Abstract. The objective of the present systematic review was the determination of methodologies preferable for treating phyllodes tumors (PTs) of the breast and whether the malignancy of the tumor is of significance to the selected treatment. In addition, to investigate if local recurrence (LR) within patients is different based on the therapeutic approach followed by the physician. All studies were gathered by utilization of the biggest online medical databases in the world including PubMed, Cochrane, Embase, Web of Science and Google Scholar. Due to the specificity of the study, the resultant set of studies included in the present analysis was not large. All included studies had to refer to patients diagnosed with PTs of the breast, include the malignancy of the tumor and the preferred treatment. Moreover, they included a reference to LR post-treatment, even if there wasn't any. The age range of patients was 20-55 years old and follow-ups should have been performed. As a result, from the initial 484 studies gathered and after proper and thorough evaluation, only 10 were of significance. The studies appeared heterogeneous in terms of population, topology, treatment methodology, additional therapeutic approaches, LR rate, age and follow-up periods. Overall, excisions were used for non-malignant tumors while mastectomy was preferable for tumors with malignancy. Radiotherapy was used both as an additional treatment for tumors and LR. Also, it was revealed that LR varied based on the malignancy and treatment methodology.

Introduction

Phyllodes tumor (PT) is a rare breast tumor; more specifically, its diagnosis reaches 0.3 to 1% of all breast tumors (1). This tumor consists of an uncommon complex group of fibroepithelial lesions with leaf-like architecture and increased stromal cellularity (2). The first reference to PT of the breast (PTB) dates back to the 1800s when Muller was the first person to report it. It was initially named ‘cystosarcoma phyllodes’ and was described as a rapidly growing tumor with a cystic lobulated section (3). Since then, a lot of names were given by the scientific community and a lot of controversies and disputes took place to properly classify this type of tumor. The World Health Organization (WHO) and its international histological classification group in 2003 recommended that this anomaly should be named ‘phyllodes tumor’ and that it can be classified into 3 categories: malignant, borderline, and benign (1). The controversy and disputes over the years, the evolution, and later the settlement on the terminology, characteristics, and identification of this tumor type signifies how rare it is and the difficulty in its precise diagnosis.

According to the latest (2019) WHO edition of breast tumours the criteria for diagnosing and grading this rare form of tumor consist of stromal cellularity, stromal atypia, presence of stromal overgrowth which is defined as the absence of epithelial elements containing stroma only in 1 low power field, well defined or permeative borders, mitotic count, and presence of heterologous elements (4). The distinction between benign and borderline PT from malignant PT is important since benign and borderline PT may recur or metastasize less frequently while malignant PT show higher rates of recurrence and hematogenous metastasis (5). Benign PT shares some common characteristics if compared to cellular fibroadenoma while malignant PT can be mistaken for spindle cell metaplastic breast carcinoma or primary breast sarcoma. Making a distinction can often be problematic and
inconsistent when performing a core biopsy (2). The presence of a bland epithelial component helps in the differential diagnosis of stromal sarcomas. It is worth mentioning that based on the reporting of findings for these tumors, they tend to be benign with borderline malignancy. Malignant PTs are less commonly reported (6).

Due to its rarity, the method of diagnosis for the PT has a very low accuracy rate. Attempting to diagnose it preoperatively has proven uncertain and inefficient and therefore, it led scientists and professionals to attempt treating and diagnosing it using various surgical techniques. One of the most important prognostic features of this form of tumor is the high local recurrence (LR) rate which reaches up to 40% for the various histological types of these phyllodes breast tumors. In its Malignant PT may show an aggressive clinical behavior with rapid growth and potential for hematogenous or lymphatic metastasis. From various data gathered by specialists throughout the years, it is safe to say that PT tends to metastasize in the lungs, bones, and soft tissue via blood. Lymph node metastasis is extremely rare with its overall metastasis rate via both blood and lymph nodes being ~4%. It is important to mention that malignant and borderline metastasis rates are higher than benign ones, for ~30% of its occurrences (1,7,8). After performing a core biopsy, some cellular fibroepithelial lesions might be extracted from the patient by open or vacuum-assisted excision although surgical excision is the preferred method for removal (2).

