% (379/1542) received irradiation according to a hypofractionated scheme. Furthermore, in the START A and B trials, only a small proportion of patients had a mastectomy in the hypofractionated arm, 15% and 8%, respectively (17,18). This may be an additional argument to explain the relatively moderate uptake in practice in our study because, among the node-negative patients, 103 (6%) underwent mastectomy. In the AMAROS trial and Belkacemi study, patients were included from 2001 to 2010 and 2012 to 2013, respectively, with all patients irradiated using a normofractionated regimen (15,37). In the ACOSOG Z0011 and Sanli et al. studies, the radiation schedule was not specified (14,30). In 2021, a French national survey showed that 96% of the radiotherapy centres surveyed chose a hypofractionated scheme for breast irradiation with or without boost (39). Ratosa et al., in their international survey, showed that 57.4% of the radiation oncologists surveyed used a hypofractionated regimen for whole breast irradiation. However, this percentage was lower for regional node irradiation and postmastectomy radiotherapy, 28.7% and 21.1%, respectively. The important point to note from this study is the heterogeneity in the choice of fractionation; for example, for whole breast irradiation, the overall preference by the responding radiation oncologists was 54.7% and ranged from 0% (9 countries) to 100% (13 countries) (40).

By this study, we tried to highlight the risk factors that could influence axillary lymph node recurrence. The rate of axillary recurrence in our study is comparable to that reported in the meta-analysis of Van Wely et al. for patients with adjuvant breast irradiation (27), 0.38% versus 0.4%, respectively. When SLNB was negative, axillary recurrences usually occurred between 24 and 48 months after the initial treatment and were associated with a poor prognosis for the patient (41–43). In this series, the median time to regional recurrence was 38.5 months. This is consistent with the literature (41–43). Several risk factors found in our study are consistent with those described in the literature: tumour size (44,45), high histological grade (31,42,44,46–48),

ER-negative status (47), triple-negative status (49), Ki67 expression (50), and number of lymph nodes removed (51).

In our study, we did not identify young age as a prognostic factor. The question of whether age is an independent prognosticator in breast cancer patients has been debated. Several studies have reported that breast cancer in young women was associated with higher mortality and recurrence rates than in older women (52–55). However, many others have shown that young age was not an independent predictor of poor survival (56–58).

We did not find any differences according to the irradiation technique, either with IMRT or 3DRT with ST or HT. However, there seemed to be a trend according to the height of the tangent beams. It is possible that no significant difference could be demonstrated due to the low number of axillary lymph node recurrence events (six cases). Notably, the 2020 NCCN guidelines recommended that ST and HT should be considered for patients who meet the criteria of the ACOSOG Z0011 trial (59). To our knowledge, no other publication has compared the lymph node recurrence rate according to irradiation techniques, particularly with IMRT. Moreover, several publications have shown that the dose delivered to the axillary area involuntarily by breast irradiation varies according to the irradiation techniques (60,61). However, to our knowledge, no comparison has been made between the dosimetric variation in the axillary area and the rate of axillary lymph node recurrence. It should also be noted that the irradiation of a larger volume with HT should be balanced against the ALARA (as low as reasonably achievable) principle, especially in patients with an expected long survival, implicating a higher risk of radiation-induced cancer (62–64) and complication incidence (62). The strengths of our study are the large number of patients included and the follow-up time compared with other studies (27,30–33); moreover, we specified the modalities and fields of irradiation. Some limitations can be disputed. It was a retrospective, single-centre study. The low number of events corresponding to axillary recurrence could be seen as a limitation but is

comparable with the Van Wely meta-analysis and the NSABP B32 trial (13,38). Median follow-up may seem low, but follow-up in radiotherapy after localized breast cancer with a favourable evolution is only 5 years in our institution, and follow-up is carried out by gynaecologists afterwards. Furthermore, in the NSABP B-04 study, the majority of axillary relapses in patients treated without ALND occurred within the first 2 years (6). In the AMAROS and ACOSOG Z0011 studies, the majority of axillary relapses in patients treated without ALND occurred within the first 5 years (14,15).

Conclusion:

In this series, the rate of axillary recurrence was low and consistent with the reported rates in the literature. The risk factors identified are found in the literature, particularly oestrogen receptor positivity and hormonotherapy. The irradiation regimen and technique used were not identified as risk factors for axillary lymph node recurrence, although there was a trend in favour of the highest tangential beams. For selected patients, such as those with positive SLNB who do not undergo completion ALND, WBI with HT seems to be an acceptable option.

Annexes:

Table 3: Descriptive analysis of quantitative variables.

	mean (standard deviation)	median [Q25–75]	min	max	n
Age (years)	61.2 (11.6)	61.0 [53.0; 70.0]	26.0	93.0	1671
Follow-up (month)	50.0 (25.7)	51.0[32.0; 63.0]	1.0	174	1671
D_{mean} heart (Gy)	1.64 (2.83)	1.00 [0.448; 2.22]	0	67.0	1452
Total dose (Gy)	61.2 (7.83)	66.0 [50.0; 66.0]	6.00	72.0	1665
Humeral head distance (cm)	3.14 (1.33)	3.10 [2.20; 4.00]	0	7.20	1538
Ki 67 (%)	18.4 (17.2)	12.0 [8.00; 22.0]	0	95.0	1443
Number of sentinel nodes removed	2.69 (1.68)	2.00 [1.00; 4.00]	0	11.0	1620
Tumoural size (mm)	14.0 (7.50)	13.0 [9.00; 17.0]	0	65.0	1655

Cm : centimetre ; Gy : Gray ; mm : millimetre.

