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PROGRAMA DE DOCTORADO DE INVESTIGACIÓN EN BIOMEDICINA

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TESIS DOCTORAL POR COMPENDIO DE PUBLICACIONES

ESTUDIO DE LOS FACTORES QUE INFLUYEN EN LA SUPERVIVENCIA GLOBAL Y CALIDAD DE VIDA DE LAS PACIENTES INTERVENIDAS POR CÁNCER DE MAMA

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DEDICATORIA:

A mi familia, en especial a mi hijo.

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ÍNDICE

INTRODUCCIÓN

La supervivencia global y la calidad de vida son los aspectos más importantes que hay que priorizar durante el tratamiento de una paciente con cáncer de mama. La mayoría de los estudios actuales buscan aumentar la supervivencia intentando mantener una calidad de vida aceptable. La supervivencia global varía según el tipo de tumor, el estadio de la enfermedad y el uso de tratamientos adyuvantes, sin embargo, existen factores comunes que pueden afectarla como la recaída local y la aparición de enfermedad a distancia. La calidad de vida también se ve alterada por distintas variables (agresividad de la cirugía, tratamientos complementarios, complicaciones, resultados estéticos o el uso de técnicas de reconstrucción mamaria inmediata) las cuales se deben tener en cuenta a la hora de elegir un tratamiento adecuado para cada tipo de paciente.

El riesgo de recurrencia local en el cáncer de mama varía según el tipo de pacientes estudiados entre un 3 a un 15 % presentándose principalmente en los primeros años de seguimiento sobre todo en las pacientes jóvenes y triple negativas. La supervivencia libre de enfermedad a los 5 años es mayor del 80 % y depende de ciertos factores que deben ser estudiados previamente para mejorar el abordaje terapéutico y la expectativa de vida. Entre estos factores encontramos la localización y las características histopatológicas de la tumoración que nos permite diferenciar esta recaída de la aparición de un nuevo tumor primario cuyo pronóstico es mas favorable. Si el tamaño de la tumoración es adecuado y se pudiera garantizar la seguridad oncológica en la resección, un abordaje conservador podría ser realizado, ya que no existen diferencias significativas en el tratamiento de la recaída utilizando cirugía conservadora o mastectomía. Para esta decisión también se debe valorar el tipo de tumor y el tiempo de reaparición ya que nos orientara sobre la agresividad del mismo. Además en las pacientes con recaída local sin infiltración axilar se debe

asociar siempre el estudio del ganglio centinela. La afectación axilar aumenta las tasa de recidiva loco regional sobre todo si se asocia a otros factores desfavorables.

La cercanía de los márgenes de resección es un tema muy discutido y en los últimos años se considera que no es un factor que aumente la tasa de recidivas ya que no importa la distancia si no la presencia o no de contacto de los mismos con la tumoración. Además nuevos estudios sugieren que el margen focalmente afecto por tumor, tampoco aumentaría estas cifras. Por otro lado la afectación de márgenes no se relaciona con la recurrencia si la paciente ha sido inicialmente mastectomizada. A pesar de todo lo anterior siempre habría que resaltar que la presencia de tumoración en contacto con los márgenes en la cirugía conservadora es la única variable que puede ser controlada por el cirujano y seria indicación indiscutible de reintervención.

La multifocalidad y la presencia de carcinoma intraductal favorecen una resección incompleta inicial, asociándose, a un aumento de la reintervenciones para lograr márgenes libres, lo que aumenta la morbilidad. Situación similar ocurre con el carcinoma lobulillar cuyas características especiales dificultan el control local si lo comparamos con el ductal. La infiltración linfovascular esta relacionada con la recaída loco regional, pero de forma mas importante, con la diseminación de la enfermedad al resto del organismo favoreciendo la aparición de enfermedad metástasica.

El receptor de progesterona negativo es un factor predictivo de recaída incluso en presencia de un receptor de estrógeno positivo, siendo de mucha importancia en el momento de decidir un tratamiento, además la ausencia del uso de terapia hormonal para el control sistémico favorece a la presencia posterior de enfermedad a distancia lo que disminuye la supervivencia global. Debido a que tiene un tratamiento especifico, la positividad de HER2 en el estudio inmuno histoquímico, en

la actualidad podría considerarse un factor de buen pronostico.

Desde el punto de vista quirúrgico, el uso de quimioterapia neoadyuvante, dificulta la delimitación de la tumoración, pudiendo estar relacionado de forma significativa con el aumento de la recidiva local en estas pacientes. Otro factor a tener en cuenta es que esta demostrado que en las pacientes triple negativas no existe mayor riesgo de recidiva local, si no de enfermedad a distancia por lo que si se afectaría su supervivencia global.

La cirugía conservadora es el tratamiento quirúrgico mas utilizado en el cáncer de mama,sin embargo existe todavía un 20 a 30 % de pacientes que requerirán una mastectomía, asociada en la mayoría de los casos de una reconstrucción mamaria para el tratamiento definitivo de su enfermedad. La reconstrucción mamaria tiene como objetivo la creación de una silueta y volumen mamario similar al original contribuyendo a mejorar los resultados estéticos y la calidad de vida de las pacientes. La radioterapia postmastectomía reduce el riesgo de recidiva locoregional y enfermedad a distancia, aumentando la supervivencia global en mujeres con afectación axilar. Anteriormente si el uso de esta terapia adyuvante era anticipado se retrasaba la reconstrucción mamaria hasta finalizar el tratamiento o incluso se descartaba lo que disminuía la calidad de vida de estas pacientes. Con la nuevas técnicas de reconstrucción y el uso de radioterapia externa cada vez mas dirigida, la reconstrucción inmediata se puede realizar con buenos resultados estéticos y un bajo indice de complicaciones.

La reconstrucción alloplastica mediante colocación de expansor y posterior recambio a una prótesis definitiva es una opción cada vez mas utilizada, aunque todavía existen controversias sobre cual es el mejor momento para la irradiación, que consecuencias estéticas obtendremos a largo plazo y que tasas de fallos en la reconstrucción o contractura capsular seria asumible para apoyar y

validar dicha técnica. Existen muchos estudios al respecto en la literatura actual pero la mayoría se centran en las complicaciones de la irradiación sin establecer su relación con la perdida de la reconstrucción, los resultados estéticos y sobre todo el grado de satisfacción de las pacientes. El tipo de radioterapia a utilizar es otro tema muy discutido. En las ultimas décadas los avances tecnológicos han permitido una mejora en la planificación del tratamiento eliminando barreras dosimétricas que se presentaban en este tipo de paciente.

Los tratamientos adyuvantes son fundamentales para disminuir el numero de recaídas locales y así aumentar la supervivencia a largo plazo. La evolución de la tecnología nos ha ayudado a mejorar la forma de administrar dichos tratamientos siendo la radioterapia intraoperatoria (IORT) una herramienta terapéutica novedosa que nos permite la administración durante la intervención quirúrgica de una única dosis de radiación ionizante directamente sobre la cavidad quirúrgica de la tumorectomía, con el objeto de mejorar el control local de la enfermedad y disminuir la toxicidad secundaria a la irradiación de tejidos sanos.

Esta técnica mejora la localización exacta del refuerzo de radiación y reduce el intervalo de tiempo de espera entre la cirugía y la radiación. Al irradiarse la paciente bajo anestesia, los errores derivados del movimiento de la paciente o los errores de posicionamiento son prácticamente inexistentes. Se ha descrito su utilización como sobredosificación o boost del tratamiento convencional con radioterapia externa y como tratamiento exclusivo en estadios iniciales del cáncer de mama. Una dosis de IORT presenta una efectividad biológica equivalente a la administración convencional de una dosis de radioterapia externa fraccionada unas 2 a 3 veces superior. Cuando se combinan dosis de 45-50 Gy de RTE con dosis de IORT entre 10-20 Gy se alcanzan mayores tasas de control local, especialmente en el control de la enfermedad residual.

Existen diferentes tipos de radioterapia intraoperatoria, el uso de una fuente de energía de rayos X de 50 kV es un procedimiento estándar que se realiza en muchos hospitales de nuestro medio con complicaciones quirúrgicas a corto y largo plazo poco descritas en la literatura actual. Las complicaciones derivadas de una cirugía conservadora en el cáncer de mama pudieran aumentar con el uso de este tipo de radiación. El estudio de los factores demográficos y técnicos que influyen para la presencia de estas es fundamental para la planificación de un adecuado tratamiento multidisciplinar.

En este trabajo se presentaran 3 estudios consecutivos de tipo descriptivo observacional realizados en las pacientes intervenidas por cáncer de mama en el Servicio de Cirugía General y Digestiva del Complejo Hospitalario Universitario Insular Materno Infantil. Existen variables comunes en el cáncer de mama que fueron seleccionadas para su estudio en los mismos, como la edad, tipo de cirugía realizada, tamaño de la lesión, tipo histológico, grado, afectación axilar, uso de tratamientos neoadyuvantes, características inmunohistoquímicas de la tumoración o la afectación de márgenes quirúrgicos.

Para cada estudio se asociaron a la vez variables específicas como la presencia de recaída local, enfermedad a distancia, tiempo transcurrido antes de la reconstrucción mamaria, uso de radioterapia y quimioterapia antes, durante o después de la misma, simetría y bilateralidad del procedimiento, presencia de complicaciones, resultados estéticos, grado de satisfacción general de las pacientes, tamaño de aplicador de radioterapia intraoperatoria utilizado (>45 mm), necesidad de reintervención quirúrgica, uso de radioterapia externa complementaria o la presencia posterior de recaída local, factores determinantes en la supervivencia y calidad de vida de las pacientes. Para el análisis estadístico se utilizo el programa IBM® SPSS® Statistics v. 21 realizando las comparaciones que eran necesarias para cada estudio. En su mayoría se utilizarón los datos

obtenidos de las historias clínicas de las pacientes intervenidas por cáncer de mama con recursos materiales propios del autor. Para la realización de las encuestas de satisfacción y calidad de vida se utilizo material electrónico y en formato papel obtenidos por el autor y colaboradores de la tesis. El programa estadístico a utilizar para procesar los datos fue facilitado por uno de los autores principales de cada publicación.

Los trabajos realizados se han publicado en 3 revistas internacionales indexadas en el Journal Citations Reports con la categoría CIRUGIA(SURGERY). Dos de estos trabajos fueron publicados en una revista cuyo índice de impacto la sitúa dentro de la primera mitad en orden decreciente de índice de impacto entre las revistas de su área (Q1-Q2). A continuación se mencionan los trabajos publicados con su respectiva revista.

1- Tejera Hernández AA, Vega Benítez VM, Rocca Cardenas JC, Gutiérrez Giner MI, Díaz Chico JC, Hernández Hernández JR. Factors predicting local relapse and survival in patients treated with surgery for breast cancer. Asian J Surg. 2019 Jul;42(7):755-760. doi: 10.1016/j.asjsur.2018.11.005. Epub 2018 Dec 7.

Datos de revista :Asian Journal of Surgery. Revista Q2(SURGERY 98/200. JCR 2017). Factor de impacto:1.895. Indexada en SCIE, Medline, ScienceDirect, Scopus, Embase, Current Contents, PubMed, Current Abstracts, BioEngineering Abstracts, SIIC Data Bases, CAB Abstracts, and CAB Health.

2- Tejera Hernández AA, Vega Benítez VM, Rocca Cardenas JC, Ortega Perez N, Rodriguez Ibarria N, Gutiérrez Giner MI, Pérez Correa P, Díaz Chico JC, Hernández Hernández JR. Inverse radiotherapy planning in reconstructive surgery for breast cancer. Int J Surg. 2019 Mar;63:77-82.

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3- Tejera Hernández AA, Vega Benítez VM, Rocca Cardenas JC, Ortega Perez N, Rodriguez Ibarria N, Díaz Chico JC, García-Granados Alayón JJ, Pérez Correa P, Hernández Hernández JR. Complications and local relapse after intraoperative low-voltage X-ray radiotherapy in breast cancer. Ann Surg Treat Res 2020;98(6):299-306. doi.org/10.4174/astr.2020.98.6.299.

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BIBLIOGRAFÍA

Ishitobi M, Okuno J, Kittaka N, et al. Distant Recurrence Risk after Late Ipsilateral Breast Tumor Recurrence: Results of a Retrospective, Single-Institution Study. Oncology. 2015;89:269-74.

Mittendorf EA, Ardavanis A, Symanowski J, et al. Primary Analysis of a Prospective, Randomized, Single-Blinded Phase II Trial Evaluating the HER2 Peptide AE37 Vaccine in Breast Cancer Patients to Prevent Recurrence. Ann Oncol.2016;27:1241-8

Steward L, Conant L, Gao F, et al. Predictive factors and patterns of recurrence in patients with triple negative breast cancer. Ann Surg Oncol. 2014;21:2165-71.

Engelhardt EG, Garvelink MM, De Haes JH, et al. Predicting and communicating the risk of recurrence and death in women with early-stage breast cancer: a systematic review of risk prediction models. J Clin Oncol. 2014;32:238-50.

Henry NL, Somerfield MR, Abramson VG, et al. Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer: American Society of Clinical Oncology Endorsement of CancerCare Ontario Guideline Recommendations. J Clin Oncol. 2016;34:2303-11.

Roué T, Labbé S, Belliardo S, et al. Predictive Factors of the Survival of Women With Invasive Breast Cancer in French Guiana: The Burden of Health Inequalities. Clin Breast Cancer. 2016;16:113-18.

Bosma SC, Van der Leij F, Van Werkhoven E, et al. Very low local recurrence rates after breast-conserving therapy: analysis of 8485 patients treated over a 28-year period. Breast Cancer Res Treat. 2016;156:391-400.

Fei F, Messina C, Slaets L, et al. Tumour size is the only predictive factor of distant recurrence after pathological complete response to neoadjuvant chemotherapy in patients with large operable or locally advanced breast cancers: a sub-study of EORTC 10994/BIG 1-00 phase III trial. Eur J Cancer. 2015;51:301-9.

Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013;14:1086-94.

Kuerer HM, Cordeiro PG, Mutter RW. Optimizing Breast Cancer Adjuvant Radiation and Integration of Breast and Reconstructive Surgery. Am Soc Clin Oncol Educ Book. 2017;37:93-105.