Materials and methods

To find the most recent studies for this systematic review, a calculated decision was made to utilize the biggest and most reliable Web Databases in the world of medicine and research. These databases were PubMed, PubMed Central, Cochrane Library, Embase, Web of Science, UpToDate, and Google Scholar. A literature search with citations and specific keywords while using the advanced search option was performed in every database in order to narrow down and provide accurate results. The year range of the studies that were considered to be relevant was 1995 to the present.

The following keywords were used: phyllodes tumor, phyllodes tumor, phyllode tumor, phyllodes tumor, phyllodes tumor, phyllodes tumor, breast phyllodes, breast phyllodes, phyllodes radiotherapy, phyllodes radiotherapy, phyllodes radiation, phyllodes radiation, cystosarcoma phyllodes, cystosarcoma phyllodes, phyllodes tumor breast, phyllodes tumor breast, phyllodes malignant, phyllodes borderline, phyllodes benign, phyllodes malignant, phyllodes borderline, phyllodes benign. These keywords were combined with the following Boolean Operators: ‘OR’, ‘AND’ and the wildcard symbol ‘*’.

The advanced search was narrowed down to look for results in only the titles of the studies. Because of the small number of results returned from the queries performed to all of the databases and due to the specificity of the studies required, all main articles that matched the criteria were also scanned manually by the authors for more references to studies that could be included in the review. Moreover, all research material gathered had to be conducted ethically following the World Medical Association Declaration of Helsinki, and any studies not conforming to these principles were not included in the initial result set.

Inclusion and exclusion criteria

Exclusion criteria. Due to the subject of this review and the fact that there is still much to learn about it, the result set of the combined searches was not massive. To further narrow down the results and make it a subset of studies that were of interest, any studies that did not measure any LR even if there weren't any, were excluded. Also, any studies that did at least consider mastectomy as an option, even if mastectomy wasn't performed eventually, were removed from the result set. If the studies remaining did not involve any malignant PTs they were also excluded along with every study that did not reference radiotherapy as a consideration and, if radiotherapy wasn't a consideration, the existence of a valid reason as to why it was not preferred. If a study did not contain any detailed information on the number of LRs after a specific treatment, for example ‘10 patients having local occurrence after they underwent a mastectomy and 20 patients having local occurrence after they underwent local excision, it was also excluded from the set.

Inclusion criteria. Furthermore, all studies should also specify a mean or median age. The age range should have been between 20 and 55 years. There should also be a reference to the method of treatment for the PT whether it was a breast-conserving surgery (BCS) or a mastectomy. There should also be at least some patients in the study with LR in order to review the rate at which the tumors reappeared locally. A distinction between malignant and benign or borderline PTs of the breast (PBT) with the actual amount of patients in each category should also be present in the study so the reviewers could better understand and identify why the researchers in these studies concluded to specific treatments and practices. A reference to follow-ups, even if the patients chose not to have any was also one factor to deem a study eligible for reviewing.

Data extraction. Two authors separately reviewed the 10 remaining studies after the inclusion and exclusion criteria were applied to the result set. The number of participants, the mean or median age, the number of patients with benign, borderline, or malignant tumors, the number of patients that underwent BCS or mastectomy, any patients that were exposed to radiotherapy, the follow-up period in months or any patients that had LR of the tumor were the main extraction items from the data. If a specific study allowed it, the authors also extracted the number of patients that had an LR after a BCS, or an LR after mastectomy. The preferred method for operating on LRs and whether it was partial/local mastectomy or local/wide excision was also extracted. If there was any history of fibroadenoma before the appearance of a PT it was deemed as important information and was also recorded.