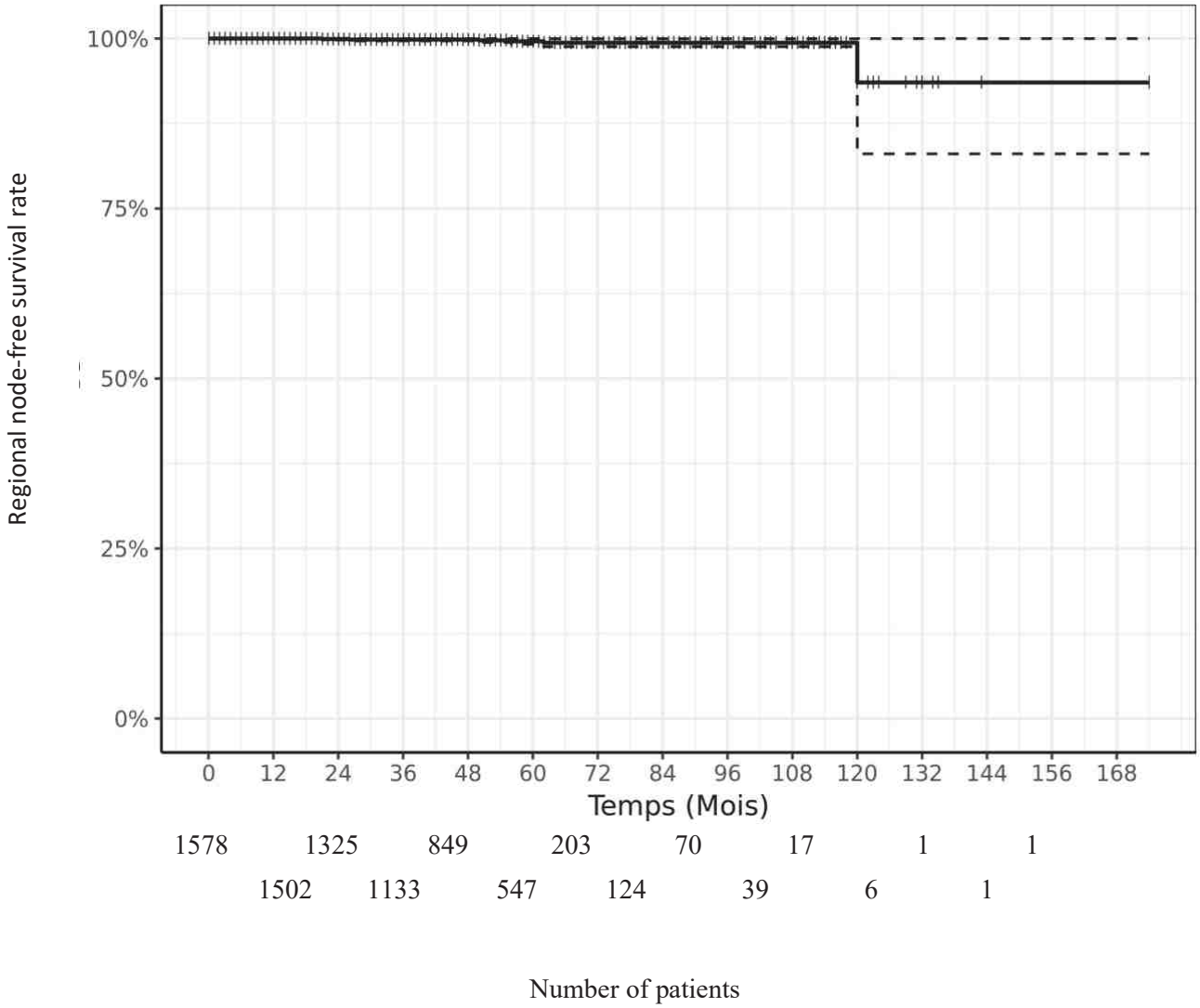
Table 4: Descriptive analysis of qualitative variables.

		n (%)
Target volumes	Whole breast irradiation	1523 (91.2%)
	Chest wall irradiation	78 (4.7%)
	Breast + IMN	0 (0.0%)
	Chest wall + IMN	1 (0.05%)
	Breast + Ln3-4	29 (1.7%)
	Chest wall + Ln3-4	6 (0.35%)
	Breast + IMN + Ln3-4	17 (1.0%)
	Chest wall + IMN + Ln3-4	17 (1.0%)
Machine	SATURNE	732 (47%)
	PRIMUS	639 (41%)
	CLINAC	141 (9.1%)
	TOMOTHERAPY	26 (1.7%)
	NOVALIS	13 (0.84%)
Adjuvant chemotherapy	No	1196 (72%)
	Yes	475 (28%)
Neoadjuvant chemotherapy	No	1636 (98%)
	Yes	35 (2.1%)
Breast-conservative surgery	No	104 (6.2%)
	Yes	1568 (94%)
Sentinel lymph node biopsy	No	16 (0.96%)
	Yes	1656 (99%)
Resection margin revision	No	1476 (91%)
	Yes	151 (9.3%)
Histological grade (SBR)	1	694 (42%)
	2	696 (42%)
	3	259 (16%)
HER 2 status	No	1538 (93%)
	Yes	119 (7.1%)
Hormonotherapy	No	176 (11%)
	Yes	1492 (89%)

Laterality	Right	844 (50%)
	Left	828 (50%)
Oestrogen receptor positivity	No	156 (9.4%)
	Yes	1502 (91%)
Local recurrence	No	1569 (99%)
	Yes	9 (0.57%)
Irradiation modality	3DRT	1644 (98%)
	IMRT	27 (2%)

3DRT: three-dimensional radiotherapy; Her2: Human epidermal growth factor receptor 2; IMN: internal mammary node; IMRT: intensity modulated radiotherapy; Ln1: lymph node level 1; Ln2: lymph node level 2; Ln3: lymph node 3; SBR: Scarff Bloom Richardson.

Figure 2: Kaplan–Meier survival curve of node progression-free survival



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Impact of incidental dose on axillary tumour control and toxicity in localized breast cancer: retrospective analysis

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Abstract:

Purpose: Dosimetric analysis of incidental axillary dose delivered to axillary lymph node levels I-III by different techniques of whole breast irradiation and analysis of prognostic factors of axillary recurrence of breast cancer.

