SUMMARY

Background: Phyllodes tumors represent a heterogeneous and minority group of the breast neoplastic pathology. The malignant transformation of a Phyllodes tumor is a rare event, representing less than 1 % of breast tumors.

Methods: Our study analyzed all cases of Phyllodes breast tumors diagnosed in two medical institutions during a period of five years. We compared long term outcome results for the patients who underwent conservative treatment and mastectomy.

Results: The analysis of the histopathological results revealed a number of 39 (0,454 % of all the neoplastic cases studied) malignant Phyllodes tumors. There has been a total of 23 mastectomies, 3 of which were performed palliatively, and in 14 cases a conservatory approach was preferred. Out of 34 patients who benefited from curative intent surgery, 9 developed a local relapse (5 in the conservative procedures group and 4 in the mastectomy group).

Discussions: Surgery plays an important role in the successful therapy of Phyllodes tumors. The tumors' histological type and subtype can influence the outcome and the treatment should be uniquely adapted to each case. Recognizing morphological features which have an important prognostic value and adapting protocols to these features can improve the treatment and outcome of this particular pathology.

Key words: rare breast tumor, Phyllodes tumors

RéSUMÉ

Étude multicentrique sur les tumeurs Phyllodes du sein pour une période de cinq ans

Contexte: Les tumeurs Phyllodes représentent un groupe hétérogène et minoritaire de la pathologie néoplasique du sein. La transformation maligne d’une tumeur Phylloide est un événement rare, représentant moins de 1 % des tumeurs du sein.

Méthodes: Notre étude a analysé tous les cas de tumeurs mammaires Phyllodes diagnostiquées dans deux établissements médicaux pendant une période de cinq ans. Nous avons comparé les résultats à long terme pour les patients qui ont subi un traitement conservateur ou une mastectomie.

Résultats: L’analyse des résultats histopathologiques a révélé un nombre de 39 (0,454 % de tous les cas néoplasiques étudiés) tumeurs malignes Phyllodes. Il y a eu au total 23 mastectomies, dont 3 ont été effectuées palliativement, et dans 14 cas une approche conservatrice a été préférée. Sur 34 patients qui ont bénéficié d’une chirurgie curative, 9 ont développé une rechute locale (5 dans les traitements conservateurs et 4 dans les mastectomies).

Discussions: La chirurgie joue un rôle important dans le succès du traitement des tumeurs Phyllodes. Le type et le sous-type histologique de la tumeur peuvent influencer le résultat et le traitement doit être adapté de manière unique pour chaque cas. Reconnaître les caractéristiques morphologiques qui ont une valeur pronostique importante et adapter des protocoles à ces caractéristiques peuvent améliorer le traitement et les résultats de cette pathologie particulière.

Mots Clés: tumeur du sein rare, tumeurs Phyllodes
The Phyllodes tumor is a unique entity characterized by a complex histopathological structure. These fibro-epithelial tumors have a hypercellular stroma and benign glandular elements covered by an epithelium which creates a foliar model. It is this exact epithelial component which differentiates the Phyllodes tumor from sarcomas and the foliar aspect is responsible for its name (“phyllo” in Greek means leaf). It was described for the first time as the cystosarcoma Phyllodes by Johannes Muller (the “fern leaf” tumor) (1). However, the term is not very precise, because Phyllodes tumors do not always have the malignant character associated with sarcomas, develop hematogenous metastasis less often and only a small minority presents a cystic morphology.

Phyllodes tumors represent a rare pathology with a total incidence reported by extensive studies of 0.3% - 2.5% of the total malignant breast tumors (2,3). A study carried out in Singapore suggested an incidence of 6.92% (4) in populations of Asian race.

Unfortunately, because of the low incidence, the tumors are not well documented, literature pinpointing only studies with either a small number of patients, or extended over many years (which does not permit a comparative analysis). Without multicenter, randomized studies, creating a treatment protocol is a strenuous task.

A high grade of variability of histologic features can be observed both in distinct Phyllodes tumors as well as in those present in the same lesion. The tumors may present atypia, necrosis, a moderate or extensive stromal growth, a moderate or accelerated mitotic activity, expansive, compressive and even invasive margins. The characterization and placement is an important part of the diagnosis because all the previously mentioned elements have a prognostic value and are associated with the capacity of producing a relapse or generating distant metastasis.

Azzopardi and Salvadori have studied all these elements and based on them classified Phyllodes tumors as benign, borderline or malignant (5, 6). Although some authors consider the borderline category as useless, this classification is recognized by WHO and is the most used (7). By using this classification, based on clinical observations, it is considered that benign Phyllodes tumors are responsible for a low rate of local recurrence and do not metastasize at a distance, borderline ones are more likely to give local relapses and have a low probability to create distant metastasis, and lastly, malignant ones have a high rate of local recurrence and metastatic potential. This placement is an arbitrary one and literature signals out some cases which do not follow the pattern. (8-11)

The malignant transformation of a Phyllodes tumor is a rare event, consisting of less than 1 % of all breast tumors. The incidence, clinical characteristics and treatment options will be discussed in the following sections.