The findings of the two authors were then compared to each other and in every scenario where there was a dispute on the data that were extracted, a joint review of the study would take place, and if there were still any discrepancies between the reviewers a group discussion would occur to resolve it. Some data were still discordant after the joint effort of the authors and could not be extracted from certain studies even after the reviewing took place. Due to that, all authors agreed to mark the data for these studies as ‘N/A’ based on the context of the uncertain information. For the detailed table
of extracted data please refer to Table I. The study data have also been registered with the National Institute for Health Research's PROSPERO database on the 21st of February 2021 (ID: CRD42021230914).

Statistical analysis. Review Manager (RevMan) v5.3, a tool developed by Cochrane to support the preparation and maintenance of systematic reviews, was used for this systematic review. It was run in Non-Cochrane mode. The tool allowed the authors to pool together all the different data that were extracted from the 10 different studies manually and provide a combined result. The outcomes of LR for both BCS patients and patients that underwent mastectomy were fed into the software as dichotomous values and were analyzed as odd ratios (ORs). The analysis was performed using the Mantel-Haenszel method and by utilizing a fixed effect analysis model. The confidence intervals were set to 95%. RevMan also assessed the statistical heterogeneity by using the I² index. The intervals for I² were set as follows: I² <25% was considered to represent low heterogeneity, I² >25% but also I² <75% was considered to represent moderate heterogeneity, and I² >75% was considered to represent high heterogeneity. Figs. 1 and 2 have been directly extracted from RevMan and represent forest plots visually indicating the statistical significance of the meta-analysis of the data the authors extracted from the selected studies.

Results

Study selection process. 484 studies were initially identified after searching all medical web databases the authors utilized and all duplicates from the result sets of these databases were removed. Filtering for a year range while performing the search in these databases helped the authors avoid the manual labor required to distinguish recent and older studies. The authors were only interested in studies that were performed over the last 25 years. After reviewing the titles of the result set, 389 studies were excluded with 95 studies remaining for abstract evaluation. After the abstract screening of these 95 studies, 73 studies were removed from the result set either because of a lack of information presented or their comparison with other elements that were irrelevant to this review. The remainder of this result set were 22 studies which the authors then closely evaluated by performing a full-text analysis, ensuring all the relevant parameters of interest were measured and sufficient details were present in each study. From this result set, 5 studies were missing important data such as referencing appropriate data for LR on patients after they underwent mastectomy or any other BCS or the outcome wasn't clear for one of the two groups the authors were interested in, for example there was a reference to local occurrence on patients that had a mastectomy but not any other form of surgery-like local excision. 6 studies were also excluded because they were...

Table I. Extracted data from final result set of studies.

| Study name, year | Population | Mean age (years) | BN/BL | MLG | BCS | MT | RT | FLW MD | LR after BCS | MT | LR after LR | LR (FA) | History (FA) (Refs.) |
|------------------|------------|------------------|-------|-----|-----|----|----|--------|--------------|----|-------------|---------|---------------------|
| Barrio et al, 2007 | 293        | 41.7             | 203   | 90  | 245 | 48 | 0  | 94.8   | 35            | 31 | 4           | 21      | 10 199 (16)         |
| Chen et al, 2005 | 172        | 50.0             | 143   | 29  | 126 | 46 | 2  | 71.2   | 19            | 19 | 0           | 14      | 5 22 (11)          |
| Cheng et al, 2006 | 182        | 37.0             | 151   | 31  | 132 | 50 | 3  | 60.5   | 20            | 20 | 0           | 17      | 3 N/A (13)         |
| Fajdić et al, 2007 | 36         | 56.0             | 30    | 6   | 29  | 7  | 0  | 98.5   | 3             | 3  | 0           | 3       | 0 N/A (17)         |
| Fou et al, 2006  | 27         | 51.0             | 0     | 27  | 18  | 9  | 0  | 52.0   | 4             | 4  | 0           | 4       | N/A (14)           |
| Jang et al, 2012 | 164        | 43.0             | 124   | 40  | 148 | 16 | 3  | 33.6   | 31            | 28 | 3           | N/A N/A N/A N/A (18) |
| Kapiris et al, 2001 | 48        | 47.0             | 0     | 48  | 24  | 24 | 10 | 108.0  | 21            | 10 | 11          | 14      | N/A N/A (10)       |
| Moffat et al, 1995 | 32        | 52.0             | 27    | 5   | 20  | 12 | 0  | 135.0  | 6             | 6  | 0           | 2       | 4 N/A (9)          |
| Roa et al, 2006   | 47         | 42.5             | 37    | 10  | 30  | 17 | 3  | 97.3   | 9             | 8  | 1           | N/A N/A N/A (12)  |
| Taira et al, 2007 | 45         | 45.0             | 36    | 9   | 42  | 3  | 0  | 101.0  | 6             | 6  | 0           | 0       | 3 (15)             |