Methods: We performed a retrospective analysis including 171 patients with localized breast carcinoma irradiated at Centre Paul Strauss. To be included, patients had to have a histological confirmation of breast cancer diagnosis, surgical treatment without axillary lymph node dissection (ALND), whole breast irradiation without axillary irradiation by a specific field, and a treatment plan available.

Results: Three patients had lymph node recurrence. There was no significant correlation between the maximal or mean dose delivered at the three axillary levels and the risk of axillary lymph node recurrence. There was no significant correlation between the irradiation technique and the risk of axillary lymph node recurrence. Two patients, both in the HT group, had lymphoedema. There was significantly more lymphoedema in the HT group than in the ST and IMRT groups ($p < 0.048$). The mean dose in level II was significantly higher in the group of patients with lymphoedema (3.45 Gy [1.08; 9.62] vs. 23.4 Gy [23.1; 23.6] ($p < 0.02$).

Conclusion: The irradiation technique has an influence on the incidental dose delivered to the axillary area but has no influence on the risk of axillary recurrence. The risk of lymphoedema was significantly related to the use of HT and the mean dose delivered at level II.

Keywords: Dosimetric analysis; Breast carcinoma, radiotherapy; three-dimensional radiotherapy; intensity-modulated radiotherapy; axillary lymph node

Introduction:

Management of breast cancer has evolved, particularly with regard to reducing treatment-related side effects without compromising treatment outcomes (1). On the surgical side, the sentinel lymph node biopsy (SLNB) replaced axillary lymph node dissection (ALND) in the small tumours and in the absence of clinical lymph node involvement. This management has reduced the incidence of lymphoedema (2–4). Among women with T1 or T2 invasive primary breast cancer, no palpable axillary adenopathy, and 1 or 2 sentinel metastatic lymph nodes, the ACOSOG Z0011 trial showed that omitting axillary treatment did not increase the risk of recurrence (4). The AMAROS trial showed that the rate of lymphoedema at 5 years was lower after SLNB and radiotherapy than after ALND, 14% versus 28%, respectively (2). To improve radiotherapy, intensity-modulated radiotherapy (IMRT) was proposed to replace three-dimensional conformal radiotherapy (3D-RT) to achieve better conformity of the target volumes and reduce unnecessary healthy tissue irradiation (5–7), with the perspective of reducing side effects that negatively impact the quality of life of patients (8). Several phase II or retrospective studies have shown a decrease in acute side effects as well as chronic breast oedema with IMRT compared to standard 3DRT (9–11). Lymphoedema is caused principally by axillary lymph node dissection (ALND) (12) and adjuvant radiotherapy, particularly when irradiation is delivered at levels I and II of the axillary area (13). There is a positive association of lymphoedema with increasing total dose of radiation and overlapping radiation fields (14). In the case of whole breast or parietal irradiation, several studies have shown that a nonzero and heterogeneous dose, depending on the technique, was delivered unintentionally to the axillary area (15,16). A study showed a trend between the irradiation technique and the risk of axillary recurrence (Schmitt et al. “A retrospective analysis of survival and prognostic factor of axillary recurrence of breast cancer.” preprint). However, to our knowledge, no study has investigated the relationship between this incident dose according to different irradiation

techniques, the risk of axillary recurrence and the risk of lymphoedema.

Methods:

Ethical approval:

This study follows the mandatory French laws required by the CNIL (*Commission Nationale de l'informatique et des libertés*) and was declared to this French institution by the MR004 form and was recorded in the HDH (Health Data Hub).

Patients:

This monocentric retrospective analysis involved patients with localized breast carcinoma treated from 01/01/2007 to 31/12/2017 in one radiation oncology department in France who met the following selection criteria: i) histologic diagnosis of breast neoplasm, ii) lumpectomy or mastectomy, iii) whole breast irradiation with or without irradiation of the internal mammary and/or supraclavicular areas, and iv) dosimetry available for analysis. The exclusion criteria were i) ALND, ii) irradiation by electron beam, and iii) axillary irradiation by a specific field. Patients lay in a supine treatment position. Treatment was delivered by 3DRT or IMRT using a normofractionated or moderately hypofractionated regimen. In the case of 3DRT, radiation beams were defined as standard tangential (ST) if beam limits were located at least 2 cm below the inferior border of the humeral head. Radiation beams less than 2 cm from the inferior border of the humeral head were defined as high tangential (HT).

One hundred sixty-three patients (95%) underwent lumpectomy, and eight patients underwent mastectomy. The median prescribed dose at the International Commission on Radiation Units and Measurements reference point in remnant breast, parietal wall, boost and total volume were 50.0 Gy (20.0–50.4), 50.0 Gy (46.0–50.0), 16.0 Gy (9.8–16) and 66.0 Gy (20.0–66.0), respectively. The median prescribed fractionations were 25 fractions (5–28), 25 fractions (23–25), 8 fractions (4–8) and 33 fractions (5–33). One hundred forty-seven patients were treated with three-dimensional radiotherapy; among them, 117 patients were treated with

ST, and 30 were treated with HT. One hundred sixty-three patients had breast or parietal irradiation without lymph node irradiation. The median breast and parietal volumes were 686.3 mL (119.0–2439.0) and 127.3.0 mL (95.0–219.6), respectively.

Contouring and planning:

Whole breast and parietal irradiation consisted of 3DRT or IMRT. 3DRT consisted of two opposing tangential beams. Regarding regional node irradiation, IMNs at levels III and IV were treated with an anterior field. IMNs were treated with a combination of photons and electrons (mixed beams). IMRT consisted of rotational or nonrotational IMRT or helical tomotherapy. The clinical target volumes (CTVs) of axillary levels I-III were delineated on the basis of the European Society for Radiotherapy and Oncology (ESTRO) contouring guidelines of early-stage breast cancer (17) on Artiview software (Aquilab, Loos, France). The PTV corresponds to an isometric margin of 0.5 cm from the CTV. The same software was used to calculate the dose delivered to the three axillary levels, Ln1, Ln2 and Ln3. To enable dosimetric analysis, we performed an equivalent dose in 2 Gy per fraction ($EqD2 = D \times ([d + \frac{\alpha}{\beta}]/[2 + \left(\frac{\alpha}{\beta}\right)])$ for patients treated with hypofractionated irradiation. We choose an α/β = 4 according to the publication by Hennequin et al. (18).