Cordeiro PG, Albornoz CR, McCormick B, Hudis CA, Hu Q, Heerdt A, et al. What Is the Optimum Timing of Postmastectomy Radiotherapy in Two-Stage Prosthetic Reconstruction: Radiation to the Tissue Expander or Permanent Implant?. Plast Reconstr Surg. 2015;135:1509-17.

Yun JH, Diaz R, Orman AG. Breast Reconstruction and Radiation Therapy. Cancer Control. 2018;25:1073274818795489.

Momoh A, Ahmed R, Kelley BP, Aliu O, Kidwell KM, Kozlow JH, et al. A systematic review of complications of implant-based breast reconstruction with prereconstruction and postreconstruction radiotherapy. Ann Surg Oncol. 2014;21:118-24.

Orecchia CM, Lazzari R, Garibaldi C, et al. Intraoperative radiation therapy with electrons (ELIOT) in early stage breast cancer. Breast. 2003;12:483-90.

Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall

survival from the TARGIT-A randomised trial. Lancet. 2014;383:603-13.

Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the 205 American Society for Radiation Oncology (ASTRO). Journal of the American College of Surgeons. 2009;209:269-77.

Morlino A, La Torre G, Lapadula L, Cammarota A.IORT in breast cancer. Our experience of the first patients treated. Ann Ital Chir. 2017;88:253-7.

Rakhra S, Bethke K, Strauss J, et al. Risk Factors Leading to Complications in Early-Stage Breast Cancer Following Breast-Conserving Surgery and Intraoperative Radiotherapy.Ann Surg Oncol. 2017;24:1258-61.

OBJETIVOS

OBJETIVO GENERAL

Estudiar los factores que influyen en la supervivencia global y calidad de vida de las pacientes intervenidas por cáncer de mama.

OBJETIVOS ESPECÍFICOS

1. Analizar las variables predictoras de recidiva local y supervivencia de las pacientes intervenidas por cáncer de mama, resaltando los factores que influyen en su aparición y su relación con la presencia de enfermedad a distancia.

2. Estudiar los efectos de la radioterapia externa en la satisfacción y calidad de vida de las pacientes.

3. Establecer si la radioterapia externa de planificación invertida, es un factor que influye en la reconstrucción mamaria, los resultados estéticos finales y el grado de satisfacción de las pacientes comparándolo con el resto de pacientes no irradiadas en las que se ha utilizado la misma técnica quirúrgica.

4. Definir los factores que influyen en la presencia de complicaciones quirúrgicas de los pacientes intervenidos por cáncer de mama asociado a el uso de radioterapia intraoperatoria de rayos X de bajo voltaje, identificando las posibles recaídas locales que se presentaran durante el seguimiento de estas.

JUSTIFICACIÓN

Existen muchos factores que debemos de tener en cuenta, cuando nos enfrentamos a una paciente diagnosticada de cáncer de mama. Encontrar el equilibrio entre el tratamiento quirúrgico oncológico y los resultados estéticos que queremos obtener no es siempre fácil, la prioridad numero uno del cirujano esta establecida por la necesidad de lograr una curación de la enfermedad intentando dejar las menores secuelas físicas posibles. La supervivencia global se define por el tiempo de vida que el enfermo presenta desde el diagnostico hasta la actualidad o hasta su fatal desenlace. Poder determinar que factores influyen en el aumento de esta supervivencia, debería ser un objetivo fundamental para todo el equipo quirúrgico, ya que al determinar estos aspectos podemos predecir las posibles complicaciones que nos encontraremos y planificar con anterioridad el mejor tratamiento a ofrecer , siendo selectivos ante las características individuales de cada paciente.

La recaída local esta asociada de una forma significativa a la presencia posterior de enfermedad metastásica, lo que disminuye directamente la supervivencia. Identificar que pacientes tienen mayor riesgo de presentar una recaída local nos permite tomar decisiones mas agresivas desde el punto de vista oncológico en busca de evitar la presencia de la misma en el futuro. Ademas nos permite realizar un seguimiento mas estrecho con la finalidad de poder diagnosticarla precozmente lo que aumentaría la probabilidades de curación.

Entendemos por calidad de vida a un conjunto de condiciones que contribuyen al bienestar de los individuos, estas son variables y dependen de factores tanto subjetivos como objetivos. En el caso de la paciente con cáncer de mama, debemos de entender que este órgano forma parte de la identidad de la mujer y que su alteración genera un disconfort tanto físico como psicológico. La

reconstrucción mamaria inmediata es una herramienta que nos permite restaurar las alteraciones físicas sufridas durante el acto quirúrgico oncológico y se debe ofrecer a todas la pacientes que cumplan con los criterios estándares necesarios para realizarla. La tecnología a avanzando mucho en los últimos años lo que nos permite ofrecer esta técnica con seguridad incluso a pacientes que van a ser irradiadas. Determinar que estas técnicas se aplican con seguridad en nuestras pacientes es una razón fundamental para la realización de este trabajo. Ademas poder conocer el grado de satisfacción que presentan , identificando las mejoras que se pueden realizar, debería ser uno de los objetivos fundamentales en una unidad que atienda pacientes con cáncer de mama.

La irradiación del lecho quirúrgico en el momento de la cirugía es una opción rápida y atractiva, que permite una localización directa del lecho tumoral con el beneficio de realizar ambos tratamientos en un solo día. La radiación se aplica de forma precisa en el área que tiene el mayor riesgo de recaída del tumor preservando el tejido sano colindante. Existe un 15 a 30% de las pacientes que no pueden completar el tratamiento adyuvante de radioterapia externa por edad avanzada, comorbilidades asociadas o lejanía a su centro hospitalario de referencia lo que aumenta su probabilidad de recaída local. Este grupo de pacientes se beneficia de forma directa de la radioterapia intraoperatoria. La dosimetría personalizada de esta técnica disminuye el riesgo de complicaciones y toxicidad, sin embargo, se han descrito un aumento de algunos tipos de complicaciones bastante característicos. Las pacientes a las que se les ha ofrecido esta novedosa técnica, deben ser estudiadas intentando sobre todo identificar las posibles complicaciones inherentes a la misma, asociando la determinación de recaídas locales.

La razones antes mencionadas justifican la realización de este trabajo cuyo objetivo principal es el de estudiar los factores que influyen en la supervivencia global y calidad de vida de las pacientes intervenidas por cáncer de mama.

ARTÍCULOS PUBLICADOS

1- Factors predicting local relapse and survival in patients treated with surgery for breast cancer.

Asian J Surg. 2019 Jul;42(7):755-760. doi: 10.1016/j.asjsur.2018.11.005. Epub 2018 Dec 7.

2- Inverse radiotherapy planning in reconstructive surgery for breast cancer.

Int J Surg. 2019 Mar;63:77-82. doi: 10.1016/j.ijsu.2019.01.017. Epub 2019 Jan 29.

3- Complications and local relapse after intraoperative low-voltage X-ray radiotherapy in breast cancer.

Ann Surg Treat Res 2020;98(6):299-306. doi.org/10.4174/astr.2020.98.6.299.

OBJETIVO ESPECÍFICO 1

Analizar las variables predictoras de recidiva local y supervivencia de las pacientes intervenidas por cáncer de mama, resaltando los factores que influyen en su aparición y su relación con la presencia de enfermedad a distancia.

Articulo:

Factors predicting local relapse and survival in patients treated with surgery for breast cancer.

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ORIGINAL ARTICLE

Factors predicting local relapse and survival in patients treated with surgery for breast cancer

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Survival;
Predictive factor

Summary *Background:* Assessment of local relapse in patients treated with surgery for breast cancer.
Materials and methods: This observational study included 673 patients treated with surgery for breast cancer between 2005 and 2010, who were monitored for a 7-year minimum follow-up period. The study was concluded on 2017 and yielded a total of 31 cases of local relapse.
Results: 4.6% of patients presented local relapse, most of them during the first 3 years of follow-up; 45% of patients with local relapse subsequently presented the disease at distant points. The association between the occurrence of local relapse and later onset of the disease at distant points was significant. The Kaplan–Meier survival analysis revealed that negative results for the presence of progesterone receptors, the use of neoadjuvant chemotherapy and the presence of the disease at distant points were factors that significantly influenced patient survival.
Conclusions: Almost half of the patients suffering relapse subsequently present the disease at distant points. Certain factors increase the aggressiveness of the disease, predict higher risk of relapse and determine its prognosis.

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1. Introduction

In breast cancer, certain factors predict higher probability of local relapse and are associated to poorer prognosis and reduced overall survival.[1] Such characteristics should be taken into account when choosing a specific treatment and planning postoperative follow-up.[2,3] In order to identify them, local relapse was analyzed in patients previously treated with surgery for breast cancer, emphasizing those factors that influenced relapse appearance and the relationship with the presence of disease at distant points.

2. Materials and method

This observational study was carried out using consecutive sampling on 673 patients treated with surgery for breast cancer between 2005 and 2010. The minimum follow-up period was 7 years. The study was concluded on January 2017. Thirty-one cases of local relapse were evaluated and compared with 31 random control patients, also treated with surgery on the same year, who did not suffer relapse. These controls were selected by a simple random sampling. During the study, whenever a case arose, a random control was selected for the group of patients also treated with surgery for breast cáncer on the same month in order to have a similar follow-up period than the observed case.

All patients presenting local-regional recurrence after conservative or radical surgery for breast cancer were included, provided that they fulfilled the following selection criteria: presenting the same location, histological type and histochemical characteristics of the first tumor. Patients presenting a new primary tumor or distant metastasis for the first time were excluded. The following variables were established and studied: age, type of previous surgery, lesion size, histological type, histological grade, axillary involvement, lymphovascular infiltration, multifocality, use of neoadjuvant therapy and immunohistochemical characteristics, as well as margin involvement, surgical technique used in the second intervention and presence of the disease at distant points. Quantitative variables were categorized, in order to make them nominal, with 2 homogeneous groups that could be compared; additionally, this prevented sample dispersion. Patients' disease-free interval and relationship between local relapse and subsequent disease at distant points were defined.

An age cutpoint was established at 50 years because of its association with menopause and consequent hormonal alterations.[4] Tumor size over 2 cm in diameter and histological grade corresponding to moderate or poor differentiation have been associated with increased relapse rates,[5] thus we chose those parameters as delimitation for a better differentiation between both groups. The following biological factors were defined: estrogen receptors, considered to be positive for values higher than 1%; Ki-67 considered to be positive for values higher than 20%; and HER2, which was defined on the basis of crosses in the immunohistochemical study more than 3 was considered positive, 1 was considered negative and 2, undetermined; in such cases, an additional *in-situ* hybridization assay was carried out, in order to confirm or rule out positivity.[6]

In order to compare nominal variables, 2×2 contingency tables were created by using the long-rank test (Mantel—Cox) with $p < 0.05$ significance level. In determining the variables that were significantly associated with local relapse in an independent way, construction of multiple multivariate-analysis models was initiated, including 4 variables at a time, so that there was one variable maximum per 5 observed events (local relapse), thus building a Kaplan—Meier survival analysis with the IBM® SPSS® Statistics v. 21 software package.

3. Results

Up to 4.6% of patients treated with surgery for breast cancer presented local relapse most of them during the first 3 years of follow-up with a mean disease-free interval of 34.5 months (Fig. 1). Radical rescue surgery was used in 94% of cases, while a conservative approach was only adopted in a small percentage of cases; both techniques produced similar outcomes in terms of subsequent appearance of the metastatic disease (Table 1). Age, tumor size, axillary involvement, multifocality, use of neoadjuvant chemotherapy, biological factors and margin involvement were independent variables significantly associated with local relapse (Table 2); 45% of patients with local relapse presented the disease at distant points, whereas metastasis was only observed in 6.4% of patients without relapse. The association between local relapse and disease at distant points was significant (Table 2).

The Kaplan—Meier survival analysis (Table 3) revealed that negative presence of progesterone receptors (Fig. 2A), use of neoadjuvant chemotherapy (Fig. 2B) and presence of the disease at distant points (Fig. 2C) significantly influenced patient survival, with higher relevance than the rest of studied variables.

4. Discussion

The risk of local relapse varies between 3 and 15% depending on the type of patient studied,[1,7] and occurs

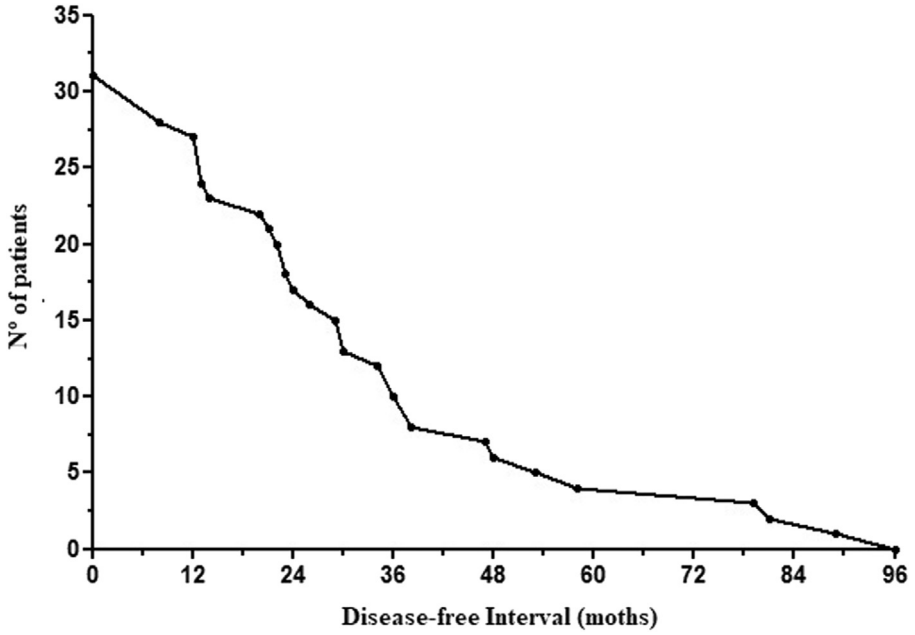

Figure 1 The median disease-free interval of recurrence.

Table 1 Surgical treatment of recurrence (n = 31).