BN/BL, benign/borderline; MLG, malignant; MT, mastectomy; RT, radiotherapy; FA, family appearance; FLW MD, follow-up median; LR, local recurrence; BCS, breast-conserving surgery.
systematic reviews and 1 was excluded because it had no relevant outcome for the purpose of this study. The outcome of the study selection process was 10 studies (9-18). The literature review can be seen in Fig. 3.

Population characteristics. From these 10 studies, the total amount of participants was 1,046. The lowest mean age of the studies was 37 years of age and the highest was 56. A total of 751 patients had benign or borderline PT. A total of 295 patients had a malignant PT. Then, 232 underwent mastectomy as a therapeutic approach while 814 were treated with any other BCS-like local or wide excision. For 21 patients radiotherapy was also offered as part of the treatment. The follow-up means in months varied, with the lowest being 33.6 months and the highest being 135 months. 154 of these patients that underwent a mastectomy, local or wide excision, and radiotherapy had an LR of the tumor. 19 had LR after mastectomy was performed while 135 had LR after other BCS operations. 134 patients had a history of fibroadenoma before being diagnosed with PT. Of all the patients who developed LR, 26 had a mastectomy to treat the LR, and 77 had milder surgery such as local or wide excision. Table II presents the baseline characteristics of the studies the authors included.

Meta-analysis

LR in patients after any BCS. The final result set data consisted of 10 studies with 1046 participants. In Fig. 1 which can be seen further below, analytical data on the odds ratio, heterogeneity, and the likelihood of LR after a BCS are being demonstrated. The odds ratio for LR after a BCS is 0.05 with 0.04 and 0.07 confidence intervals (CIs). The heterogeneity of the results is at 85% which, as stated earlier is considered high. Based on the CI and the p-value in the figure it is fair to say that the result is statistically significant and that LR is not very common for patients that were treated for PBT with BCS.

Now contrary to benign and borderline tumors being treated with BCS treatments, mastectomy is preferred in malignant PTs due to their potentially aggressive behavior. One could argue that since the treatment is harsher and a lot more tissue is being removed, maybe it is more effective as well. Based on the results, the percentage that corresponds to Figure 2. Forest plot indicating LR on patients after they have been treated with mastectomy. LR, local recurrence; BCS, breast-conserving surgery; M-H, Mantel-Haenszel; CI, confidence interval.

Figure 2. Forest plot indicating LR on patients after they have been treated with mastectomy. LR, local recurrence; BCS, breast-conserving surgery; M-H, Mantel-Haenszel; CI, confidence interval.

LR in patients after mastectomy. On the following forest plot (Fig. 2), analytical data on the odds ratio, heterogeneity, and the likelihood of LR after a mastectomy can be observed. The heterogeneity, at 84% is at par with the LR after a BCS and is considered high. The odds ratio is at 0.03 with 0.02 and 0.05 CIs. The LR on patients that were treated with mastectomy for PBT is not common as concluded from the P-value which signifies that the result is statistically significant.