Statistical analysis:

Categorical data were analysed as frequency counts and percentages, whereas measured data were evaluated using medians and ranges. Fisher's exact test was used for the comparison of categorical variables. A Mann–Whitney test was used for the comparison of quantitative variables. The statistical analysis was carried out with R v3.6.0 software.

Results:

One hundred and seventy-one patients were included. The patients and treatment characteristics are summarized in Tables 1 and 2.

The median age was 61.2 years (SD 11.6). The median follow-up was 38.5 months (2.0–

123.0). The median body mass index (BMI) was 25.7 (16.0–49.4). There was significantly more regional node irradiation (IMN and supraclavicular) with IMRT ($p = 0.021$).

Dosimetric analysis:

The volumes of Ln1, Ln2 and Ln3 and the mean and maximal doses delivered at axillary levels in Ln1, Ln2 and Ln3 are summarized in Table 1. The average volumes of Ln1, Ln2 and Ln3 were 148 mL (SD 44.2), 33.8 mL (SD 12.4) and 36.5 mL (SD 70.7), respectively. For Ln1, the median maximal and mean doses were 52.8 Gy (min-max: 15.3–69.9) and 24.5 Gy (0.6–57.8), respectively. For Ln2, the median maximal and mean doses were 30.3 Gy (0.2–61.7) and 8.05 Gy (0.1–50.5), respectively. For Ln3, the median maximal and mean doses were 12.4 Gy (0.1–53.7) and 4.45 Gy (0.0–50.7), respectively.

There was a significant correlation between BMI and the volumes of Ln1, Ln2 and Ln3 ($p < 0.001$ for all) (Figure 2). There was a significant correlation between BMI and the mean dose in Ln1, Ln2 and Ln3 ($p < 0.001$; $p < 0.001$ and $p = 0.04$, respectively). There was a significant correlation between BMI and the maximal dose in Ln2 and Ln3 ($p < 0.001$ for both). There was a significant correlation between BMI and irradiated breast volume ($p < 0.001$). There was a significant correlation between the targeted breast or parietal volume and the mean dose of Ln1, volume of Ln1 and Ln2 and maximal dose of Ln2 and Ln3 (Table 3). There was a significant difference according to the irradiation technique (i.e., 3DRT vs. IMRT) concerning the mean dose of Ln1, Ln2 and Ln3 and the maximal dose of Ln3 ($p < 0.001$ and $p = 0.016$ and $p = 0.015$ and $p < 0.001$) (Figure 1). HT significantly influenced the mean doses of Ln1, Ln2 and Ln3 and the maximal doses of Ln3 (Table 4), with a significant difference according to regional node irradiation (IMN and supraclavicular area) and the mean doses of Ln1, Ln2 and Ln3 ($p < 0.01$ and $p < 0.001$ and $p < 0.001$, respectively).

Three patients developed lymph node recurrence. There was no significant correlation between the maximal or mean dose delivered at the three axillary levels and the risk of axillary

lymph node recurrence. There was no significant correlation between the irradiation technique and the risk of axillary lymph node recurrence.

Two patients, both in the HT group, had grade 1 lymphoedema. There was significantly more lymphoedema in the HT group than in the ST and IMRT groups ($p < 0.048$). The dose in level II was significantly higher in the group of patients with lymphoedema than the mean dose in the group of patients without lymphoedema, 20.9 Gy and 22.8 Gy versus 3.63 Gy [1.20; 9.98], respectively, ($p < 0.045$).

Discussion:

In the current study, we showed that the delivered dose to axillary levels I, II and III varies significantly according to patient BMI and irradiation techniques. The values are consistent with several other previously published studies (15,16,19). HT fields deliver a significantly higher mean dose at levels I, II and III than ST fields and IMRT. Reznik et al. were the first to compare the dosimetric impact of ST and HT fields. They showed better coverage of the axillary area by the HT field technique. The average doses delivered in levels I, II, and III with ST were 66% (SD = 13%), 44% (SD = 18%) and 31% (SD = 20%), respectively, compared to 86% (SD = 9%), 71% (SD = 19%) and 73% (SD = 17%), respectively, of the prescribed dose with HT (20).

In 2014, Belkacemi et al. retrospectively studied the dose distribution in the SLNB area visualized in 25 patients by clips. Dosimetry was calculated in 3DRT with ST and HT fields. The mean doses delivered in axillary levels I, II, and III and in the SLNB area were significantly lower with ST fields than with HT fields and were 22 Gy vs. 38 Gy ($p = 0.004$), 3 Gy vs. 11 Gy ($p = 0.019$), 2 Gy vs. 5 Gy ($p = 0.003$), and 30 Gy vs. 45 Gy ($p = 0.02$), respectively (21). In 2016, Lee et al. described a significantly lower dose delivered in the axillary area with IMRT compared to field-in-field 3D radiotherapy (FIF-3DRT) ($p = 0.001$ for all three levels) (22). The axillary delivered dose appears to be lower, and this difference could be explained by the

degree of optimization in IMRT, the definition of HT, axillary volume and the irradiation supraclavicular area. The definition of HT radiation fields varied among the studies. For two studies, they were defined by an upper limit of the field reaching the humeral head (20,21), and for another, they were defined as when the upper limit of the field was less than 2 cm from the humeral head (4). Only two studies defined the delineated axillary volume (21,23) based on the Radiation Therapy Oncology Group (RTOG) recommendations (24). In the current study, volume was delineated according to the ESTRO contouring guidelines (17). Finally, in the case of supraclavicular irradiation, we showed that the dose at levels I, II and III was higher than that in the absence of supraclavicular lymph node irradiation (Table 6). It is likely that a significant part of the dose delivered to level IV contributes to the dose delivered to the other volumes and, in particular, to level III because of the proximity of these volumes.

