

# Mammary Paget's disease and radiotherapy: a systematic literature review

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**Abstract. – OBJECTIVE:** Paget disease of the breast (PDB) is a rare form of cutaneous breast cancer. Up to date, no randomized studies evaluated the different management strategies. This systematic review investigates the role of radiotherapy and its best technical profile in the treatment of this disease, with great attention to doses and fractionation regimens.

**MATERIALS AND METHODS:** A systematic search was performed on PubMed, Embase and Scopus in order to detect case reports, case series and prospective as well as retrospective clinical studies describing histologically proven PDB and providing information about pertinent radiation treatments. Searching strategy followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines.

**RESULTS:** Inclusion criteria were met by six papers, dealing with radiation treatments performed postoperatively and in exclusive settings. No evaluations were performed on preoperative radiotherapy.

**CONCLUSIONS:** Actually, the standard treatment of PDB reflects oncological principles of breast carcinoma therapy, including the role of breast-preserving surgery. The traditional radiotherapeutic dose is 50 Gy, with daily fractionation of 2 Gy. Adjuvant radiotherapy following breast preserving surgery represents the current standard of care; prospective studies could be of help in defining the role of exclusive radiotherapy, hypofractionated schemes and smaller target volumes.

*Key Words:*

Breast cancer, Paget of the breast, Radiotherapy.

## Introduction

Paget disease of the breast (PDB) is a rare form of cutaneous breast cancer. Distinction from

non-breast Paget disease is possible even if the two diseases share similar morphological and histological findings, due to their involvement of cutaneous areas well supplied with apocrine glands, such as genital and perianal areas<sup>1-3</sup>. PDB represents 1-3% of all breast cancers; it is more frequent in females during their sixth and seventh decades (mean age at diagnosis 62.6 years) and shows a worse prognosis in men<sup>4,5</sup>.

The typical lesion is an eczematous eruption of the nipple, caused by the infiltration of the squamous epithelium of the nipple/areolar complex by malignant epithelial cells.

It is generally a solitary lesion, but in 32-41% of the cases it can be associated with a ductal in situ (DISC) or invasive (IDC) carcinoma<sup>1,6</sup>.

PDB may involve any part of the breast; in up to 50% of the patients appears as a palpable mass, which may include invasive disease in 90-94% of the cases; 66-68% of patients without clinically detectable breast lesions are diagnosed with DISC<sup>7</sup>.

PDB of the nipple without association of DISC/IDC in the underlying mammary parenchyma is defined as Stage Tis. Carcinomas of the breast associated with Paget disease are classified according to actual diameter and features of the parenchymal neoplasm<sup>8</sup>. Up to date, no randomized studies evaluated the different management strategies in patients with PDB (such as nipple excision, radiotherapy, central lumpectomy, quadrantectomy with or without irradiation, total mastectomy).

Radical mastectomy with or without axillary dissection was considered the treatment of choice, due to the high incidence of multifocal underlying

cancer foci, mainly in centrally located lesions, generally considered a contraindication to breast conserving surgery (BCS)<sup>4</sup>. However, since the beginning of 2000, BCS has been largely used in patients with PDB and IDC, as well as in patients with SLNB<sup>9,10</sup>.

Recent studies suggest that in selected patients BCS followed by radiotherapy may achieve the same results as mastectomy, even if the risk of an undetected or underestimated underlying carcinoma exists in postoperative residual disease<sup>4,9</sup>. Furthermore, data regarding the most appropriate distance between carcinoma and the nipple for a successful BCS, have not been confirmed up to date. In patients with small breast, central excision may result in poor cosmesis and skin sparing mastectomy, in order to allow a successful breast and nipple reconstruction in the future, are warmly recommended<sup>4</sup>.

This systematic review investigates the role of radiotherapy and its best technical profile in the treatment of PDB, with great attention to doses and fractionation regimens.