Now contrary to benign and borderline tumors being treated with BCS treatments, mastectomy is preferred in malignant PTs due to their potentially aggressive behavior. One could argue that since the treatment is harsher and a lot more tissue is being removed, maybe it is more effective as well. Based on the results, the percentage that corresponds to
Keeping this in mind, professionals in the field currently
accurate data kept by the institutions treating the patients due
to the nature of the staff that maintains the registry and since
instances tend to be inconclusive or different from other
there are also some limitations, such as the lack of follow-up data from
because they arise from stromal elements in the breast (20,21). Radiotherapy is the
in situations where the tumor is proven large in size, malignant and aggressive
Lumpectomy and mastectomy can also occur in situations
malignant breast tissue to ensure the tumor won’t recur. This process is also known as wide excision. Lumpectomy
is an extremely rare in its
Based on one of the largest retrospective systematic reviews
to date on the matter, which was performed by Gnerlich et al,
scientists still face a limitation when attempting to report
and rely on their findings since most authorities monitoring
the prognosis, diagnosis, and outcomes of PT tend to focus
on collecting data for malignant cases only, making it hard to
cross-reference rates and outcomes since, as reported
earlier in this study, a malignant PT is extremely rare in its occurrence (20).
Even more so, when scientists attempt to conclude the
occurrence of the tumor itself (20).

Table II. Baseline characteristics of studies included.

| First author (Refs.) | Country (year) | Population | Mastectomy | BCS | RT | Mean age (years) | Mean follow-up (months) |
|----------------------|----------------|------------|-------------|-----|----|-----------------|------------------------|
| Moffat CJC (9)       | England (1995) | 32         | 12          | 20  | N/A| 52.0            | 135.0                  |
| Kapiris I (10)       | England (2001) | 48         | 24          | 24  | 10 | 47.0            | 108.0                  |
| Chen WH (11)         | Taiwan (2005)  | 172        | 46          | 126 | 2  | 50.0            | 71.2                   |
| Roa JC (12)          | Chile (2006)   | 47         | 17          | 30  | 3  | 42.5            | 97.3                   |
| Cheng SP (13)        | Taiwan (2006)  | 182        | 50          | 132 | 3  | 37.0            | 60.5                   |
| Fou A (14)           | USA (2006)     | 27         | 9           | 18  | N/A| 51.0            | 52.0                   |
| Tairo N (15)         | Japan (2007)   | 45         | 3           | 42  | N/A| 45.0            | 101.0                  |
| Barrio AV (16)       | USA (2007)     | 293        | 48          | 245 | N/A| 41.7            | 94.8                   |
| Fadjic J (17)        | Croatia and Germany (2007) | 36 | 7 | 29 | N/A | 56.0 | 98.5 |
| Jang JH (18)         | Korea (2012)   | 164        | 16          | 148 | 3  | 43.0            | 33.6                   |

RT, Radiotherapy; BCS, breast-conserving surgery.

LR BCS vs. mastectomy. In both measurements, it was identified that LR was not common. Both forest plots had 95% CI, a low OR, and a very low p-value which made the results statistically significant and of high heterogeneity. It is interesting to notice that the percentage of individuals having an LR after BCS was higher at 16.58% than the percentage of individuals having LR after mastectomy at 8.19%. Is it due to the bigger amount of patients undergoing BCS that a noticeable higher rate of LR persists? Or is it because BCS techniques are milder than a mastectomy? The important result to mind here is that LR is not as common in patients who were treated with local excision, wider excision, or mastectomy. Also, a higher LR rate occurs for patients treated with any form of BCS when compared to individuals who underwent a mastectomy.

Discussion

There is still much to discover about PT. Not a lot of extensive studies exist on the subject and due to its very rare occurrence and the minimal amount of data existing to date; it is unlikely that at this point a solid treatment process can be followed as the gold standard. Numerous scientists attempted to perform retrospective studies on the matter but their findings did not suggest a conclusive result in terms of disease-free survival or overall survival rates after treating this rare neoplasm. We strongly consider that breast cancer management should be a part of gynecological care. Worldwide more and more gynecologists are being specialized in breast cancer management since it can be diagnosed in women of a younger age who want to preserve the possibility of a future pregnancy.