	Metastasis	No Metastasis	p-Value
Breast conserving surgery	1 (50)	1 (50)	0.886
Radical rescue surgery	13 (45)	16 (55)	

The relationship between the chosen surgical treatment for recurrence and the subsequent presence of metastatic disease was not significant($p > 0.05$).

mostly during the first few years of follow-up, especially in younger and triple-negative patients.[3,4,8] The free-of-disease survival rate at 5 years is higher than 80% and depends on certain factors that should be considered in follow-up.[9] In our study, recurrence rates were acceptable and occurred mainly in the first 3 years.

Tumor location and histopathological characteristics are essential to differentiate relapse from new primary tumors, which have a better prognosis.[10,11] Younger patients present a widely-studied hormonal component, which facilitates tumoral recurrence[12]; additionally, they survive more years, which influenced the observed disease-free interval.[3,4]

If the relapse lesion has an adequate size and oncologic safety of the resection can be guaranteed, a conservative approach may be adopted, since no significant differences were found between relapse treatment through conservative surgery or mastectomy[7,11,13,15]; although the second was chosen in most studies.[7,11,14,15] To make this decision, the type of tumor and the time to recurrence should also be evaluated, because they give information on the aggressivity.[7,11] Furthermore, in patients with local relapse without axillary invasion, the sentinel node must always be examined.[13,15,16] In our center, we prefer mastectomy, although in certain cases with favorable prognostic factors, a conservative management is possible.

In some published series, the initial tumor size is the most important factor for local relapse, with differences between T3 or 4 and T1 or 2 statistically significant.[5] Axillary involvement increases the rate of local-regional relapse, especially when associated to other unfavorable factors.[17–19] The presence of axillary micro-metastases should also be identified and differentiated; this factor is not significantly associated with increased relapse, especially in patients receiving external axillary radiotherapy.[20] In our study, both factors showed significant differences in relation to the presence of relapse.

Clearly, the closeness of resection margins is a debated issue. In recent years, it has been considered that this factor does not increase the rates of recurrence, because what matters is not the distance, but the occurrence (or not) of contact with the ink.[21,22] Furthermore, recent studies have suggested that a focally involved margin would not increase such figures either, so that re-intervention of the patient would not be necessary.[4] Moreover, margin involvement is not related with recurrence in patients initially mastectomized.[23] In spite of all the above mentioned, it should always be highlighted that the presence of a tumor in contact with the margins of conservative surgery is the only variable that can be controlled by the surgeon and it would undisputedly be an indication for re-intervention.

Multifocality and the presence of intraductal carcinoma may lead to incomplete initial resection, which is associated with more re-interventions necessary to get free margins with the consequent morbidity increase.[12,23,24] A similar situation occurs with lobular carcinoma, since its special characteristics make local control more difficult, as compared with ductal carcinoma.[25–28] Lymphovascular

Table 2 Characteristics of patients.

	Local recurrence n(%)		p-Value
	Present	Absent	
Cases	31 (50)	31 (50)	
Age (years)			0.058
<50	19 (61)	11 (35)	
≥50	12 (39)	20 (65)	
First surgical treatment			0.611
Breast conserving surgery	26 (84)	24 (77)	
Mastectomy	5 (16)	7 (23)	
Tumor size (mm)			**<0.001**
<20	5 (16)	20 (65)	
≥20	26 (84)	11 (35)	
Clinical lymph node status			**0.008**
Positive	21 (68)	11 (35)	
Negative	10 (32)	20 (65)	
Multifocality			**0.004**
Yes	26 (84)	14 (45)	
No	5 (16)	17 (55)	
Neoadjuvant chemotherapy			**<0.001**
Yes	20 (65)	5 (16)	
No	11 (35)	26 (84)	
Histological type			0.107
Ductal	26 (84)	29 (94)	
Lobular	5 (16)	2 (6)	
Ductal carcinoma *in situ*			0.317
Yes	17 (55)	21 (68)	
No	14 (45)	10 (32)	
Lymphovascular involvement			0.165
Yes	12 (39)	6 (19)	
No	19 (61)	25 (81)	
Histological grade			0.367
<G2	5 (16)	8 (26)	
≥G2	26 (84)	23 (74)	
Estrogen receptor			**<0.001**
Positive	17 (55)	26 (84)	
Negative	14 (45)	5 (16)	
Progesterone receptor			**<0.001**
Positive	9 (29)	22 (71)	
Negative	22 (71)	9 (29)	
HER2			**0.006**
Positive	9 (29)	2 (7)	
Negative	22 (71)	29 (94)	
Positive margins			**0.003**
Yes	18 (58)	7 (23)	
No	13 (42)	24 (77)	
Metastasis			**<0.001**
Yes	14 (45)	2 (6)	
No	17 (55)	29 (94)	

Table 3 Kaplan–Meier survival analysis.

Independent variables	OR (95%CI)	p-Value
Progesterone receptor negative	1.8 (1.2–2.7)	**0.002**
Neoadjuvant chemotherapy	1.6 (1.1–2.4)	**0.009**
Metastasis	1.9 (1.3–2.7)	**<0.001**
Positive margins		0.058
Tumor size ≥ 20 mm		0.096
Clinical lymph node positive		0.468
Multifocality		0.471
Estrogen receptor negative		0.968
HER2		0.751

OR: odds ratio; CI: confidence interval.

infiltration is related with local-regional relapse but, more importantly, with the dissemination of the disease to the rest of the body, which promotes the appearance of metastatic disease.[18]

A result of negative progesterone receptor is predictive of relapse, even in the presence of positive estrogen receptor,[29] and is a very important factor in the choice of treatment. Furthermore, not using hormonal therapy for systemic control promotes subsequent development of the disease at distant points, which reduces overall survival.[30] Given that positive HER2 in the immunohistochemical study is treated a specific way, it could be currently considered a good-prognosis factor[31]; however, it was not significant in our study, similarly to Ki-67 a cell proliferation marker usually elevated accordingly to the aggressiveness of the tumor.[6]

From a surgical point of view, the use of neoadjuvant therapy impairs tumor delimitation and might be significantly associated with increased local relapse in these patients.[9] However, these patients usually present large initial tumors, with axillary involvement or unfavorable biological factors (where we include triple-negative ones), all of which could potentially account for unfavorable outcomes rather than the treatment[25,32]. A further issue to take into account is that triple-negative patients do not present higher risk of local relapse, but of disease at distant points, which would effectively influence overall survival.[8]

The relationship between local relapse and subsequent presence of metastatic disease was significant; global survival decreased, in agreement with some published series, which reported rates below 40%.[29,32] Survival was lower depending on the time of onset and the location, with the poorest rates for brain metastases.[24] We observed such a relationship in our study.

In spite of the prolonged follow-up time, these Results should be considered with caution because, from a statistical point of view, this experience corresponded to only one centre and was conducted on a limited amount of patients; however, most of our outcomes were in agreement with those reported in the literature.

Local relapse rates have decreased throughout the time, due to the use of early-diagnosis techniques – based on screening the population at risk – selective surgical approach to small non-palpable tumors and adjuvant treatments that become more and more specific for different types of patient. However, there will always be factors influencing a patient's prognosis and these should be taken into account in planning the follow-up.

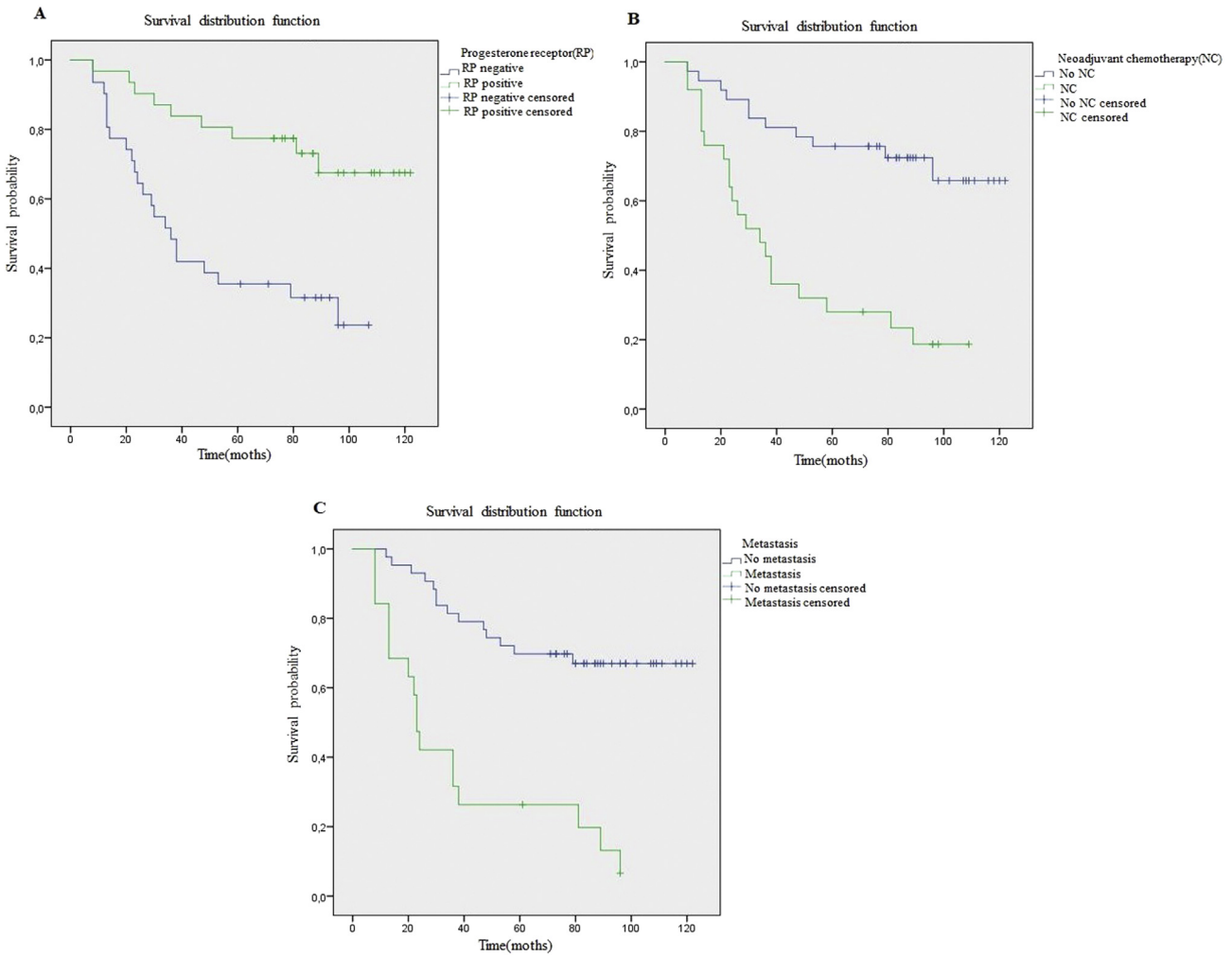

Figure 2 Survival probability curves. A result of negative progesterone receptor (A), the use of neoadjuvant therapy with chemotherapy (B) and the presence of disease at distant points (C) are factors that reduced overall survival ($p < 0.05$).

5. Conclusions

Patients treated with surgery for breast cancer should be closely monitored, especially during the first few years post-intervention, since most cases of relapse occur in that period. Conservative management of relapse is possible, provided that suitable margins can be obtained; supporters of this approach remark that this is the most important factor to consider. Almost half of patients suffering recurrence subsequently presented the disease at distant points, which reduced their quality of life and global survival. Certain factors may increase the aggressiveness of the disease, predict higher risk of relapse and determine the prognosis of recurrence; thus, these factors should be evaluated in order to enhance the therapeutic approach and life expectancy.

Author contributions

Tejera Hernández, Ana Alicia. Surgical intervention and patient follow-up, data search and collection, data processing, statistical analysis, drafting and preparation of the manuscript, bibliographic research and manuscript review.

Vega Benítez, Víctor Manuel. Surgical intervention and patient follow-up, data search and collection, drafting and preparation of the manuscript, bibliographic research and manuscript review.

Rocca Cardenas, Juan Carlos. Data processing, statistical analysis and bibliographic research.

Gutiérrez Giner, María Isabel. Surgical intervention and patient follow-up.

Díaz Chico, Juan Carlos. Data processing and statistical analysis.

Hernández Hernández, Juan Ramón. Surgical intervention and patient follow-up, drafting and preparation of the manuscript, bibliographic research and manuscript review.

Disclosure

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This article has been approved by the Ethics Committee of our hospital. Does not contain patient data or human experiments.