## Materials and Methods

A systematic search of the literature was performed using the words “Mammary Paget Disease and Radiotherapy”; “Mammary Paget Disease and Radiation Therapy”; “Mammary Paget Disease and Therapy” on PubMed, EMBASE and Scopus, examining papers between 1990 and August 2020. Case reports, case series and prospective as well as retrospective clinical studies describing histologically proven PDB and providing information about pertinent radiation treatments were included. Papers not focused on PDB or on isolated radiotherapy, or not showing details of radiotherapeutic treatments and not English-speaking papers before 1990 were excluded.

## Results

The search followed PRISMA guidelines<sup>11</sup>. The search disclosed 604 papers, 469 of which were considered potentially pertinent. After the first screening, 441 papers were excluded, as the title and abstract were considered irrelevant to the radiotherapeutic treatment of PDB; 28 papers were selected for an extensive analysis. Twenty-two of these were excluded from the search, actually being reviews (4 papers), not reporting RT details

(7 papers) or being published before 1990 (11 papers). The PRISMA flowchart (Figure 1) depicts the exclusion procedure. The residual 6 articles were reviewed, as they fulfilled the inclusion criteria (Table I)<sup>11-16</sup>.

Bulens et al<sup>15</sup> reviewed a group of 13 patients with PDB restricted to the nipple and treated with radiotherapy alone. Inclusion criteria were the absence of clinical or radiologic evidences of neoplastic masses and the absence of microcalcifications on mammographies. Biopsies were performed, avoiding complete excision of the lesions; the breast received radiotherapy, at a dose ranging between 30 and 65 Gy, with a boost to the disease site, reaching a total dose of 60-70 Gy. In relation to lymph nodes, 5 patients had no axillary involvement, 3 underwent surgical dissection of the axilla and 2 nodal irradiation. No local recurrences or metastases were detected at the follow up; cosmetic results were considered fine. Due the low incidence of axillary involvement, as well as to the absence of nodal recurrences, these authors suggested a whole breast irradiation, reaching a dose of 50 Gy (2 Gy daily fractions), followed by an electron boost (6 MeV, 0.5 cm bolus) reaching a total dose of 65 Gy without any treatment to regional nodes<sup>15</sup>.

Pierce et al<sup>16</sup> reported a series of 30 patients with no palpable masses or radiographic findings, treated with external beam radiotherapy to the

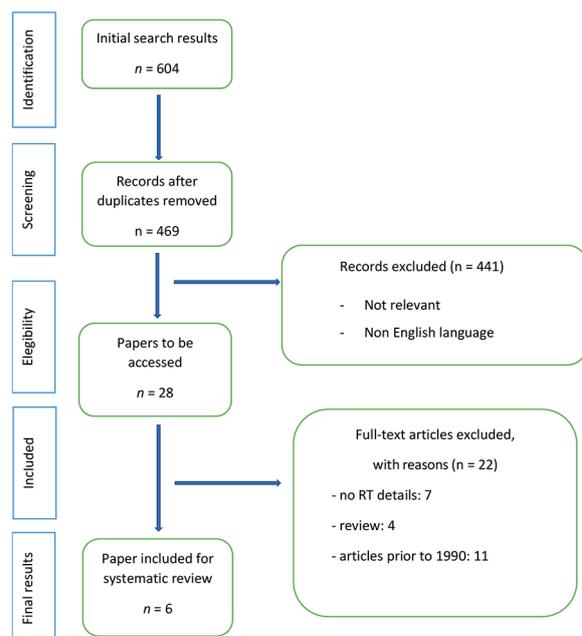


Figure 1. PRISMA flow-chart.