Keeping this in mind, professionals in the field currently take all necessary measures to ensure treatment of this tumor will allow for greater life expectancy, the well-being of patients, and the ability to have a pregnancy even after being treated. Therefore, most physicians tend to remove the tumor via surgery along with the extraction of 1 cm or more of surrounding healthy breast tissue to ensure the tumor won't recur. This process is also known as wide excision. Lumpectomy and mastectomy can also occur in situations where the tumor is proven large in size, malignant and aggressive. Because of this characteristic, PT might recur after their initial extraction. And due to their irresponsiveness to other breast cancer treatments such as chemotherapy, drugs, or hormone therapy, PTs are being treated similarly to sarcomas. Another reason they are being treated as such is that they arise from stromal elements in the breast (20,21). Radiotherapy is the standard for treating sarcomas and a lymph node sampling on a percentage of the patients that underwent this treatment backs up this theory (20).

Based on one of the largest retrospective systematic reviews to date on the matter, which was performed by Gnerlich et al, scientists still face a limitation when attempting to report and rely on their findings since most authorities monitoring the prognosis, diagnosis, and outcomes of PT tend to focus on collecting data for malignant cases only, making it hard to cross-reference rates and outcomes since, as reported earlier in this study, a malignant PT is extremely rare in its occurrence (20).
Despite these facts though, in most studies on this subject, some common factors lead to the utilization of radiotherapy, as mentioned earlier, as a method for additional treatment after extraction. Factors such as the size of the tumor, its malignancy, the age of the patient, the date of the diagnosis, and the sampling of the node are taken into consideration. Various studies attempted to compare results for patients that were diagnosed with PT and were treated with an alternative therapeutic method. Some patients underwent a mastectomy, others underwent lumpectomy or wide excision. Mastectomy was mostly used on women of older age and/or patients with larger tumors. The survival rate for women who underwent mastectomy was lower than for women who were treated with wide excision (21) but that is due to the more aggressive and malignant nature of the tumor. All studies signify though, that when radiotherapy is utilized as a part of the treatment in malignant PT with a high risk of post-treatment LR (20,22-24) the patients have a higher survival rate based on follow-ups and monitoring.

It is also noteworthy that there isn't any significant difference when utilizing radiotherapy as a treatment option between patients with a low and high risk of recurrence (20) and this is due to, again, the lack of collected data on the marginal width of the tumor. The systematic review by Gnerlich et al (20) indicates that although the common consensus is to perform radiotherapy for patients with a tumor width of at least 1 cm, there are cases where patients with less than 1 cm width underwent radiotherapy.

Another common characteristic between studies is the indication of decreased rates in LR for patients who underwent radiotherapy in comparison to patients that underwent surgery for removal alone. Similarly, patients that underwent mastectomy instead of any other BCS had a decreased rate of LR. That is why, as observed by the studies the authors investigated, mastectomy was preferable as a second treatment option. Moreover, the period for any LR if any, increased. This led to the conclusion that patients, who were exposed to radiotherapy or underwent a mastectomy, or were treated with both to remove any borderline or malignant PTB had a higher survival rate. This is because their follow-up exams did not suggest any local occurrence of the tumor after extraction (23).

Based on this and other studies' findings, surgical excision and radiotherapy tend to be the preferred methods of treating PT. The authors concluded that standard common practices for other more common malignancies helped in the treatment and survival rates of patients suffering from a PT. Because of this tumor's unpredictable behavior though and due to the lack of excess data to this date, the scientific community still has a way to go in order to advance in an improved understanding of this rare form of cancer and identify the appropriate treatment practices physicians should adapt to help minimize LR and improve the disease-free and overall survival rates.

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Availability of data and materials

The data of the present study was registered with PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=230914, accession no. CRD42021230914). The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

IB participated in the conceptualization, designed methodology, analyzed data and wrote and prepared original draft. AK designed the methodology, analyzed data, wrote and prepared the original draft. DD and NK analyzed data. SMG designed methodology, analyzed data and prepared original draft. KS designed methodology and prepared original draft. CD and SK designed Methodology and interpretation of data. IB and AK confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The authors hereby declare that the research material presented in the present study has been conducted ethically in accordance with the World Medical Association declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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