References

1. Engelhardt EG, Garvelink MM, De Haes JH, et al. Predicting and communicating the risk of recurrence and death in women with early-stage breast cancer: a systematic review of risk prediction models. *J Clin Oncol*. 2014;32:238—250.
2. Henry NL, Somerfield MR, Abramson VG, et al. Role of patient and disease factors in adjuvant systemic therapy decision making for early-stage, operable breast cancer: American society of Clinical oncology endorsement of CancerCare ontario guideline recommendations. *J Clin Oncol*. 2016;34:2303—2311.
3. Roué T, Labbé S, Belliardo S, et al. Predictive factors of the survival of women with invasive breast cancer in French guiana: the burden of health inequalities. *Clin Breast Cancer*. 2016;16:113—118.
4. Bosma SC, Van der Leij F, Van Werkhoven E, et al. Very low local recurrence rates after breast-conserving therapy: analysis of 8485 patients treated over a 28-year period. *Breast Cancer Res Treat*. 2016;156:391—400.
5. Fei F, Messina C, Slaets L, et al. Tumour size is the only predictive factor of distant recurrence after pathological complete response to neoadjuvant chemotherapy in patients with large operable or locally advanced breast cancers: a sub-study of EORTC 10994/BIG 1-00 phase III trial. *Eur J Cancer*. 2015;51:301—309.
6. Lester S, Bose S, Chen YY, et al. Protocol for the examination of specimens from patients with invasive carcinoma of the breast. *Arch Pathol Lab Med*. 2009;133:1515—1538.
7. Kolben T, Schwarz TM, Goess C, et al. Surgical management of ipsilateral breast tumor recurrence. *Int J Surg*. 2015;23:141—146.
8. Van Roozendaal LM, Smit LH, Duijsens GH, et al. Risk of regional recurrence in triple-negative breast cancer patients: a Dutch cohort study. *Breast Cancer. Res Treat*. 2016;156:465—472.
9. Strasser-Weippl K1, Goss PE. Competing risks in low-risk breast cancer. *Am Soc Clin Oncol Educ Book*. 2013:32—39.
10. Liu Y, Dong C, Chen L. The clinicopathological features of second primary cancer in patients with prior breast cancer. *Medicine (Baltim)*. 2017;96:e6675.
11. Trombetta M, Hannoun-Levi JM. Treatment of second ipsilateral breast tumor event: a need for a new type of evidence for avoiding mastectomy. *Eur J Surg Oncol*. 2017;43:849—850.
12. Tamura N, Tsuda H, Yoshida M, et al. Clinicopathological predictive factors for ipsilateral and contralateral events following initial surgery to treat ductal carcinoma in situ. *Breast Cancer*. 2016;23:510—518.
13. McGinity AC, Lautner MA, Jatoi I. Management of the clinically node-negative axilla in primary and locally recurrent breast cancer. *Surg Oncol Clin N Am*. 2014;23:463—471.
14. Wadasadawala T, Vadgaonkar R, Bajpai J. Management of isolated locoregional recurrences in breast cancer: a review of local and systemic modalities. *Clin Breast Cancer*. 2017;17:493—502.
15. Vila J, Garcia-Etienne CA, Vavassori A, et al. Conservative surgery for ipsilateral breast tumor recurrence. *J Surg Oncol*. 2014;110:62—67.
16. Maaskant-Braat AJ, Roumen RM, Voogd AC, et al. Sentinel node and recurrent breast cancer (SNARB): Results of a nationwide registration study. *Ann Surg Oncol*. 2013;20:620—626.
17. Houvenaeghel G, Classe JM, Garbay JR, et al. Survival impact and predictive factors of axillary recurrence after sentinel biopsy. *Eur J Cancer*. 2016;58:73—82.
18. Hasebe T, Iwasaki M, Hojo T, Kinoshita T, Tsuda T, Shibata T. Histological factors for accurately predicting first locoregional recurrence of invasive ductal carcinoma of the breast. *Cancer Sci*. 2013;104:1252—1261.
19. Lee SB, Yu JH, Park H, et al. Sentinel node biopsy after neoadjuvant chemotherapy for breast cancer with axillary node metastasis: a survey of clinical practice. *Asian J Surg*. 2018 Jul 23:30028—30029. https://doi.org/10.1016/j.asjsur.2018.06.004. pii: S1015-9584.
20. McBride A, Allen P, Woodward W, et al. Locoregional recurrence risk for patients with T1,2 breast cancer with 1-3 positive lymph nodes treated with mastectomy and systemic treatment. *Int J Radiat Oncol Biol Phys*. 2014;89:392—398.
21. Houssami N, Macaskill P, Marinovich ML, et al. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. *Ann Surg Oncol*. 2014;21:717—730.
22. Bodilsen A, Bjerre K, Offersen BV, et al. Importance of margin width in breast-conserving treatment of early breast cancer. *J Surg Oncol*. 2016;113:609—615.
23. Klein J, Kong I, Paszat L, et al. Close or positive resection margins are not associated with an increased risk of chest wallrecurrence in women with DCIS treated by mastectomy: a population-based analysis. *SpringerPlus*. 2015;4:335.
24. Zhang X, Dai H, Liu B, et al. Predictors for local invasive recurrence of ductal carcinoma in situ of the breast: a meta-analysis. *Eur J Cancer Prev*. 2016;25:19—28.
25. Rezai M, Kraemer S, Kimmig R, et al. Breast conservative surgery and local recurrence. *Breast*. 2015;24:100—107.
26. Hanagiri T, Nozoe T, Mizukami M. Clinicopathological characteristics of invasive lobular carcinoma of the breast. *Asian J Surg*. 2009;32:76—80.
27. Mao K, Yang Y, Wu W, et al. Risk of second breast cancers after lobular carcinoma in situ according to hormone receptor status. *PLoS One*. 2017;12:e0176417.
28. Lee RK, Kim HJ, Lee J. Role of breast magnetic resonance imaging in predicting residual lobular carcinoma in situ after initial excision. *Asian J Surg*. 2018;41:279—284.
29. Bogina G, Lunardi G, Coati F, et al. Progesterone receptor status and clinical outcome in breast cancer patients with estrogen receptor-positive locoregional recurrence. *Tumori*. 2015;101:398—403.
30. Ishitobi M, Okuno J, Kittaka N, et al. Distant recurrence risk after late ipsilateral breast tumor recurrence: Results of a retrospective, single-institution study. *Oncology*. 2015;89:269—274.
31. Mittendorf EA, Ardavanis A, Symanowski J, et al. Primary analysis of a prospective, randomized, single-blinded phase II trial evaluating the HER2 peptide AE37 vaccine in breast cancer patients to prevent recurrence. *Ann Oncol*. 2016;27:1241—1248.
32. Steward L, Conant L, Gao F, et al. Predictive factors and patterns of recurrence in patients with triple negative breast cancer. *Ann Surg Oncol*. 2014;21:2165—2171.

OBJETIVOS ESPECÍFICOS 2 Y 3

2. Estudiar los efectos de la radioterapia externa en la satisfacción y calidad de vida de las pacientes.

3. Establecer si la radioterapia externa de planificación invertida, es un factor que influye en la reconstrucción mamaria, los resultados estéticos finales y el grado de satisfacción de las pacientes comparándolo con el resto de pacientes no irradiadas en las que se ha utilizado la misma técnica quirúrgica.

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Inverse radiotherapy planning in reconstructive surgery for breast cancer.

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Original Research

Inverse radiotherapy planning in reconstructive surgery for breast cancer

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ABSTRACT

Background: Post-mastectomy radiotherapy reduces the risk of local-regional relapse and distant disease, and increases global survival in women with axillary involvement. With the new reconstruction techniques and increasing use of directed external radiotherapy, immediate reconstruction can be performed with good cosmetic results and low complication rates.

Materials and methods: Observational study with consecutive sampling conducted in patients undergoing reconstructive surgery for breast cancer, between 2010 and 2016, with a 12-months minimum follow-up period. A group of patients radiated after receiving an expander (RT-Expander) were compared with a control group of non-radiated patients (Non-RT), who had been treated with the same surgical technique. We compare general complications, reconstruction failure, aesthetic results and satisfaction degree with software IBM® SPSS® Statistics v. 21 and BREAST-Q scores.

Results: Reconstruction failure was observed in 15.6% of patients in a similar proportion in both groups. External radiotherapy was not an independent significant factor influencing the occurrence of general complications, capsular contracture grade ≥3 or reconstruction failure. The Kaplan-Meyer curve showed no differences in reconstruction survival between groups. Aesthetic results were excellent-very good in 78.1% of patients. Absence of a contralateral procedure for symmetrization, occurrence of general complications, occurrence of capsular contracture grade ≥3 and reconstruction failure were significantly associated to fair-poor cosmetic results. The satisfaction degree of operated patients was similar in both groups.

Conclusions: The evolution of external radiotherapy towards more directed techniques, which modulate the dose administered to the mammary tissue and adjacent structures, allowed us to make immediate reconstruction a reality for most patients, with complication rates, cosmetic results and satisfaction degrees similar to those of non-radiated patients.

1. Introduction

Conservative surgery is the most widely used surgical treatment in breast cancer [1]. However, 20–30% of patients will still require mastectomy, associated to breast reconstruction in most cases, for a complete treatment of their disease [2]. Breast reconstruction is aimed at recreating the original breast shape and volume, thus contributing to enhance cosmetic results and patient's quality of life [3]. Post-mastectomy radiotherapy reduces the risk of local-regional relapse and distant disease, and increases global survival in women with axillary involvement [4]. In former times, when the need for this adjuvant therapy was anticipated, breast reconstruction was delayed until the end of the treatment or even ruled out [4,5]. With the new reconstruction techniques and increasing use of directed external radiotherapy, immediate reconstruction can be performed with good cosmetic results and low complication rates [5,6].

Alloplastic reconstruction, by placing an expander and subsequently changing to a definitive prosthesis, is being increasingly chosen by

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several authors [6,7]. However, there is still controversy on the most suitable time for radiation, long-term cosmetic consequences and acceptable rates of reconstruction failure or capsular contracture for supporting and validating this technique [6–8]. A number of studies on this topic can be found in the current literature, although most of them are focused on the complications of radiation and do not establish a relationship with reconstruction failure, cosmetic results and, in particular, patient's satisfaction. The radiotherapy type to be used is also a much debated topic [9]. In the last decades, technological advances resulted in improved treatment planning and elimination of dose barriers usually affecting this type of patient [9,10].

The goal of this study was to establish whether inverted external radiotherapy planning, used in our hospital, is an influencing factor on breast reconstruction, final cosmetic results and patient's satisfaction, as compared with non-radiated patients undergoing the same surgical technique.

2. Material and method

Observational study with consecutive sampling conducted in patients undergoing surgery for breast cancer, with mastectomy and placement of an expander, which was subsequently changed to a definitive prosthesis. Included patients were treated between 2010 and 2016, with a 12-months minimum follow-up period, ending January 2018. A group of patients radiated after receiving an expander (RT-Expander) were compared with a control group of non-radiated patients (Non-RT), who had been treated with the same surgical technique. It is decided to administer adjuvant radiotherapy to patients with axillary involvement, positive margins or with tumors larger than 5 cm.

RT-Expander patients underwent mastectomy plus immediate placement of sub-muscular expander and musculofascial coverage, associated to an expansion of 50% total volume. Axillary emptying was conducted according to the results of the sentinel lymph node. Volume expansion was continued 14 days post-operative and CT simulation was conducted one month post-operative. If, at that moment, high tension was observed (expander could not be pinched or moved) it was partially emptied (minimum 50 cc) and tension was again assessed before CT simulation. The prescribed dose of external radiotherapy was 50 Gy standard fractionation (2 Gy fraction) both to the breast volume and the ipsilateral lymph node areas, when indicated. Inverse planning techniques were used for radiotherapy, such as volumetric modulated arc therapy (VMAT) or intensity-modulated radiation therapy IMRT, which allow taking expander valves and transition to healthy tissue into account, thus avoiding high-dose spots and enhancing dose homogeneity. The same surgical technique was used in Non-RT patients, performing weekly expansions according to patient's tolerance and completing breast reconstruction at the end.

Patients were examined at the doctor's office each month and data were retrospectively collected from the institutional database, except for those from the satisfaction questionnaire BREAST-Q, which was prospectively administered until August 2018. Patients who did not complete the questionnaire, those who abandoned follow-up before 12 months postoperative, those who had undergone previous conservative treatment including external radiotherapy and those who underwent replacement surgery in a different centre, were excluded from the study.

Demographic variables were classified and studied in a dichotomous way: age (≥50 years), body mass index (BMI ≥30), bra size (≥C), presence or absence of comorbidities (smoking, diabetes mellitus and blood hypertension), follow-up time and survival time. Axillary procedure and bilaterality of reconstruction were also evaluated, as well as the occurrence of complications (hematoma, seroma, necrosis, infection, contracture and exposure). Reconstruction failure was defined as the loss of the expander or the definitive prosthesis during postoperative follow-up. The same type of expander and prosthesis were used in all cases.

Capsular contracture was classified into two groups according to the Baker scale [11] (Grade I-II/Grade III-IV). Cosmetic results were evaluated by the surgeon according to a 4-category scale (excellent, very good, fair, poor), where excellent and very good were associated, as well as fair and poor, in order to reduce sample dispersion.

Radiotherapy-associated variables were analyzed with the Mann-Whitney *U* test for numerical variables and the Fisher's exact test for dichotomous variables, with significance considered for $p < 0,05$. Kaplan-Meyer survival curve was obtained for reconstruction by using the Long Rank (Mantel-Cox) test. The IBM® SPSS® Statistics v. 21 software was used.

Besides radiotherapy, other facts potentially affecting cosmetic results were evaluated (age, BMI, bra size, bilaterality, occurrence of general postoperative complications, capsular contracture and reconstruction failure) by using the Fisher's exact test.

Finally, patient satisfaction degree was evaluated by using the BREAST-Q questionnaire (reconstruction module), which was applied a minimum of one year after the end of adjuvant treatment [12]. The used scales included satisfaction with breasts, satisfaction with results, psychosocial wellbeing, sexual wellbeing and physical wellbeing. Questionnaire results were converted into a 0–100 scale, where the latter corresponded to maximum satisfaction degree. These results were related to the use of external radiotherapy by using the statistical analysis system QScore software (V1.0 of the Breast-Q).

The work has been reported in line with the STROCSS criteria [13].

3. Results

The study included 64 patients: 41 (Non-RT) y 23 (RT-Expander) (Table 1). Demographic characteristics were similar for both groups; no significant differences were found in age, BMI and bra size. Comorbidities occurred in almost half of the patients in each group (p: NS). The most frequent axillary procedure (80% of cases) was sentinel lymph node biopsy (SLNB); no differences were found between groups. Procedure bilaterality, mean follow-up time and mean replacement time were similar for both groups (p: NS).

Complications occurred in 20.3% of patients (Table 2): 19.5% Non-RT and 21.7% RT-Expander, including: hematoma, seroma, necrosis,

Table 1
Characteristics of the patients n = 64.

	Non-RT n = 41(%)	Expander-RT n = 23(%)	p
Age			0.598
≥50	23(56,1)	15(65,2)	
< 50	18(43,9)	8(34,8)	
Body mass index			1000
≥30	18(43,9)	10(43,5)	
< 30	23(56,1)	13(56,5)	
Bra size			0.794
≥C	16(39,1)	10(43,5)	
< C	25(60,9)	13(56,5)	
Comorbidities[a]			0.291
Yes	19(46,3)	7(30,4)	
No	22(53,7)	16(69,6)	
Axillary procedure			0.148
SLNB	37(90,2)	17(73,9)	
Lymph node dissection	4(9,8)	6(26,1)	
Laterality			1000
Unilateral	8(19,5)	5(21,7)	
Bilateral	33(80,5)	18(78,3)	
Mean follow up time (months)	54,97 (DE 24,76)	43,96 (DE 20,70)	0.134
Mean time of exchange[b]	13,15(DE 8.04)	13,13(DE 8047)	0.887

[a] Mellitus diabetes, arterial hypertension or smoker; SLNB: Sentinel lymph node biopsy.