**Table I.** Reviewed articles.

Name, year	N. patients	Volume	Dose/volume	Dose/fraction	Boost	Treatment
Bulens et al <sup>15</sup> , 1990	13	Entire breast	30-65 Gy	2 Gy/day	Up to 60-70 Gy	Only radiotherapy
Pierce et al <sup>16</sup> , 1997	30	Entire breast	50 Gy (45-54 Gy)	1.8-2 Gy/day	Up to 61.5 Gy	BCS + radiotherapy
Bijker et al <sup>12</sup> , 2001	61	Entire breast	50 Gy (45-50 Gy)	2 Gy	/	BCS + radiotherapy
Marshall et al <sup>13</sup> , 2003	36	Entire breast	50 Gy (45-54 Gy)	2 Gy	Up to 61.5 Gy (range 50.4-70 Gy)	BCS + radiotherapy
Kawase et al <sup>14</sup> , 2005	30	Entire breast	50 Gy	/	/	9 cases BCS + chemoradiotherapy; 3 cases BCS + radiotherapy; 18 cases radiotherapy alone
Dalberg et al <sup>11</sup> , 2007	19	Entire breast or chest wall	50 Gy	2 Gy/day	/	8 cases BCS + Radiotherapy 11 cases mastectomy + radiotherapy

breast, with a median dose of 50 Gy (range 45-54 Gy) and a median daily fractionation of 2 Gy (range 1.8-2Gy). Seven % of these patients received an additional boost to the disease site, with a median dose of 61.5 Gy (range 50.4-70Gy); 86% of these patients were treated with electrons and 3% with 100 kilovolt photons, cobalt or a double plane of iridium implants. One patient received an unknown boost dose. A bolus was utilized in 33% of the cases; it was applied to the residual nipple and areolar complex in 6 patients, on the residual scar in 2 patients and on the whole breast in 2 patients. In addition, one patient was irradiated on the supraclavicular nodes with a dose of 46, and another one was irradiated on the supraclavicular, axillary and internal mammary lymph nodes with a total dose of 50 Gy. In the 11% of these patients, these authors reported complications, among which persistent chest wall pain, chronic mammary infection and radiation dermatitis. During the follow-up, two patients developed distant metastases. The five years disease-free survival was 95% for the whole cohort<sup>16</sup>.

Bijker et al<sup>12</sup> described the results of whole breast irradiation performed 8 weeks after BCS in 61 patients with a prescribed dose of 50 Gy. Seven % of these patients showed only PDB, while 93% showed PDB-DCIS. Patients with cancers located less than 5 cm from the nipple e fully excised, with negative margins of resection, were included

in the study. Cancers with nodal involvement or distant metastases were discarded. A five-year local recurrence rate of 5.2% was observed. Thus, BCS followed by irradiation was considered a reasonable approach in patients with PDB and localized DCIS with clean surgical margins<sup>12</sup>. In 36 patients with PDB without palpable masses or mammographic findings, treated with BCS followed by radiotherapy, Marshall et al<sup>13</sup> observed excellent results in terms of local control, disease free survival and overall survival after 10 and 15 years, respectively. In particular, 94% of these patients received a total or partial excision of the nipple or of the areolar complex, 100% receive breast irradiation and 97% were submitted to a boost either to residual nipple or to the tumoral bed. The median value of the prescribed dose was 50 Gy (range 45-54 Gy) to the whole breast, while the total boost dose was 61.5 Gy (range 50.4-70 Gy) to the residual nipple or tumoral bed. Four out of these patients developed a recurrence in the treated breast. There were two cases of DCIS, while the remaining two proved to be invasive DCIS. At the primary procedure, the surgical margins were clear in two patients and were not evaluated in the other two. Two other patients (6%) developed a recurrence in the omolateral breast, in association with distant metastases. A valid control of the disease at the local level was achieved in 97% of this cohort of patients. No specific factors capable to

predict local recurrences of the disease were detected. Thus, prior to adjuvant radiotherapy, these authors recommended to proceed to the surgical excision of the entire nipple and areolar complex, in order to obtain microscopically disease-free margins, as well to remove all the microcalcifications visualized in pretreatment mammographies. This paper definitely showed improved survival in patients submitted to breast irradiation<sup>13</sup>.