Borm et al. evaluated the dose delivered in levels I, II and III according to the irradiation protocols of the AMAROS, MA-20 and ACOSOG Z0011 trials. They delineated the clinical target volumes according to ESTRO guidelines on three patients classified according to their own shape (slender, standard and obese). Margins for planning target volume (PTV) were not specified in the study. In the AMAROS study, the dose to the axilla was given at full patient thickness at Ln1 and Ln2 (lateral to the coracoid process) and at 3 cm depth at Ln3 (2).

The authors showed that for HT, a similar dose distribution compared to the AMAROS treatment plan was found at axillary levels I and II. This supported earlier assumptions that irradiation may have been involved in the good results after SLND alone in the ACOSOG Z0011 trial. However, in our study, regardless of the irradiation technique and radiation scheme, the average dose delivered involuntarily at the axillary level was much lower than in the AMAROS and Z0011 trials presented in the study by Borm et al. (19) (Table 5). We are aware that it is difficult to know the exact dose received by patients in the Z0011 trial (4), but it is possible that the practical application of the results of this trial must be carried out with caution

in view of the difference in dose delivered to the axillary area when comparing the results of Borm et al. with our own (19).

We found that the risk of lymphoedema was significantly related to the use of HT and the mean dose delivered at level II. It has been described in the literature that there is an increased risk of lymphoedema in the case of level II irradiation because it contains a higher concentration of lymph nodes (13). The rate of lymphoedema in our study was low compared to the ACOSOG Z0011, ALMANAC and NSABP B32 trials (4,12,25). In the ACOSOG Z0011 trial, the one-year rate of lymphoedema in the SLND alone group was 2% (4). In the ALMANAC trial, the 18-month rate of lymphoedema in the SLND alone group was 7% (25). In the NSABP B32 trial, the 36-month rate of lymphoedema in the SLND alone group was 7.5% (12). It could then be useful to delineate Ln2 to reduce the delivered dose, particularly in the context of patients with a higher risk of lymphoedema, such as those who have had ALND.

Some limitations can be disputed in this study. This was a retrospective, single-centre study with a small number of events. However, compared to previously published dosimetric studies, our study included more patients. The low number of events is inherent to localized pathology.

Conclusion:

The irradiation technique has an influence on the nonvoluntary dose delivered to the axillary area but has no influence on the risk of axillary recurrence. The average dose delivered involuntarily at the axillary level was much lower than that in the Z0011 trial. This difference may require careful application of the findings from trial Z0011. The risk of lymphoedema was significantly related to the use of HT and the mean dose delivered at level II. Consideration of Ln2 as an organ at risk could be a solution for patients most at risk of lymphoedema.

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Annexes:

Table 1: Patient characteristics and dosimetric analysis of axillary levels I, II and III.

	mean (sd)	median [Q25–75]	min	max	n
Age at diagnosis (years)	61.2 (11.6)	62.0 [52.0; 70.0]	33.0	85.0	171
Distance between the upper beam boundary and humeral head (cm)	3.12 (1.21)	3.00 [2.30; 4.03]	0.500	5.70	148
Average heart dose (Gy)	1.51 (1.87)	0.720 [0.440; 1.85]	0.120	10.2	158
Total dose (Gy)	60.9 (8.30)	66.0 [50.0; 66.0]	20.0	66.0	171
Follow-up time (month)	40.7 (20.3)	38.0 [29.0; 48.0]	2.00	123	171
Fractionation	28.8 (6.53)	33.0 [19.0; 33.0]	5.00	33.0	171
Body mass index	26.9 (5.56)	25.7 [22.4; 31.2]	16.0	49.4	170
Ki 67 (%)	19.5 (17.9)	15.0 [8.00; 21.5]	2.00	80.0	166
Number of sentinel lymph nodes removed	2.40 (1.60)	2.00 [1.00; 3.00]	0	9.00	169
Size (mm)	14.6 (7.71)	13.0 [9.50; 19.0]	1.00	45.0	163
Target breast volume	778.4 (448)	686.3 [453.6; 1040.4]	119.0	2439.0	163
Target parietal volume	135.2 (37.6)	127.3 [120.3; 139.8]	95.0	219.6	8
Ln1 vol	148 (44.2)	142 [111; 176]	67.7	281	171
Ln1 Dmax	52.8 (14.1)	53.4 [47.9; 62.8]	15.3	69.9	171

Ln1 Dmean	24.5 (12.1)	24.7 [14.2; 33.5]	0.607	57.8	171
Ln2 vol	33.8 (12.4)	31.3 [26.1; 38.0]	14.7	85.6	171
Ln2 Dmax	30.3 (18.4)	36.2 [15.0; 46.3]	0.200	61.7	171
Ln2 Dmean	8.05 (10.6)	3.70 [1.25; 10.3]	0.100	50.5	171
Ln3 vol	36.5 (70.7)	29.1 [24.8; 35.8]	13.4	946	171
Ln3 Dmax	12.4 (16.4)	3.40 [1.30; 18.5]	0.100	53.7	171
Ln3 Dmean	4.45 (11.5)	0.800 [0.405; 1.85]	0	50.7	171

Dmax: maximal dose; Dmean: mean dose; Gy: Gray; mm: millimetre; Ln1: axillary level 1; Ln2: axillary level 2; Ln3: axillary level 3; sd: standard deviation; vol: volume of axillary level.