[b] Mean interval time between expansor insertion and exchange to implant (months).

Table 2
Complications rates.

	Non-RT n = 41(%)	Expander-RT n = 23(%)	p
General complications[a]			0.831
Yes	8(19,5)	5(21,7)	
No	33(80,5)	18(78,3)	
Capsular contracture			0.474
Grade ≥ 3	5(12,2)	5(21,7)	
Grade < 3	36(87,8)	18(78,3)	
Reconstructive failure			1000
Yes	6(14,6)	4(17,3)	
No	35(85,4)	19(82,7)	

[a] Hematoma, seroma, necrosis, infection, exposure.

infection, exposure, capsular contracture or reconstruction failure, with no significant differences between groups. Capsular contracture grade ≥3 was more frequent in the RT-Expander group (21.7% vs. 12.1% Non-RT), although differences were not statistically significant (p:NS). Reconstruction failure was observed in 15.6% of patients in a similar proportion in both groups (17.3% RT-Expander vs. 14.6% Non-RT; p:NS). External radiotherapy was not an independent significant factor influencing the occurrence of general complications, capsular contracture grade ≥3 or reconstruction failure.

The Kaplan-Meyer curve (Fig. 1) showed no differences in reconstruction survival between groups (RT-Expander vs. Non-RT; p:0.097).

Aesthetic results were excellent-very good in 78.1% of patients. Table 3 shows the cosmetic results. No differences were found in RT-Expander patients: 36% excellent-very good vs. 35.7% fair-poor, p:NS. Age ≥50 was a significant factor for obtaining excellent to very good results p: 0.013. Body mass index and breast size (measured through the bra size) were not significant variables p:NS. Absence of a contralateral procedure for symmetrization, occurrence of general complications, occurrence of capsular contracture grade ≥3 and reconstruction failure were significantly associated to fair-poor cosmetic results. The

Table 3
Aesthetic results.

	Excellent- very good n = 50(%)	Fair-poor n = 14(%)	p
Age			0.013
≥50	34(68,0)	4(28,6)	
< 50	16(32,0)	10(71,4)	
Body mass index			0.762
≥30	21(42,0)	7(50,0)	
< 30	29(58,0)	7(50,0)	
Bra size			0.064
≥C	17(34,0)	9(64,3)	
< C	33(66,0)	5(35,7)	
Laterality			**0,000**
Unilateral	4(8,0)	9(64,3)	
Bilateral	46(92,0)	5(35,7)	
General complications[a]			**0,000**
Yes	4(8,0)	9(64,3)	
No	46(92,0)	5(35,7)	
Capsular contracture			**0,000**
Grade ≥ 3	3(6,0)	7(50,0)	
Grade < 3	47(94,0)	7(50,0)	
Reconstructive failure			**0,000**
Yes	0(0,0)	10(71,4)	
No	50(100,0)	4(28,6)	
Postmastectomy radiotherapy			1000
Yes	18(36,0)	5(35,7)	
No	32(64,0)	9(64,3)	

The numbers in bold are the statistically significant results.
[a] Hematoma, seroma, necrosis, infection, exposure.

satisfaction degree of operated patients was similar in both groups. No significant differences related to the use of radiotherapy during reconstruction were observed (Table 4). During follow-up, a case of locoregional relapse was observed in the non-irradiated group of patients. Besides, in the same group three patients presented distant metastases, currently undergoing chemotherapy treatment. External radiotherapy

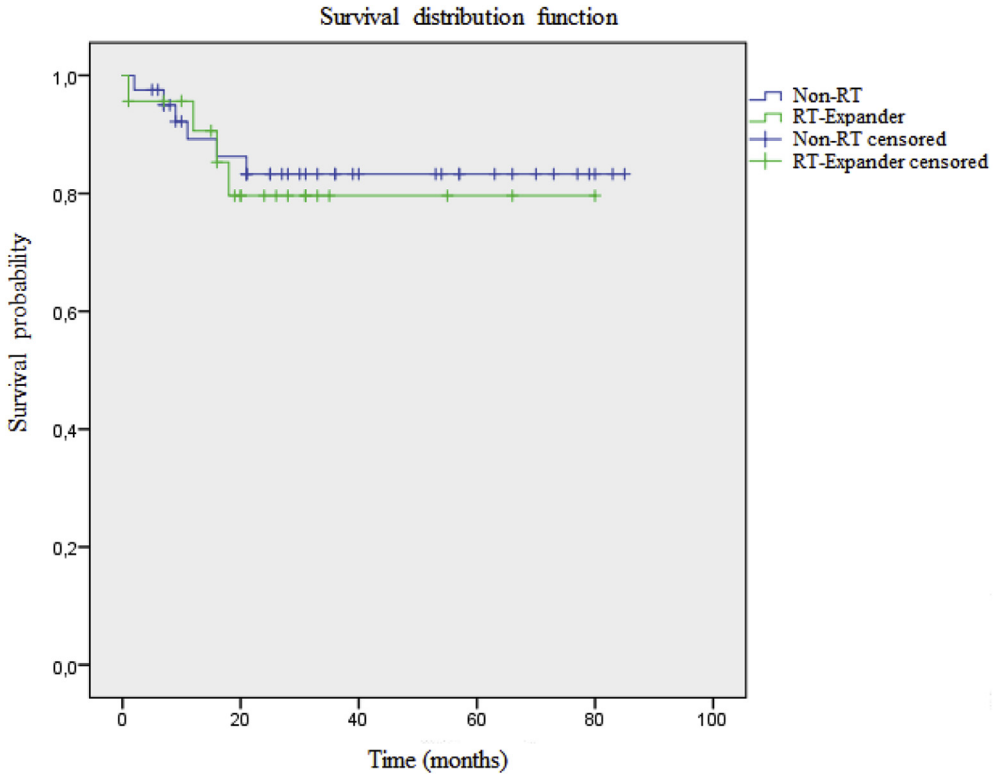

Fig. 1. Reconstruction survival probability curves. The Kaplan-Meyer curve showed no differences between groups (RT-Expander vs. Non-RT; p:0.097).

Table 4
BREAST-Q scores.

BREAST-Q Scale	Non-RT n = 41	Expander-RT n = 23	p
Satisfaction with breasts	70,8	59,1	0,075
Satisfaction with outcome	75,8	79,3	0,611
Psychosocial well-being	85,1	90,9	0,191
Sexual well-being	73,1	76,9	0,513
Physical well-being	72,6	73,0	1000

was not a significant independent factor influencing the presence of locoregional relapse or distant disease.

4. Discussion

Immediate reconstruction reduces psychological impact and enhances quality of life in patients who undergo mastectomy [3]. External radiotherapy induces deterioration of endothelial cells and micro-circulation, which alters skin annexes, degenerates smooth muscle and increases subcutaneous fibrosis [9]. Planning a suitable radiotherapy treatment should cover the target volume to be treated (reconstructed breast, associated or not to the thoracic wall and ipsilateral lymph node areas) with the total prescribed dose, while minimizing the dose received by adjacent healthy tissues (heart, lungs and contralateral breast) [9,10]. In earlier times, it was the general opinion that reconstruction hindered the technical capacity for achieving optimal radiotherapy plans [9]. Such a concept has changed due to the results from a number of studies [10,14], which demonstrated that modifications in the standard fields of radiotherapy planning allow for better dosages.

The emergence of inverse planning techniques (VMAT or IMRT) which consist of multiple fields defined for reconstruction of the volume to be treated allowed for reduction of high-dose spots on healthy tissues and homogenization of dose distribution [14,15]. Combining both techniques and performing them with inspiratory breath holding contributed to improve radiotherapy planning [14–17].

There are some technical challenges to using these treatments during breast reconstruction. Radiation to the internal mammary chain, which is close to the heart, as well as bilateral breast reconstruction, are the largest technical difficulties, the first one being the most determining factor [14]. The presence of bilateral implants increases difficulty planning because the contralateral breast is considered a risk organ that should not be radiated, although its presence does not hinder the quality of the administered radiotherapy [18]. The future of external radiotherapy in breast reconstruction will probably be based on the use of hybrid techniques with conformal dose and breath-holding.

In our study, this type of radiation was administered to two groups, which were rather homogeneous in age, body mass index, bra size, comorbidities, axillary procedure and laterality of the intervention. Furthermore, the same technique was used in all patients, alloplastic reconstruction in two phases. The lack of differences in such variables allows us to establish that the observed results were not influenced by them.

The mean follow-up time was in line with other studies [5,6,19] i.e. 43.9 months for RT-Expander vs. 54.9 months for Non-RT, which seems to be sufficient to obtain significant results in the short and medium-term. The mean replacement time in radiated patients (13.13 months) was very similar to that of other authors [6,20], whereas it was rather longer in non-radiated patients (13.15 months). The delay was probably due to the fact that patients had to wait to receive adjuvant chemotherapy and, since our hospital is a public health centre, to restricted availability of operating room for the second surgery.

Results showed that RT-Expander patients had a similar rate (slightly higher) of general complications 21.7% vs. 19.5% Non-RT, with differences not reaching statistical significance. Complications reported in the literature [8,21] range between 2 and 94% depending on the criteria used to classify them. Our rate was acceptable since all complications were included, even capsular contracture of any degree and reconstruction failure.

Severe capsular contracture may occur in up to 30% radiated patients [11]. Modulated intensity radiotherapy and volumetric arc therapy allow for complex dose distributions with enhanced safety and minimized times, thus reducing the aggressiveness of the expander [16,22]. Moreover, since the expander – but not the definitive prosthesis – is radiated, wide capsulotomy may be performed during replacement surgery, thus reducing the rates of severe capsular contracture [6]. Performing capsulotomy after radiotherapy may additionally enhance cosmetic results by eliminating potential defects produced by radiation and adjusting the skin and tissues to the definitive implant [6,20]. A further technical detail that might reduce capsular contracture consists in irrigating the prosthesis with povidone-iodine, although studies on this topic are scarce [23].

Reconstruction failure may vary between 4 and 45% with a variety of associated factors in every study [6,20,24]. Infection was the most common complication before removing the expander or the prosthesis, occurring in 80% of cases. Although breast surgery is considered clean surgery, 5–10% infection rates have been reported, in particular in patients receiving neoadjuvant chemotherapy [25,26]. We routinely used antibiotic prophylaxis in patients undergoing breast reconstruction. Higher infection rates than expected for clean surgery have been increasingly observed in breast surgery, possibly due to biofilm formation from mammary duct endogenous microbiota contaminating the operated tissues [27]. Infection may be treated with antibiotics for a prolonged period but, in our cases, we preferred removing the prosthetic material prematurely and offering a delayed reconstruction. Extrusion was the second most frequent complication leading to reconstruction failure. In our experience, this complication must be quickly treated. Although the defect could be covered with a skin flap [28], we preferred premature removal. Only 30% of patients with reconstruction failure chose a new reconstruction with autologous tissue.

Cosmetic outcomes depend on the chosen technique, adjuvant treatments and patient's expectations. Radiotherapy may alter such results depending on the chosen radiation technique, administered dose, and whether or not a boost to the tumor bed is performed. However, further prospective clinical trials are needed to analyze these parameters [6,16]. Radiating the expander with only a half of the volume, could be a beneficial factor for the quality of reconstruction [29]; thus we always do so in our protocol, however with the disadvantage of increasing the waiting time for replacement. Furthermore, radiating in this way produces better cosmetic results, although with higher reconstruction failure rates. Both factors support the results observed in our case series.

Age is another factor to be taken into account. Older patients showed better cosmetic results probably because of lower expectations; as opposite to higher thoroughness shown by surgeons in younger patients [30]. Symmetrization has to be conducted during replacement surgery in order to minimize final differences between both breasts [20]. Furthermore, previous errors may be corrected and it is possible to work with tissues of a real quality [20,31]. This factor was important for producing good breast reconstructions in our series.

The consequences of complications are variable and may produce visible alterations in the breast, such as deformities or hypertrophic scars [21]. Severe capsular contracture increases breast firmness, which produces a distorted shape and increases asymmetry, thus impairing the basic objective of reconstruction [11,27]. Loss of the expander or the prosthesis leads to delays in the reconstruction process with alterations to the skin and tissues to be used, which may occasionally be irreversible, as well as to the need for several surgical interventions to achieve resolution [6,8,21]. All of these factors described in the literature showed positive correlation with unfavorable cosmetic results in our patients.

Overall, the results of our study should be interpreted cautiously,

since they come from the experience in only one centre, with a restricted number of cases. Although follow-up time was long, a longer period of study could lead to an increased number of cases of capsular contracture and to worse cosmetic results, given that such factors tend to worsen with the years, in most series. Assessment of cosmetic results by surgeons might be subjective and vary with the time, as well as influenced by personal experience and initial expectations. It must be considered that in the current literature there are studies reporting a higher index of adverse events and complications, in some cases associated with a decrease in satisfaction and cosmetic results. Most of these studies do not specify the type of radiation therapy used and the selection of the surgical technique is very varied, therefore it is difficult to compare our results [32,33].

Patients' satisfaction was evaluated during follow-up, through the BREAST-Q scores. Most of our patients showed high satisfaction degree and the use of external radiotherapy was not a factor influencing satisfaction. However, although patients are satisfied at present, longer term follow-up is required to assess whether any additional surgical procedure will be needed to maintain the quality of reconstruction, a topic that few authors have been able to study [34,35]. Furthermore, the personal experience of a patient through diagnosis and treatment of her disease is a subjective factor that may influence her satisfaction and cannot be objectively measured.

5. Conclusion

The evolution of external radiotherapy towards more directed techniques, which modulate the dose administered to the mammary tissue and adjacent structures, allowed us to make immediate reconstruction a reality for most patients, with complication rates, cosmetic results and satisfaction degrees similar to those of non-radiated patients. Multidisciplinary coordination between surgery and radiotherapy teams is essential for producing good results. Early identification of factors that are unfavorable to reconstruction is essential for surgical planning in these patients. A correct selection of patients and surgical technique, together with adequate previous information, allows us to develop realistic expectations on breast reconstruction, which lead to higher satisfaction and enhanced quality of life.