Kawase et al<sup>14</sup> evaluated a greater cohort of 104 patients, twelve of which were submitted to BCS, while the other 92 received a mastectomy. Patients with altered nipples, in the absence of palpable masses or mammographic evidences, underwent only to a nipple and areolar complex excision, while patients with mammographic abnormalities or palpable masses were considered for BCS. All the operated patients received adjuvant radiotherapy, with a median dose of 50 Gy. A local recurrence was observed in a patient submitted to BCS. This study showed a disease specific 10 years survival rate of 47% in patients with positive lymph nodes and of 93% in those with negative nodes, while not significant differences were found between the two therapeutic approaches. Therefore, these authors suggest treating patients according to the histologic features of the primary neoplasm as well as to their nodal status<sup>14</sup>.

Dalberg et al<sup>11</sup> verified the effects of radiotherapy in 19 patients affected by PDB. Eight of these were submitted to adjuvant radiotherapy after BCS, while the other 11 received a chest wall irradiation after a mastectomy. A dose of 50 Gy was prescribed, in daily fractions, five fractions every week, delivered by a cobalt unit or a linear accelerator (4-6 MV). In case of involvement of axillary lymph nodes or in large volume tumors (>2 cm) axillary, supraclavicular and parasternal lymph nodes were included in the irradiation field. The disease specific 10 years survival rate was 94% in BCS patients and 85% in those treated with mastectomy. The observed 10 years disease free specific survival rate was 80% in BCS patients and 82% in mastectomy patients. In terms of DFS, no differences were noted between the two surgical procedures<sup>11</sup>.

The contribution of preoperative radiotherapy was not evaluated at all in these papers.

## Discussion

The role of radiotherapy and its most appropriate setting in the treatment of PDB is still de-

bated, as conclusive data are lacking due to the limited incidence of the disease. This systematic review reports the results of retrospective studies, as randomized clinical trials on this topic are definitely scarce. Breast conservative surgery with lumpectomy, followed by adjuvant radiotherapy, represents an effective therapeutic regimen for patients with PD-DCIS or PD-IDC<sup>15,16</sup>. Adjuvant radiotherapy is also recommended after T3 or T4 mastectomies or in case of positive margins<sup>8</sup>. The appropriate time interval between surgery and radiotherapy has not been unequivocally defined; thus, in daily clinical practice recommendations for generic breast cancers are still adhered to<sup>17</sup>. Data demonstrate the crucial role of radiotherapy in the adjuvant setting (median dose 50 Gy) for this uncommon indication.

Two papers published before 1990, and thus excluded from this review according to our criteria, disclose great relevance to the topic and may anyhow add significant information<sup>18,19</sup>. In 1987, Fourquet et al<sup>18</sup> evaluated 20 patients with PDB involving the nipple; three of these were submitted to conservative surgery, followed by radiotherapy, while the remaining 17 received radical radiotherapy on the breast as well as on axillary and internal mammary lymph nodes. The median prescribed dose was 57 Gy for the single breast; 90% of these patients received a boost, with a median total dose of 72 Gy to the tumor site (range 55-83 Gy). No PDB related deaths were recorded in a subsequent 7.5-year follow-up; the recurrence free survival rate reached 81%. Treatment failed in three patients, in which actually the neoplastic lesion was incompletely excised<sup>18</sup>.

Stockdale et al<sup>19</sup> reported a series of 28 patients with PDB submitted to nipple biopsy and radical radiotherapy of the involved skin; 19 of these had no palpable lumps or mammographic findings; 16 of these 19 patients were disease free for 5 years; the three other patients developed recurrences and later on were addressed to a radical mastectomy<sup>19</sup>.

The impact of conservative surgery on this scenario was verified by Dixon and Polgar in their papers that evidenced high recurrence rates after this approach<sup>20,21</sup>. Dixon et al<sup>20</sup> evaluated 10 patients with no palpable masses, submitted to the excision of the nipple and areolar complex, with a cone of underlying breast tissue. One of these patients had an invasive cancer, while the other 9 had DCIS. After 56 months, local recurrence rate was 40%. Cone excision in itself was considered an inappropriate treatment<sup>20</sup>.