Table 2: Qualitative variables.

		n (%)
Lymph node recurrence	No	165 (98%)
	Yes	3 (1.8%)
Adjuvant chemotherapy	No	136 (80%)
	Yes	35 (20%)
Neoadjuvant chemotherapy	No	162 (95%)
	Yes	9 (5.3%)
Conservative surgery	No	8 (4.7%)
	Yes	163 (95%)
Sentinel lymph node	No	2 (1.2%)
	Yes	169 (99%)
Scarff Bloom Richardson grade	1	64 (39%)
	2	70 (42%)
	3	31 (19%)
HER	0	159 (94%)
	1	10 (5.9%)
Histology	Invasive ductal carcinoma	155 (88%)
	Invasive lobular carcinoma	14 (8.2%)
	Medullary carcinoma	1 (0.59%)
Triple negative	No	157 (92%)
	Yes	14 (8.2%)
	Yes	150 (88%)
Laterality	Right	100 (58%)
	Left	71 (42%)
Lymphoedema	No	164 (99%)
	Yes	2 (1.2%)
Normofractionation	No	44 (26%)
	Yes	127 (74%)
Oestrogen receptor positivity	Yes	153 (89%)
	No	17 (9.9%)
	ND	1 (0.58%)
Regional node irradiation	Yes	8 (4.7%)
	No	163 (95%)
Radiation technique	3DRT	117 (68%)
	HT	30 (18%)
	IMRT	24 (14%)
Standard tangential	No	30 (20%)

Yes	119 (80%)

3DRT: three-dimensional radiotherapy; HER2: human epidermal growth factor receptor 2; IMRT: intensity-modulated radiation therapy.

Table 3: Influence of breast volume on axillary dose and volume.

	correlation coefficient (95% CI)	n	p	test	correlation coefficient
Ln1 Dmax	0.0714 (-0.0795; 0.219)	171	0.35	Pearson	-
Ln1 Dmean	0.306 (0.164; 0.436)	171	**<0.001**	Pearson	-
Ln1 vol	0.480 (0.356; 0.588)	171	**<0.001**	Pearson	-
Ln2 Dmax	0.276 (0.131; 0.409)	171	**<0.001**	Pearson	-
Ln2 Dmean	0.117 (-0.0338; 0.262)	171	0.13	Pearson	-
Ln2 vol	0.220 (0.0720; 0.358)	171	**<0.01**	Pearson	-
Ln3 Dmax	-	171	**<0.001**	Spearman	0.363
Ln3 Dmean	-0.0713 (-0.219; 0.0796)	171	0.35	Pearson	-
Ln3 vol	0.143 (-0.00736; 0.287)	171	0.062	Pearson	-

Dmax: maximal dose; Dmean: mean dose; Ln1: axillary level 1; Ln2: axillary level 2; Ln3: axillary level 3; vol: volume of axillary level.

Table 4: Influence of tangential beam height on axillary dose.

	HT (n = 30)	ST (n = 119)	n	p
Ln1 Dmax, median	52.0 [46.8; 62.0]	53.6 [46.0; 63.2]	149	0.59
Ln1 Dmean, median	34.3 [27.0; 37.9]	23.2 [13.1; 30.2]	149	**<0.001**
Ln2 Dmax, median	41.9 [33.1; 47.1]	34.1 [11.8; 46.0]	149	0.066
Ln2 Dmean, median	8.10 [3.05; 14.5]	3.25 [1.00; 8.82]	149	**<0.01**
Ln3 Dmax, median	15.9 [3.76; 36.9]	2.40 [1.10; 12.7]	149	**<0.001**
Ln3 Dmean, median	1.45 [0.602; 3.00]	0.700 [0.400; 1.30]	149	**<0.01**

Dmax: maximal dose; Dmean: mean dose; HT: high tangential beam; Ln1: axillary level 1; Ln2: axillary level 2; Ln3: axillary level 3; ST: standard tangential beam

Table 5: Comparison of the axillary dose delivered between ACOSOG Z0011, AMAROS and our retrospective study.

	AMAROS	ACOSOG		Retrospective study	
		ST	HT	ST	HT
Ln1 Dmean (Gy)	52.6 ± 6.5	42.2 ± 13.8	48.4 ± 4.1	23.2 [13.1; 30.2]	34.3 [27.0; 37.9]
Ln2 Dmean (Gy)	49.4 ± 3.7	35.6 ± 17.6	47.5 ± 3.9	3.25 [1.00; 8.82]	8.10 [3.05; 14.5]
Ln3 Dmean (Gy)	47.3 ± 1.7	12.0 ± 12.8	44.7 ± 5.6	0.700 [0.400; 1.30]	1.45 [0.602; 3.00]

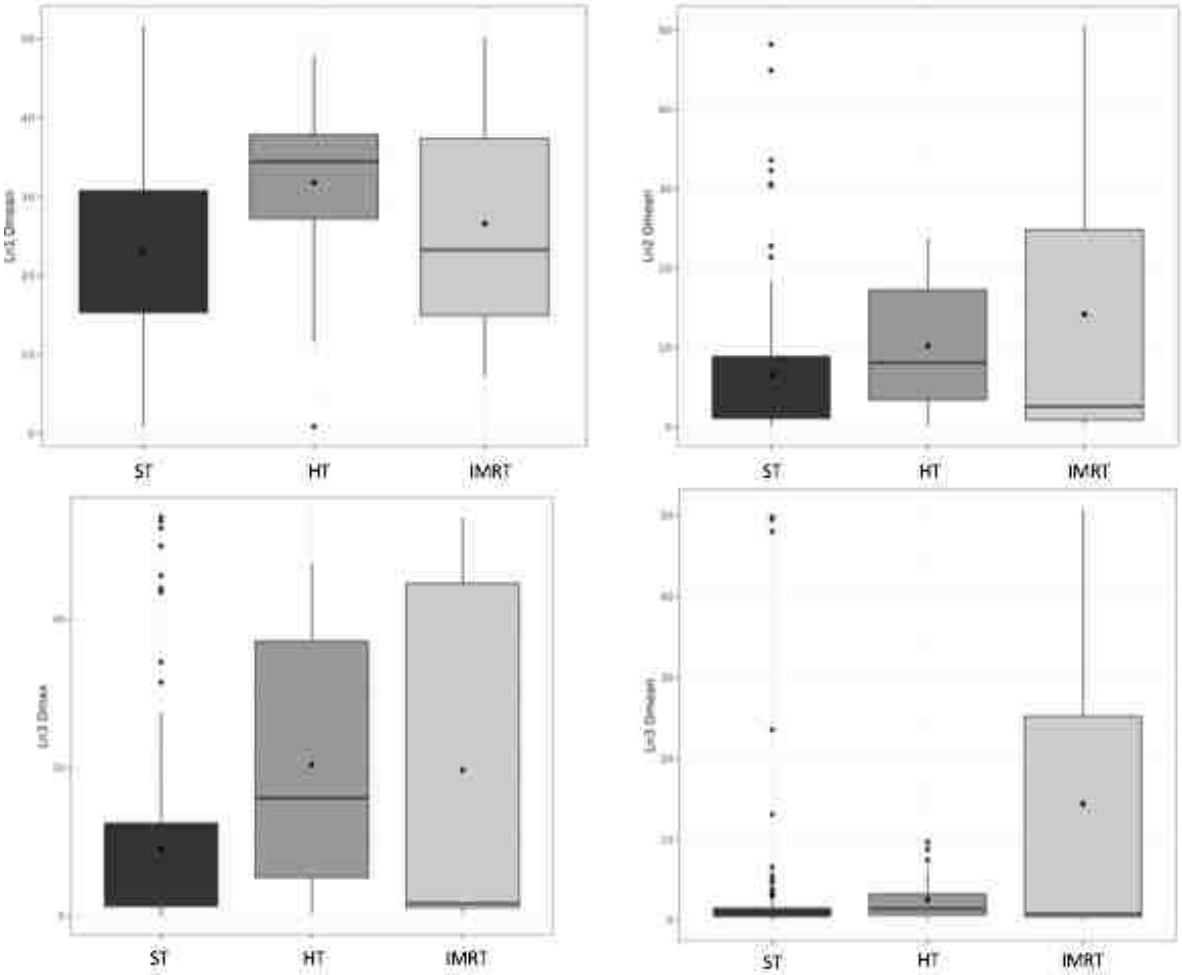
Dmean: mean dose; HT: high tangential beam; Ln1: axillary level 1; Ln2: axillary level 2; Ln3: axillary level 3; ST: standard tangential beam.