Ethical approval

This study is aprove for the ethical comit of our hospital and is only a observational study.

Sources of funding

Authors declare dont have any funding.

Author contribution

Tejera Hernández, Ana Alicia[1,2]. Surgical intervention and patient follow-up, data search and collection, data processing, statistical analysis, drafting and preparation of the manuscript, bibliographic research and manuscript review.

Vega Benítez, Víctor Manuel[1,2]. Surgical intervention and patient follow-up, data search and collection, drafting and preparation of the manuscript, bibliographic research and manuscript review.

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Rodriguez Ibarria, Nieves[1,3] Drafting and preparation of the manuscript, bibliographic research.

Gutiérrez Giner, María Isabel[1,2]. Surgical intervention and patient follow-up.

Pérez Correa, Pedro[1,2]. Surgical intervention and patient follow-up, data search and collection.

Diaz Chico, Juan Carlos[1]. Data processing and statistical analysis.

Hernández Hernández, Juan Ramón[1,2]. Surgical intervention and patient follow-up, drafting and preparation of the manuscript, bibliographic research and manuscript review.

Conflicts of interest

Authors declare no conflict of interest.

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Data statement

We are not linking to or uploading our research data.

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This article has been approved by the Ethics Committee of our hospital. Does not contain patient data or human experiments.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.01.017.

References

[1] C.B. Matsen, L.A. Neumayer, Breast cancer: a review for the general surgeon, JAMA Surg 148 (2013) 971–979.
[2] D.R. Van, T.R. Lopez, R.J. Schipper, M.H. Martens, J. Serroyen, M.B. Lobbes, et al., No increase of local recurrence rate in breast cancer patients treated with skin-sparing mastectomy followed by immediate breast reconstruction, Breast 22 (2013) 1166–1170.
[3] B. Kaya, S. Serel, Breast reconstruction, Exp. Oncol. 35 (2013) 280–286.
[4] J.S. Haviland, J.R. Owen, J.A. Dewar, R.K. Agrawal, J. Barrett, P.J. Barrett-Lee, et al., The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials, Lancet Oncol. 14 (2013) 1086–1094.
[5] H.M. Kuerer, P.G. Cordeiro, R.W. Mutter, Optimizing breast cancer adjuvant radiation and integration of breast and reconstructive surgery, Am Soc Clin Oncol Educ Book 37 (2017) 93–105.
[6] P.G. Cordeiro, C.R. Albornoz, B. McCormick, C.A. Hudis, Q. Hu, A. Heerdt, et al., What is the optimum timing of postmastectomy radiotherapy in two-stage prosthetic reconstruction: radiation to the tissue expander or permanent implant? Plast. Reconstr. Surg. 135 (2015) 1509–1517.
[7] J.H. Yun, R. Diaz, A.G. Orman, Breast reconstruction and radiation therapy, Cancer Control 25 (2018) 1073274818795489.
[8] A. Momoh, R. Ahmed, B.P. Kelley, O. Aliu, K.M. Kidwell, J.H. Kozlow, et al., A systematic review of complications of implant-based breast reconstruction with prereconstruction and postreconstruction radiotherapy, Ann. Surg. Oncol. 21 (2014) 118–124.
[9] S.B. Motwani, E.A. Strom, N.R. Schechter, The impact of immediate breast reconstruction on the technical delivery of postmastectomy radiotherapy, Int. J. Radiat. Oncol. Biol. Phys. 66 (2006) 76–82.
[10] E. Chung, R.B. Marsh, K.A. Griffith, J.M. Moran, L.J. Pierce, Quantifying dose to the reconstructed breast: can we adequately treat? Med. Dosim. 38 (2013) 55–59.
[11] S.L. Spear, J.L. Baker Jr., Classification of capsular contracture after prosthetic breast reconstruction, Plast. Reconstr. Surg. 96 (1995) 1119–1123.

[12] L. Mundy, K. Homa, A. Klassen, A. Pusic, C. Kerrigan, Breast cancer and reconstruction: normative data for interpreting the BREAST-Q, Plast. Reconstr. Surg. 139 (2017) 1046–1055.
[13] R.A. Agha, M.R. Borrelli, M. Vella-Baldacchino, R. Thavayogan, D.P. Orgill, for the STROCSS Group, The STROCSS statement: strengthening the reporting of cohort studies in surgery, Int. J. Surg. 46 (2017) 198–202.
[14] N. Ohri, P.G. Cordeiro, J. Keam, Quantifying the impact of immediate reconstruction in postmastectomy radiation: a large, dose-volume histogram-based analysis, Int. J. Radiat. Oncol. Biol. Phys. 84 (2012) 153–159.
[15] R.B. Jimenez, C. Goma, J. Nyamwanda, Intensity modulated proton therapy for postmastectomy radiation of bilateral implant reconstructed breasts: a treatment planning study, Radiother. Oncol. 107 (2013) 213–217.
[16] A.Y. Ho, Z.I. Hu, B.J. Mehrara, E.G. Wilkins, Radiotherapy in the setting of breast reconstruction: types, techniques and timing, Lancet Oncol. 18 (2017) 742–753.
[17] M.J. Parkes, S. Green, A.M. Stevens, T.H. Clutton-Brock, Assessing and ensuring patient safety during breath-holding for radiotherapy, Br. J. Radiol. 87 (2014) 20140454.
[18] A.Y. Ho, N. Patel, N. Ohri, et al., Bilateral implant reconstruction does not affect the quality of postmastectomy radiation therapy, Med. Dosim. 39 (2014) 18–22.
[19] S.L. Spear, A. Majidian, Immediate breast reconstruction in two stages using textured, integrated-valve tissue expanders and breast implants: a retrospective review of 171 consecutive breast reconstructions from 1989 to 1996, Plast. Reconstr. Surg. 101 (1998) 53–63.
[20] P.G. Cordeiro, C.M. McCarthy, A single surgeon's 12- year experience with tissue expander/implant breast reconstruction: part I. A prospective analysis of early complications, Plast. Reconstr. Surg. 118 (2006) 825–831.
[21] S.H. Voineskos, S.G. Frank, P.G. Cordeiro, Breast reconstruction following conservative mastectomies: predictors of complications and outcomes, Gland Surg. 4 (2015) 484–496.
[22] A.T. Falk, P. Fenoglietto, D. Azria, C. Bourgier, New external radiotherapy technologies for breast cancer, Cancer Radiother. 18 (2014) 480–485.
[23] G.C. Yalanis, E.W. Liu, H.T. Cheng, Efficacy and safety of povidone-iodine irrigation in reducing the risk of capsular contracture in aesthetic breast augmentation: a systematic review and meta-analysis, Plast. Reconstr. Surg. 136 (2015) 687–698.
[24] P.R. Anderson, G. Freedman, N. Nicolaou, et al., Postmastectomy chest wall radiation to a temporary tissue expander or permanent breast implant–is there a difference in complication rates? Int. J. Radiat. Oncol. Biol. Phys. 74 (2009) 81–85.
[25] A. Teija-Kaisa, M. Eija, S. Marja, L. Outi, Risk factors for surgical site infection in breast surgery, J. Clin. Nurs. 22 (2013) 948–957.
[26] A. Hamahata, K. Kubo, H. Takei, T. Saitou, Y. Hayashi, H. Matsumoto, et al., Impact of immediate breast reconstruction on postoperative adjuvant chemotherapy: a single center study, Breast Canc. 22 (2015) 287–291.
[27] R.N. Wixtrom, R.L. Stutman, R.M. Burke, A.K. Mahoney, M.A. Codner, Risk of breast implant bacterial contamination from endogenous breast flora, prevention with nipple shields, and implications for biofilm formation, Aesthet. Surg. J. 32 (2012) 956–963.
[28] M.D. Prince, J.S. Suber, M.L. Aya-Ay, J.D. Cone Jr., J.N. Greene, D.J. Smith Jr.et al., Prosthesis salvage in breast reconstruction patients with periprosthetic infection and exposure, Plast. Reconstr. Surg. 129 (2012) 42–48.
[29] J. Berbers, A. van Baardwijk, R. Houben, E. Heuts, M. Smidt, K. Keymeulen, et al., Reconstruction: before or after postmastectomy radiotherapy?' A systematic review of the literature, Eur. J. Cancer 50 (2014) 2752–2762.
[30] J.E. Vogel, C. Chu, M. McCullough, E. Anderson, A. Losken, G.W. Carlson, Breast cancer in women under age 40 years: treatment by total mastectomy and reconstruction, Ann. Plast. Surg. 66 (2011) 557–560.
[31] S.N. Razdan, H. Panchal, C.R. Albornoz, A.L. Pusic, C.C. McCarthy, P.G. Cordeiro, et al., Impact of contralateral symmetry procedures on long-term patient-reported outcomes following unilateral prosthetic breast reconstruction, J. Reconstr. Microsurg. (2018 Aug 12), https://doi.org/10.1055/s-0038-1667365.
[32] L.J. Magill, F.P. Robertson, G. Jell, A. Mosahebi, M. Keshtgar, Determining the outcomes of post-mastectomy radiation therapy delivered to the definitive implant in patients undergoing one- and two-stage implant-based breast reconstruction: a systematic review and meta-analysis, J. Plast. Reconstr. Aesthetic Surg. 70 (2017) 1329–1335.
[33] R. Jagsi, A.O. Momoh, J. Qi, J.B. Hamill, J. Billig, H.M. Kim, et al., Impact of radiotherapy on complications and patient-reported outcomes after breast reconstruction, J. Natl. Cancer Inst. 110 (2018) 157–165.
[34] G. Santos, C. Urban, M.I. Edelweiss, G. Zucca-Matthes, V.M. de Oliveira, G.H. Arana, et al., Long-term comparison of aesthetical outcomes after oncoplastic surgery and lumpectomy in breast cancer patients, Ann. Surg. Oncol. 22 (2015) 2500–2508.
[35] W.A. Cohen, L.R. Mundy, T.N. Ballard, A. Klassen, S.J. Cano, J. Browne, et al., The BREAST-Q in surgical research: a review of the literature 2009-2015, J. Plast. Reconstr. Aesthetic Surg. 69 (2016) 149–162.

OBJETIVO ESPECÍFICO 3

Definir los factores que influyen en la presencia de complicaciones quirúrgicas de los pacientes intervenidos por cáncer de mama asociado a el uso de radioterapia intraoperatoria de rayos X de bajo voltaje, identificando las posibles recaídas locales que se presentaran durante el seguimiento de estas.

Articulo:

Complications and local relapse after intraoperative low-voltage X-ray radiotherapy in breast cancer.

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Complications and local relapse after intraoperative low-voltage X-ray radiotherapy in breast cancer

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Purpose: To study those factors that influence the occurrence of surgical complications and local relapse in patients intervened for breast cancer and receiving intraoperative radiotherapy.
Methods: Observational study on patients intervened for breast cancer with conservative surgery and intraoperative radiotherapy with low-voltage X-ray energy source (INTRABEAM), from 2015 to 2017 with 24 months minimum follow-up. Variables possibly associated to the occurrence of postoperative complications were analyzed with the Student t-test and the Fisher exact test; $P < 0.05$ considered significant. Subsequently, the construction of multiple multivariate analysis models began, thus building a logistic regression analysis using the IBM SPSS Statistics ver. 23 software. Local relapse was described.
Results: The study included 102 patients, mean age of 61.2 years; mean global size of tumor, 12.2 mm. Complications occurred in 29.4%. Fibrosis was the most frequently observed complication, followed by postoperative seroma. Using a 45 mm or larger applicator were significantly associated with the occurrence of complications. Tumor size 2 cm or larger and reintervention showed borderline significant association. Only one case of local relapse was observed.
Conclusion: Certain factors may increase the risk of complication after the use of intraoperative radiotherapy. Using external complementary radiotherapy does not seem to increase the rate of complications. Select patients and the involvement of a multidisciplinary team are essential for achieving good results.
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Key Words: Breast neoplasms, Complications, Local neoplasm recurrence, Radiotherapy

INTRODUCTION

Intraoperative radiotherapy (IORT) is based on the administration, during surgical intervention, of a single dose of ionizing radiation directly on the surgical tumorectomy cavity, with the aim of enhancing local control of the disease, while reducing secondary toxicity to the surrounding tissues, which results from radiation [1]. This technique enhances identification of an exact location to apply the radiation boost and reduces the time interval between surgery and radiation. Given that patients are radiated while they are under anesthesia, errors occasioned by the patient's movements or by wrong positioning

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are almost inexistent [2]. This technique has been used both as a boost to conventional external radiotherapy (ERT) and as the only treatment at initial stages of breast cancer [2,3]. The biological efficacy of an IORT dose is equivalent to that of the conventional administration of an ERT dose fractionated 2–3 times higher. When a 45- to 50-Gy doses of ERT is used in combination with a 10- to 20-Gy dose of IORT, higher rates of local control of the disease are attained, especially regarding the control of residual disease [4].

There are different types of IORT. Using a 50-kV X-ray energy source is a standard procedure carried out in a number of hospitals in our area, whose short- and long-term surgical complications have been scarcely described in the current literature [5,6]. Possible complications from a conservative surgical intervention for breast cancer might worsen from using this type of radiation [7]. Thus, studying demographic and technical factors that may influence such complications is essential for adequate planning of a multidisciplinary treatment.

The goal of this study was to establish what factors influence the occurrence of surgical complications in patients undergoing breast cancer surgical intervention, associated with low-voltage X-ray IORT. Additionally, identification of possible cases of local relapse during follow-up was pursued.

METHODS

This was an observational study with consecutive sampling, on patients intervened for breast cancer with conservative surgery and IORT with low-voltage X-ray energy source (máximo 50 kV) con el dispositivo Intrabeam (Carl Zeiss Meditec, Oberkochen, Alemania), from 2015 to 2017 with 24 months minimum follow-up, which terminated in 2019. A group of irradiated patients, who presented postoperative complications (IORT-COM) were compared with a second group of patients, who had been irradiated with the same technique but did not present complications in follow-up (IORT). Furthermore, the number of patients presenting local relapse and the characteristics possibly influencing its occurrence were determined.