Polgar et al<sup>21</sup> evaluated 33 patients showing only PDB or DCIS, submitted to BCS, without any radiotherapeutic addition. Local recurrence rate was similar to the one showed by patients receiving BCS and irradiation; however, the odds of distant metastases was higher and BCS without adjuvant radiotherapy was considered inadequate<sup>21</sup>. Available data prove that management of PDB is conditioned by the possibility of an underlying breast cancer. Due to the high incidence of the association between breast carcinoma and Paget disease, a comprehensive diagnostic work-up with ultrasound, mammography and magnetic resonance is encouraged, in order to detect occult neoplasms in patients with Paget disease<sup>22</sup>.

It should also be taken into account that these neoplasms disclose unfavorable biological features (such as high grade, ER and PR negative status, as well as HER-2 overexpression) generally considered indicators of poor prognosis and brief survival. Therefore, adjuvant treatment plays a relevant role in improving disease control and should be adjusted to the histological nature of the underlying cancer. Nevertheless, according to literature, all patients submitted to BCS should undergo radiotherapy on the operated breast<sup>23</sup>. This kind of conservative approach should be preferred, even if quality of life and outcomes scores reported by patients have not been thoroughly analyzed in the literature<sup>24</sup>. At the moment, the standard treatment for PDB should conform with to the oncological principles of breast cancer therapy, including the role of BCS<sup>6</sup>. The usual absolute contraindications to the radiotherapeutic treatment (such as pregnancy and active autoimmune diseases, i.e. scleroderma) actually prevent its clinical application<sup>8</sup>.

Traditionally, the recommended dose is 50 Gy, with a daily fractioning of 2 Gy, plus the possibility of a boost on the tumor site of 10-16 Gy at 2 Gy per day, according to the status of the surgical margins and to other prognostic factors<sup>8</sup>. Moderate hypofractionation schemes, with a total of 15 or 16 applications or even fast one-week treatments with daily doses of 5.2 Gy can be considered. At the moment, no standardized protocols for hyperfractionated regimens have been clinically evaluated<sup>5-28</sup>.

While the role of adjuvant radiotherapy has been actually verified, the contribution of radiotherapy alone remains controversial.

Breast irradiation alone for the treatment of PDB has been reported in a limited number of papers, with inconsistent results<sup>14,15,18,19</sup>. Stotter et

al<sup>29</sup> affirmed that a radical irradiation of the breast could be effective in the treatment of DCIS<sup>29</sup>. These results support the concept that radical radiotherapy can be an alternative treatment for patients with PD of the nipple, without clinical or radiological evidences. Indeed, in case of a small tumoral volume, high doses of curative radiotherapy (60-65 Gy) can be administered with no collateral effects on the surrounding tissues, reaching a high probability of local control<sup>29</sup>. Nevertheless, considering the limited number of papers in the literature on this topic, as well as disagreement in described results, at the moment radiotherapy alone is not a recommended treatment for PD-IDC.

Conversely, radiation treatment shows significant psychological advantages for the patient; surgery can be restricted to a salvage therapy in case of local recurrence, without compromising the actual prognosis<sup>29</sup>.

## Conclusions

Standard fractionated adjuvant radiotherapy following BCS represents the current standard of care for Paget disease of the breast. Recent evidences of hypofractionated schemes feasibility and the ability to reliably identify smaller target volumes (such as utilizing magnetic resonance guided radiotherapy) may represent a further progress in the treatment of this disease. Prospective studies are needed both to define the role of radiotherapy alone as well as the importance of introducing predictive biomolecular indices and multimodal variables in large data-bases and clinical decision support systems, in order to reduce the negative impact of the limited incidence of this infrequent disease.

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## Conflict of Interest

The Authors declare that they have no conflict of interests.

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## Authors' Contribution

Concept – AP, AD.; Design – AP, LB.; Supervision – AP, LB, TA, AD; Materials – AS, ML, VV; Data collection and/or processing – AS, ML, VV; Analysis and/or interpretation – AP, RG, GS.; Literature search – VV, AS, ML; Writing – VV, AP, LB Critical review – AP, LB, RG, AD, TA, GS.

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