Table 6: Influence of supraclavicular irradiation on axillary dose.

	Supraclavicular irradiation			
	Yes (n = 8)	No (n = 163)	n	p
Ln1 Dmean (Gy)	38.6 [30.5; 43.6]	24.6 [13.6; 32.6]	171	**<0.01**
Ln2 Dmean (Gy)	35.9 [28.6; 44.6]	3.30 [1.15; 9.40]	171	**<0.001**
Ln3 Dmean (Gy)	49.5 [47.6; 49.7]	0.700 [0.403; 1.50]	171	**<0.001**

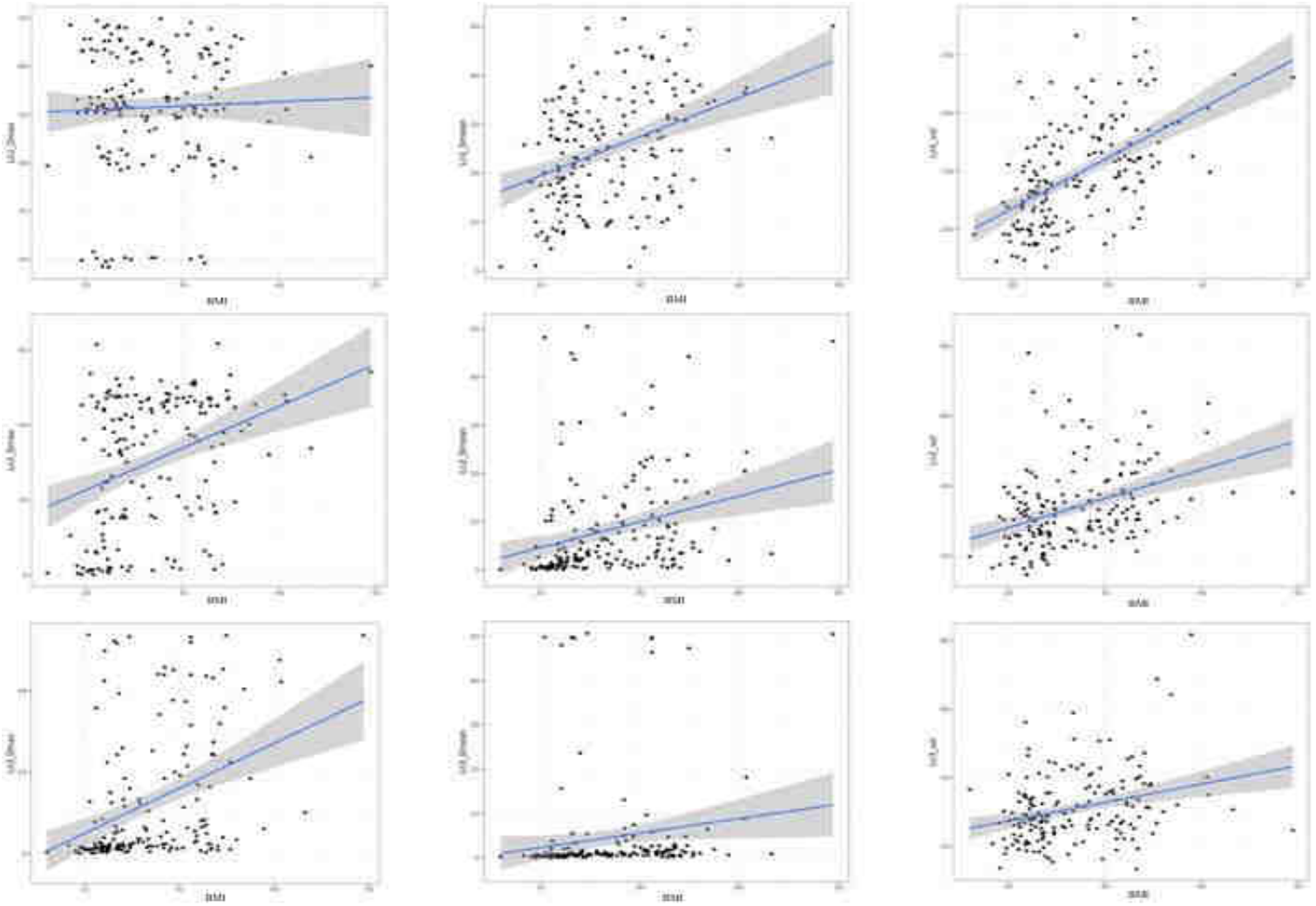
Dmean: mean dose; Gy: Gray; Ln1: axillary level 1; Ln2: axillary level 2; Ln3: axillary level 3

Figure 3: Box plot representing axillary dose according to irradiation technique



HT: high tangential beam; Ln1: axillary level 1; Ln2: axillary level 2; Ln3: axillary level 3; ST: standard tangential beam

Figure 4: Relationship between BMI, maximal dose, mean dose and volume of Ln1, 2 and 3.