Inclusion criteria were selected following the protocol of the multicenter controlled randomized clinical trial TARGIT-A. This study presents a long-term follow-up and its criteria are the most used internationally in the application of intraoperative low-voltage X-ray radiotherapy [2,3]. Based on this, the inclusion criteria were: patients had to be 46 years old or older, with unifocal tumor of 3 cm or smaller, histological results corresponding to infiltrating carcinoma (except lobular), clinically and radiologically negative results in axilla and positive hormonal receptors.

All patients were managed with the same irradiation technique. An initial measurement of the cavity was carried out with a simulation CT in order to estimate the magnitude of the volume to be irradiated and the applicator to be used. Subsequently, tumorectomy was conducted and the breast tissue around the cavity was adjusted to the sphere used to apply radiation by making a tobacco-pouch. After verifying that the placement was correct and the margins were adequate, through intraoperative assessment, a single radiation dose of 20 Gy was applied on the applicator surface, which corresponded to 5–7 Gy at 1-cm depth. Dosage and treatment time varied depending on the applicator size. Finally, the applicator was removed and the incision was closed. The treatments lasted from 15 to 45 minutes depending on the source and the applicator.

Subsequently, depending on the definitive histological findings (unexpected lobular carcinoma, surgical margins involved, lymph node involvement, or surgical reintervention), additional complementary ERT could be applied. Patients, who failed to complete the follow-up, those who did not meet the inclusion criteria, and those who refused to complete the complementary treatments established in the above protocol, were excluded from the study. Patients were followed up in outpatient clinics and their data were collected retrospectively from the institutional database.

Complication was defined for any alteration of the expected course of both the local and systemic response [8]. The identification of this was done by the surgeon through direct observation during the entire postoperative follow-up of the patient (2 years).

Complications which emerged during the follow-up period were identified (seroma, hematoma, infection, dehiscence, necrosis, or fibrosis) and described as percentages according to their relevance. Additionally, the relationship between the occurrence of complications and the use of complementary ERT was studied, in order to evaluate possible differences between patients managed exclusively with intraoperative radiotherapy (IORT-EX) and those requiring complementary external radiotherapy (IORT-CER).

Demographic variables were classified and studied dichotomously: age (≥70 years), size (≥T2), axillary

Table 1. Mean age, applicator size and months freer of disease (n = 102)

Variable	IORT (n = 72)	IORT-COM (n = 30)	P-value
Age (yr)	60.86 ± 8.05	61.6 ± 8.72	0.91
Applicator size (mm)	38.06 ± 5.47	38.67 ± 5.24	0.43
Period free of disease (mo)	28.88 ± 9.83	29.6 ± 10.6	0.46

Values are presented as mean ± standard deviation.
IORT, intraoperative radiotherapy; COM, complications.

Table 2. Patient characteristics

Variable	Complications		P-value
	Absent (IORT)	Present (IORT-COM)	
No. of cases	72 (71)	30 (29)	
Age (yr)			0.860
<70	61 (85)	25 (83)	
≥70	11 (15)	5 (17)	
Tumor size (mm)			0.053
<20	67 (93)	24 (80)	
≥20	5 (7)	6 (20)	
Lymph node status			0.494
Positive	19 (26)	6 (20)	
Negative	53 (74)	24 (80)	
Radioguided surgery			0.119
Yes	31 (43)	18 (60)	
No	41 (57)	12 (40)	
Applicator size (mm)			0.028
<45	60 (83)	19 (63)	
≥45	12 (17)	11 (37)	
Ductal carcinoma *in situ*			0.412
Yes	32 (44)	16 (53)	
No	40 (56)	14 (47)	
Histological grade			0.366
<G2	43 (60)	15 (50)	
≥G2	29 (40)	15 (50)	
Lymphovascular involvement			0.192
Yes	26 (36)	15 (50)	
No	46 (64)	15 (50)	
Progesterone receptor			0.592
Positive	62 (86)	27 (90)	
Negative	10 (14)	3 (10)	
Ki67%			0.178
Positive	24 (33)	6 (20)	
Negative	48 (66)	24 (80)	
HER2			0.431
Positive	7 (10)	1 (3)	
Negative	65 (90)	29 (97)	
Margins (mm)			0.500
<1	17 (24)	9 (30)	
≥1	55 (76)	21 (70)	
Reintervention			0.075
Yes	1 (1)	3 (10)	
No	71 (99)	27 (90)	
Adjuvant chemotherapy			0.259
Yes	25 (35)	7 (23)	
No	47 (65)	23 (77)	
Complementary external radiotherapy			0.776
Yes	31 (43)	12 (40)	
No	41 (57)	18 (60)	
Local relapse			0.517
Yes	1 (1)	0 (0)	
No	71 (99)	30 (100)	

Values are presented as number (%).
IORT, intraoperative radiotherapy; COM, complications.

involvement, presence of associated *in situ* carcinoma, lymphovascular infiltration (LVI), histological grade, ki 67%, hormonal receptors, Her 2, close margin (≤1 mm), radioguided surgery, applicator size (≥45 mm); as well as the occurrence of complications, surgical reintervention, use of complementary ERT, chemotherapy or local relapse.

Variables possibly associated with the occurrence of postoperative complications were analyzed by using the Student t-test for numerical variables and the Fisher exact test for dichotomous ones; $P < 0.05$ was considered significant. Subsequently, the construction of multiple multivariate analysis models began, thus building a logistic regression analysis. The statistical analysis was conducted with the IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA). Finally, the main characteristics of patients with relapse were evaluated, and possible differences, as compared to patients without relapse, were identified.

This study was approved by Complejo Hospitalario Universitario Insular Materno Infantil Institution Review Board (IRB) with the number 2019-293-1.

RESULTS

The study included 102 patients: 72 IORT and 30 IORT-Com (Table 1). Both groups showed similar demographic characteristics with a mean age of 61.2 years, without significant differences. The mean follow-up time was 29.2 months, similar for both groups (p:NS). The mean global size of tumors was 12.2 mm and the most frequently used applicator size was 40 mm (34 patients) closely followed by 35 mm (33 patients). The reintervention rate was 3.92% and all reinterventions were needed due to involvement of the surgical margins.

A proportion of 29.4% of patients presented complications (Table 2): seroma, hematoma, infection, dehiscence, necrosis, or fibrosis. Such complications did not require surgical intervention. The use of an applicator of 45 mm or larger was an independent factor significantly associated to the occurrence of surgical complications ($P \leq 0.05$). Tumor size of 2 cm or larger ($P = 0.053$) and the need for reintervention ($P = 0.075$) showed borderline significant association. The remaining variables were not significantly associated. The logistic regression analysis (Table 3) revealed that only the use of an applicator of 45 mm or larger was a statistically significant variable, and the most relevant one obtained in the study.

Table 4 describes the complication types. They occurred independently or in combination. Results are expressed individually. Fibrosis was the most frequent complication (17%) and it appeared generally late in these patients (4 to 6 months postoperative); seroma was the second most frequent complication and occurred in 11% of cases; infection, hematoma, dehiscence, and necrosis were rare complications. No significant differences were observed between the complication rates

Table 3. Logistic regression analysis

Variable[a]	Wald	Exp (B)	95% CI	P-value
Tumor size ≥ 20 mm	3.076	0.297	0.077–1.153	0.079
Applicator size ≥ 45 mm	4.784	0.323	0.118–0.889	0.029
Reintervention	3.098	0.114	0.010–1.279	0.078

CI, confidence interval.
[a]Statistically significant variables in the univarible analysis.

Table 4. Types of complication[a]

Variable	Complementary external radiotherapy		P-value
	Absent (IORT-EX)	Present (IORT-CER)	
No. of cases	59 (58)	43 (42)	
Fibrosis (17%)	11 (19)	6 (14)	0.530
Seroma (11%)	7 (12)	4 (9)	0.757
Infection (5.8%)	4 (7)	2 (5)	>0.999
Hematoma (2.9%)	2 (3)	1 (2)	>0.999
Dehiscence (2.9%)	2 (3)	1 (2)	>0.999
Necrosis (0.9%)	1 (2)	0 (0)	>0.999

Values are presented as number (%).
IORT, intraoperative radiotherapy; EX, exclusive; CER, complementary external radiotherapy.
[a]Some patients may have more than one complication at a time.

with or without complementary ERT. Only one case of local relapse was observed in a patient with a 42-month period free of disease, without significant differences as compared with the rest of the patients. No cases of distant disease were recorded.

DISCUSSION

Irradiating the surgical bed during the surgical procedure is a rapid, attractive option that allows for direct localization of the tumor bed and the application of both treatments on the same day. Radiation is accurately applied on the area with the highest risk of tumor relapse, while preserving the healthy surrounding tissue [2,3]. Some 15%–30% of patients are unable to complete an adjuvant treatment with ERT due to their advanced age, associated comorbidities, or distance from home to the reference hospital; all of which increases their probability of suffering local relapse [9,10]. Such patients may directly benefit from this technique. The patient-tailored dosage in this technique reduces the risk of complications and toxicity. However, higher rates of certain, characteristic complications have been described [7,10]. In our study, both patient groups were homogeneous regarding mean follow-up time, mean age, and months free of disease; thus, our sample was homogeneous and both groups were comparable.

Elderly patients are at higher risk of developing complications due to associated comorbidities, complementary medication or age-related physiological changes, which might impair immune response and wound healing [11]. This variable was not significant in the study. Tumors larger than 2 cm require removal of a considerable amount of breast tissue [12,13]. In such cases, the size of the remaining cavity requires a larger applicator; furthermore, longer application time is needed to reach an optimal dose, which may in turn prolong the operation time [14]. All of these characteristics contributed to the statistical significance of this factor in our sample.

Radioguided surgery for nonpalpable tumors may be conducted with hookwires or through radioactive isotopes. Since they are small, easy-to-locate lesions, small resections can be performed; thus reducing postoperative complications [2,13]. The need for axillary emptying or for application of complementary ERT may increase such complications [15,16]. Both of these factors were not statistically significant.

The applicator is chosen on the basis of the preoperative simulation CT and intraoperative measurements of the surgical bed. The larger the cavity, the harder is it to choose a suitable applicator. Larger applicator size has been associated to higher complication rates [17]. It is associated with more severe surgical injury, increased risk of bleeding, and larger irradiation area with possible higher risk of subsequent fibrosis [17,18]. This was the most relevant factor in our study.

The presence of associated *in situ* carcinoma is related to the need for more reinterventions to achieve free margins and possibly to larger extension of the disease [19]. In our study, it was not a significant factor. Immunohistochemical factors such as LVI, histological grade, ki 67%, hormonal receptors, Her 2, were studied as an integrated part of the study, in order to assess their relationship with possible subsequent relapse, and were not significantly related to the occurrence of complications. Close, but not involved, margins may require higher radiation administered through complementary ERT [2,3]. Such complementary radiation is related to higher toxicity and increased local heat and redness, with subsequent fibrosis and scar retraction [20]. Margins smaller than 1 mm or the use of complementary ERT because of these margins were not significant factors in our study.

The need for surgical reintervention increases the risk of complications. Capillary regeneration and neovascularization are interrupted and the possibility of bleeding is higher. Although the previous scar can be used to conduct the surgical reintervention, the act of removing more breast tissue will affect the final esthetic outcome [7,11]. If the wound edges are not freshened, more necrosis of the skin flaps may occur with dehiscence of the surgical wound. Reopening the surgical cavity increases the degree of contamination and the infection rate [7,10,21]. Furthermore, a second surgical intervention produces a physical and psychological impact on patients, doubtlessly affecting their quality of life. This variable, surgical reintervention, showed a borderline statistical significance in our study. Enlarging our sample to a larger amount of cases would result in a statistical tendency towards definitive significance. We consider it a relevant factor in preventing the occurrence of complications. Adjuvant chemotherapy is used in patients with a higher cell proliferation index, axillary involvement or unfavorable biological factors, and it does not seem to have an influence on the occurrence of complications.

There are several types of surgical complications. The variability of complication rates in published studies stems from the criteria used to consider an adverse event to be a complication, and range from 5% to 40% of cases [6,10,15,22]. Our rate was similar to those reported in the most current literature. We included all complications requiring medical treatment, aspiration, draining or debridement (Clavien Dindo I-II) [22]. No severe complications occurred. No significant rate of difference was found between patients with or without subsequent ERT, for any complication.

Fibrosis, or late-onset induration, was the most frequent complication. It is related to chronic nonsevere toxicity, which occurs in most patients receiving an IORT boost plus subsequent complementary ERT [23,24]. In our series, no significant differences were found in the occurrence of such complications, depending on the type of schedule used. Since this is a late-onset complication, controversy exists on whether

it should be considered a postoperative complication or a long-term consequence of radiotherapy, which might worsen with the years and become associated with retraction of the intervened zone and reduction of the global size of the breast.

IORT increased the occurrence of postsurgical seroma [15,25]. Early closing of the surgical cavity by breast remodeling, which we systematically carry out, could account for the lower amount of seromas observed in our series, as compared with other published series. In the beginnings of this technique, there was a tendency to remove a larger amount of healthy tissue, in order to guarantee free margins, which increased seromas. With more experience, it became clear that it was not necessary to modify the tumorectomy technique because of the use of IORT. This type of seroma usually appears late, and less than 5% of cases require more than 2 aspirations for resolution [6,15,25].

The time the cavity remains open for performing the technique increases the risk of subsequent contamination of the surgical wound [18,26]. Although our results are adequate, we currently use antibiotic prophylaxis in such cases, even when the procedure is considered clean surgery. During the technique, a tobacco-pouch is necessary to adjust the cavity to the applicator, which means more surgical manipulation of the tissue and may increase hematoma. In our series, the amount of hematomas requiring treatment was low. Cases presenting dehiscence or necrosis of the skin flaps occurred in patients with wound infection managed with drainage.

Since only one case of local relapse was observed, statistically relevant prognostic factors are difficult to obtain. The involved patient was younger than 70 years at the time of diagnosis, size was smaller than T2, without axillary involvement, with associated *in situ* carcinoma, LVI, high histological grade, ki 67% positive, progesterone receptor negative, Her 2 negative, free margins, applicator size 35 mm, without complications or need for reintervention. During follow-up, chemotherapy and hormonal therapy were used as adjuvant treatment. Some of the above-mentioned factors (associated *in situ* carcinoma, LVI, high histological grade, high ki 67% and progesterone receptor negative) are typical factors known to be related to local relapse [27-30].

In general, the results of our study should be considered cautiously, since they correspond to the experience in only one center and with a limited number of cases. Although the follow-up time was long, an even longer period might have yielded more cases of local relapse. The assessment and classification of complications is made by surgeons and, although based on objective criteria, some degree of subjectivity, variability in time and surgeon's experience, may exist. The here-presented results include the first cases managed in our center; thus, the learning curve might have prolonged the surgical times, possibly resulting in more complications.

Based on these results, we consider that IORT is a safe and effective technique, which can be easily reproduced and should be used in most breast-units where the necessary equipment is available. Complications are similar to those of a traditional conservative treatment. A considerable proportion of patients will need to complete the treatment with ERT, although it does not seem to increase complications. Regarding local relapse, long-term follow-up is needed to determine whether the technique actually increases its rate; however, up to this date, available patient series do not show such a phenomenon.

In conclusion, fibrosis, or late-onset induration, is the most frequently observed complication, followed by postoperative seroma. The use of an applicator of 45 mm or larger was an independent factor significantly associated to the occurrence of surgical complications. Tumor size of 2 cm or larger and the need for reintervention showed borderline significant association. These factors must be taken into account to prevent their occurrence and to apply an early treatment to reduce psychological impact and enhance patient quality of life. The use of complementary ERT does not seem to increase the complication rate. IORT does not increase the risk of local relapse in the medium-term, although larger patient series and longer follow-up periods are needed to demonstrate this. Patient selection and the involvement of a multidisciplinary team are essential for achieving good results.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Orecchia R, Ciocca M, Lazzari R, Garibaldi C, Leonardi MC, Luini A, et al. Intraoperative radiation therapy with electrons (ELIOT) in early-stage breast cancer. Breast 2003;12:483-90.
2. Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet 2010;376:91-102.
3. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet 2014;383:603-13.
4. Smith BD, Arthur DW, Buchholz TA, Haffty BG, Hahn CA, Hardenbergh PH, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). J Am Coll Surg 2009;209:269-77.
5. Morlino A, La Torre G, Lapadula L, Cammarota A. IORT in breast cancer. Our experience of the first patients treated. Ann Ital Chir 2017;88:253-7.
6. Rakhra S, Bethke K, Strauss J, Hayes JP, Hansen N, Khan SA, et al. Risk factors leading to complications in early-stage breast cancer following breast-conserving surgery and intraoperative radiotherapy. Ann Surg Oncol 2017;24:1258-61.
7. Gulcelik MA, Dogan L, Karaman N, Turan M, Kahraman YS, Akgul GG, et al. Intraoperative boost radiation effects on early wound complications in breast cancer patients undergoing breast-conserving surgery. Turk J Med Sci 2017;47:1185-90.
8. de Glas NA, Kiderlen M, Bastiaannet E, de Craen AJ, van de Water W, van de Velde CJ, et al. Postoperative complications and survival of elderly breast cancer patients: a FOCUS study analysis. Breast Cancer Res Treat 2013;138:561-9.
9. Athas WF, Adams-Cameron M, Hunt WC, Amir-Fazli A, Key CR. Travel distance to radiation therapy and receipt of radiotherapy following breast-conserving surgery. J Natl Cancer Inst 2000;92:269-71.
10. Epstein M, Silverstein M, Lin K, Kim B, Khan S, De Leon C, et al. Acute and chronic complications in breast cancer patients treated with intraoperative radiation therapy. Ann Surg Oncol 2016;23:3304-9.
11. Tesarova P. Specific aspects of breast cancer therapy of elderly women. Biomed Res Int 2016;2016:1381695.
12. Hwang KT, Han W, Lee SM, Choi J, Kim J, Rhu J, et al. Prognostic influence of 3-dimensional tumor volume on breast cancer compared to conventional 1-dimensional tumor size. Ann Surg Treat Res 2018;95:183-91.
13. Fei F, Messina C, Slaets L, Chakiba C, Cameron D, Bogaerts J, et al. Tumour size is the only predictive factor of distant recurrence after pathological complete response to neoadjuvant chemotherapy in patients with large operable or locally advanced breast cancers: a sub-study of EORTC 10994/BIG 1-00 phase III trial. Eur J Cancer 2015;51:301-9.
14. Sethi A, Emami B, Small W Jr, Thomas TO. Intraoperative radiotherapy with INTRABEAM: technical and dosimetric considerations. Front Oncol 2018;8:74.
15. Ebner F, Schramm A, Bottke D, Friedl TW, Wiegel T, Fink V, et al. Comparison of seroma production in breast conserving surgery with or without intraoperative radiotherapy as tumour bed boost. Arch Gynecol Obstet 2016;294:861-6.
16. Meiers P, Cil T, Guller U, Zuber M. Sentinel lymph node biopsy in early-stage breast cancer patients: improved survival through better staging? Langenbecks Arch Surg 2013;398:687-90.
17. Lee JJB, Choi J, Ahn SG, Jeong J, Lee IJ, Park K, et al. In vivo dosimetry and acute toxicity in breast cancer patients undergoing intraoperative radiotherapy as boost. Radiat Oncol J 2017;35:121-8.
18. Valente SA, Fanning A, Stewart RA, Grundfest S, Tendulkar RD, Cherian S, et al. Intraoperative radiation for breast cancer with Intrabeam™: factors associated with decreased operative times in patients having IORT for breast cancer. Front Oncol 2017;7:237.
19. Zhang X, Dai H, Liu B, Song F, Chen K. Predictors for local invasive recurrence of ductal carcinoma in situ of the breast: a meta-analysis. Eur J Cancer Prev 2016;25:19-28.
20. Key S, Miglierini P, Dupre PF, Guilbert S, Lucia AS, Abgral R, et al. Cosmetic outcome and chronic breast toxicity after intraoperative radiation therapy (IORT) as a single modality or as a boost using the Intrabeam(®) device: a prospective study. Ann Surg Oncol 2017;24:2547-55.
21. Zur M, Shai A, Leviov M, Bitterman A, Shiloni E, Ben Yosef R, et al. Short-term complications of intra-operative radiotherapy for early breast cancer. J Surg Oncol 2016;113:370-3.
22. Panhofer P, Ferenc V, Schutz M, Gleiss A,

Dubsky P, Jakesz R, et al. Standardization of morbidity assessment in breast cancer surgery using the Clavien Dindo Classification. Int J Surg 2014;12:334-9.
23. Cracco S, Semprini G, Cattin F, Gregoraci G, Zeppieri M, Isola M, et al. Impact of intraoperative radiotherapy on cosmetic outcome and complications after oncoplastic breast surgery. Breast J 2015;21:285-90.
24. Sedlmayer F, Reitsamer R, Wenz F, Sperk E, Fussl C, Kaiser J, et al. Intraoperative radiotherapy (IORT) as boost in breast cancer. Radiat Oncol 2017;12:23.
25. Tuschy B, Berlit S, Romero S, Sperk E, Wenz F, Kehl S, et al. Clinical aspects of intraoperative radiotherapy in early breast cancer: short-term complications after IORT in women treated with low energy x-rays. Radiat Oncol 2013;8:95.
26. Silverstein MJ, Epstein M, Kim B, Lin K, Khan S, Snyder L, et al. Intraoperative radiation therapy (IORT): a series of 1000 tumors. Ann Surg Oncol 2018;25:2987-93.
27. Hasebe T, Iwasaki M, Hojo T, Shibata T, Kinoshita T, Tsuda H. Histological factors for accurately predicting first locoregional recurrence of invasive ductal carcinoma of the breast. Cancer Sci 2013;104:1252-61.
28. Pata G, Guaineri A, Bianchi A, Amoroso V, Pasinetti N, Pasini M. Long-term outcomes of immunohistochemically defined subtypes of breast cancer less than or equal to 2 cm after breast-conserving surgery. J Surg Res 2019;236:288-99.
29. Choi HJ, Ryu JM, Kim I, Nam SJ, Kim SW, Yu J, et al. Nomogram for accurate prediction of breast and axillary pathologic response after neoadjuvant chemotherapy in node positive patients with breast cancer. Ann Surg Treat Res 2019;96:169-76.
30. Abbott AM, Dossett LA, Loftus L, Sun W, Fulp W, Sokol GH, et al. Intraoperative radiotherapy for early breast cancer and age: clinical characteristics and outcomes. Am J Surg 2015;210:624-8.

CONCLUSIONES

1. En el cáncer de mama existen factores que aumentan la agresividad de la enfermedad, predicen un mayor riesgo de recaída y determinan el pronóstico de las mismas, por lo que deben ser estudiados previamente para mejorar el abordaje terapéutico y la expectativa de vida. El estudio de las pacientes intervenidas por cáncer de mama debe ser estrecho, sobre todo en los primero años, ya que es en donde se evidencia el mayor número de recaídas locales. Un nuevo abordaje conservador es posible, siempre que se puedan obtener márgenes adecuados, quienes apoyan esta técnica insisten en que este es el factor más importante a tener en cuenta. Casi la mitad de las pacientes que recidivaron en nuestro estudio presentaron posteriormente enfermedad a distancia, lo que supone un deterioro de la calidad de vida y una disminución de su supervivencia global. Ademas la presencia de receptores de progesterona negativo, el uso de neoadyuvancia con quimioterapia y la presencia de enfermedad a distancia, fueron los factores mas importantes que influenciaron de forma significativa en la supervivencia de las pacientes, superando en relevancia al resto de las variables estudiadas. Las tasas de recidivan local han disminuido con el avance del tiempo debido a las técnicas de diagnostico precoz mediante el screening de la población de riesgo, el abordaje quirúrgico selectivo de los tumores pequeños, no palpables y el uso de tratamiento adyuvantes cada vez mas específicos para cada tipo de paciente. Sin embargo siempre existirán factores que nos condiciones el pronostico de las pacientes y deben ser tenido en cuenta a la hora de planificar el seguimiento de las mismas.

2. La evolución de la radioterapia externa hacia técnicas mas dirigidas que modulan la dosimetría administrada en el tejido mamario y su estructuras adyacentes permite que la reconstrucción mamaria inmediata sea una realidad para la mayoría de las pacientes con tasa de

complicaciones, resultados estéticos y satisfacción similares a las obtenidas en pacientes no irradiadas. La coordinación multidisciplinar entre el equipo quirúrgico y el radioterapéutico es fundamental para obtener buenos resultados.

3. La identificación precoz de factores desfavorables en la reconstrucción es básica para la planificación quirúrgica de estas pacientes. La correcta selección de las pacientes y de la técnica quirúrgica asociada a una adecuada información previa, nos permite obtener expectativas reales sobre la reconstrucción mamaria, lo que conlleva a un mayor grado de satisfacción y un aumento en la calidad de vida.

4. Con los resultados obtenidos entendemos que la radioterapia intraoperatoria es una técnica segura y eficaz que se puede reproducir con facilidad y que debería ser utilizada en la mayoría de las unidades de mama que puedan disponer del equipo necesario para su realización. Las complicaciones son similares a las de un tratamiento conservador habitual. Existe un porcentaje no desdeñable de pacientes que requerirán completar el tratamiento con radioterapia externa, pero esto no parece aumentar las complicaciones. Con respecto a la recidiva local será un seguimiento a largo plazo el que nos permita establecer si existe un aumento real de las mismas, pero hasta los momentos en las series disponibles no parece observarse este fenómeno

RESUMEN

Existen factores que permiten predecir un mayor riesgo de recaída local en el cáncer de mama. La presencia de receptores de progesterona negativo, el uso de neoadyuvancia con quimioterapia y la presencia de enfermedad a distancia, son variables conocidas que han demostrado ser fundamentales para determinar la supervivencia de las pacientes, por lo que se deben de tener en cuenta a la hora de planificar un tratamiento quirúrgico. .

La coordinación entre el equipo quirúrgico y el radioterapéutico es fundamental para obtener buenos resultados globales. Si se realiza una correcta selección de las pacientes y de la técnica quirúrgica asociada, se puede realizar una cirugía de reconstrucción mamaria con seguridad , generando un buen grado de satisfacción de las pacientes y mejorando su calidad de vida .

La radioterapia intraoperatoria es una técnica consolidada que nos permite asociar un tratamiento adyuvante a el acto quirúrgico. Las modificaciones quirúrgicas necesarias para realizar la técnica son mínimas y las complicaciones no son significativas en comparación a el abordaje quirúrgico convencional. El beneficio para las pacientes es evidente y la seguridad de las mismas es la prioridad al momento de seleccionarla.

La investigación en el cáncer de mama debe continuar ofreciendo respuestas a nuestras pacientes, siendo fundamental la selección de diversos tratamientos en el marco de un equipo multidisciplinar. Visualizar la enfermedad desde diferentes puntos de vista nos permite obtener mejores resultados, lo que se demuestra en un aumento de la supervivencia y de la calidad de vida.

PALABRAS CLAVE

Cáncer de mama, recaída local, supervivencia, complicaciones, radioterapia post-mastectomía, calidad de vida, radioterapia intraoperatoria.

SUMMARY

There are factors that allow predicting an increased risk of local relapse in breast cancer. The presence of negative progesterone receptors, the use of neoadjuvant chemotherapy, and the presence of distant disease are known variables that have been shown to be fundamental in determining the survival of patients, so they must be taken into account when to plan a surgical treatment. .

Coordination between the surgical team and the radiotherapy team is essential to obtain good overall results. If a correct selection of the patients and the associated surgical technique is performed, a breast reconstruction surgery can be performed safely, generating a good degree of patient satisfaction and improving their quality of life.

Intraoperative radiotherapy is a consolidated technique that allows us to associate an adjuvant treatment with the surgical act. The surgical modifications necessary to perform the technique are minimal and the complications are not significant compared to the conventional surgical approach. The benefit for the patients is evident and their safety is the priority when selecting it.

Research in breast cancer must continue to offer answers to our patients, with the selection of various treatments being essential within the framework of a multidisciplinary team. Visualizing the disease from different points of view allows us to obtain better results, which is demonstrated in an increase in survival and quality of life.

KEYWORDS

Breast cancer, local relapse, survival, complications, post-mastectomy radiotherapy, quality of life, intraoperative radiotherapy.