BMI: Body mass index; Ln1: axillary level 1; Ln2: axillary level 2; Ln3: axillary level 3.

Conclusions

La revue systématique de la littérature conduite sur l'irradiation axillaire prophylactique « de diffusion » dans le cancer du sein a inclus 13 articles. La technique d'irradiation, la dose initiale prescrite au sein, les volumes délimités et la dose reçue aux niveaux axillaires étaient hétérogènes. La dose moyenne délivrée aux niveaux axillaires I, II et III lors d'une radiothérapie 3D-conformationnelle utilisant des champs standards était comprise entre 22 Gy et 43,5 Gy, 3 Gy et 35,6 Gy, et 1,0 Gy et 20,5 Gy, respectivement. Les doses moyennes délivrées aux niveaux axillaires I, II et III avec une radiothérapie 3D-conformationnelle utilisant des champs tangentiels élargis étaient comprises entre 38 Gy et 49,7 Gy, 11 Gy et 47,1 Gy et 5 Gy et 44,7 Gy, respectivement. Enfin, les doses moyennes délivrées aux niveaux axillaires I, II et III à l'aide de la radiothérapie à modulation d'intensité étaient comprises entre 14,5 Gy et 42,6 Gy, 3,4 Gy et 35 Gy, et 1,2 Gy et 25,5 Gy, respectivement. Cependant, l'interrogation quant à savoir si cette observation peut être traduite en un effet thérapeutique est encore débattue.

La revue de la littérature et le questionnaire national réalisé pour décrire les pratiques dans le cancer du sein a interrogé 47 centres de radiothérapie. Le questionnaire en ligne était composé de 22 questions. Cette enquête a montré que les pratiques françaises restaient hétérogènes malgré la publication de référentiels nationaux et internationaux, notamment en ce qui concerne les techniques d'irradiation, les doses prescrites et les indications d'irradiation des aires ganglionnaires.

L'étude rétrospective évaluant les facteurs pronostiques de récidives ganglionnaires dans le cancer du sein de stade localisé a inclus 1645 patientes pour un total de 1672 seins irradiés. Le taux de récidive ganglionnaire axillaire était de 0,38 %, influencé positivement par l'hormonothérapie (99,7% [99,3%; 100,0%] contre 72,3% [intervalle 40,9%; 100,0%], p <

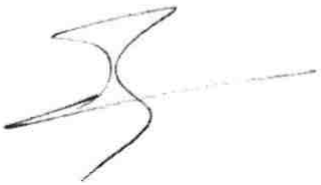
0,01) et la positivité des récepteurs aux œstrogènes (99,7% [intervalle 99,3%; 100,0%] contre 72,1% [intervalle 40,9%; 100,0%], p < 0,012). La présence d'une rechute locale a une influence négative sur la survie sans récidive ganglionnaire (99,5 % [intervalle 99,0 % - 100,0 %] contre 40,0 % [intervalle 9,35 % - 100,0 %], p<0,001).

L'étude dosimétrique portant sur 171 patients n'a pas mis en évidence de lien significatif entre la dose maximale et moyenne délivrée au creux axillaire et le risque de récidive ganglionnaire axillaire. Deux patientes, toutes les deux dans le groupe "tangentiels hauts" ont eu un lymphœdème. Il y avait significativement plus de lymphœdème dans le groupe "tangentiels hauts" que dans les groupes « tangentiels standards » et RCMI (p =0,048). La dose moyenne au niveau II était significativement plus importante chez les patients ayant eu un lymphœdème (3,45 Gy [1.08 ; 9.62] vs. 23,4 Gy [23,1 ; 23,6] (p < 0,02).

Vu

Strasbourg le 29/06/2021

Le président du Jury de Thèse



Professeur Georges NOEL

Vu et approuvé

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RESUME : Dans le cancer du sein, la radiothérapie est un élément majeur de la prise en charge. Les indications de la radiothérapie sont validées en réunion de concertation pluridisciplinaire, mais des questions restent en suspens, notamment en ce qui concerne la radiothérapie hypofractionnée, l'irradiation partielle du sein, l'irradiation de la chaîne mammaire interne et de l'aire ganglionnaire axillaire. La récidive axillaire chez les patientes atteintes d'un carcinome mammaire invasif reste un enjeu et la question de savoir si l'irradiation du sein peut inclure involontairement les niveaux I, II et III et diminuer le risque de récidive axillaire reste un sujet de discussion.

Dans un premier temps nous avons réalisé une revue de la littérature pour évaluer la couverture des niveaux axillaires lors de l'irradiation du sein avec différentes techniques.

Dans un deuxième temps nous avons réalisé un questionnaire national sur les pratiques en radiothérapie mammaire tant sur le fractionnement, la prescription de la dose et le choix des volumes cibles.

Enfin dans un troisième temps nous avons réalisé une étude rétrospective monocentrique pour évaluer les facteurs pronostiques de récidives ganglionnaires axillaires.

Rubrique de classement : Oncologie option Radiothérapie

Mots-clés :

Cancer du sein, radiothérapie, aire axillaire, aire ganglionnaire, radiothérapie tridimensionnelle, radiothérapie conformationnelle avec modulation d'intensité

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