**METHODS**

Our study analyzed all the patients diagnosed with this certain breast disease in the Oncological Institute “Prof. Dr. Alex. Trestioreanu” Bucharest and “Coltea” Clinical Hospital between 2011 and 2015 (5 years). The analysis was possible with the permission and written consent of the two previously mentioned institutions.

In order to create the patient groups we utilized queried databases used for reporting in the DRG system (Diagnosis Related Groups). The classification system is a classification scheme of the patients based on the diagnosis. This system is similar to the international disease classification system (International Classification of Diseases – ICD), in which the diagnoses are classified into classes and subclasses.

Repeated hospitalizations were queried with diagnoses and procedures performed on these occasions. These tools are very useful for tracking and monitoring patients, with a given limitation, that they must be admitted in the same medical institution.

The exclusion criteria was represented by cases the data of which broke technical specifications of the minimum data patient set and cases where we could not register the result of the histopathological examination.

For this study we classified Phyllodes tumors following histologic criteria based on the World Health Organization (WHO) nomenclature into benign, borderline and malignant.

Breast surgical procedure codes were divided into two classes: mastectomies and conservative procedures. Conservative surgery included all procedures that partially spare the breast, such as sectorectomy, quadrantectomy or atypical oncoplastic resections. Mastectomies included variations that preserve the skin or the nipple-areolar complex (skin sparing, nipple sparing), but with total excision of the mammary gland.

**The identified limits of the study**

The known and identified limits of this study are the following: a reduced number of patients, the retrospective character of the study and the fact that the patient groups were selected and are known by the person who conducted the study, and the lack of homogeneity of some data and/or investigations that were sometimes performed in different medical institutions or private practice.
A FIVE-YEAR MULTI-CENTRIC STUDY OF PHYLLODES TUMORS OF THE BREAST - SCÅNASU et al vol. 51, no. 4, 470

Case Processing Summary

<table>
<thead>
<tr>
<th>Mastectomy</th>
<th>Total N</th>
<th>N of Events</th>
<th>Censored</th>
<th>N</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservative</td>
<td>14</td>
<td>5</td>
<td>9</td>
<td></td>
<td>64.3%</td>
</tr>
<tr>
<td>Radical mastectomy</td>
<td>20</td>
<td>4</td>
<td>1</td>
<td>16</td>
<td>80.0%</td>
</tr>
<tr>
<td>Overall</td>
<td>34</td>
<td>9</td>
<td>25</td>
<td></td>
<td>73.5%</td>
</tr>
</tbody>
</table>

Means and Medians for Survival Time

<table>
<thead>
<tr>
<th>Mastectomy</th>
<th>Mean (95% Confidence Interval)</th>
<th>Median (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservative</td>
<td>Estimate (Std. Error)</td>
<td>9.021 (.464)</td>
</tr>
<tr>
<td>Radical mastectomy</td>
<td>12.229 (.307)</td>
<td>11.626 (12.831)</td>
</tr>
<tr>
<td>Overall</td>
<td>11.431 (.414)</td>
<td>10.619 (12.242)</td>
</tr>
</tbody>
</table>

a. Estimation is limited to the largest survival time if it is censored.

Overall Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Log Rank (Mantel-Cox)</th>
<th>df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi-Square</td>
<td>10.426</td>
<td>1</td>
<td>.001</td>
</tr>
</tbody>
</table>

Test of equality of survival distributions for the different levels of mastectomy.

Figure 1-Kaplan-Meier analysis of conservative surgery and mastectomy procedures for the local recurrence event.
RESULTS

The analysis of the histopathological results revealed a number of 39 (0.454% of all the neoplastic cases studied) malignant Phyllodes tumors. There has been a total of 23 mastectomies, 3 of which were performed palliatively, and in 14 cases a conservative approach was preferred. A total of 18 axillary lymphadenectomies were completed, with ganglia invasion being confirmed in 3 cases.

There was a very low rate of postoperative complications which had a favorable outcome with conservative treatment. No intra-operative or in-hospital mortality was encountered for this group. Furthermore, there was not a single reported case of arm lymphedema after surgery.

Out of the collected data, we considered that local recurrence was one of the most reliable and important element. Local recurrence is mentioned upon repeated hospitalizations in the 5 year period of the study. A number of 3 cases were excluded because of the palliative objective of the initial surgery.

The analysis of the 34 cases which underwent curative surgery depicts a local recurrence for 9 patients. Out of these 9 cases, 5 had stood conservative treatment and 4 had a mastectomy.

For patients who suffered a curative mastectomy the mean time for recurrence is 12.2 months.

For patients who suffered a conservative surgery the mean time for recurrence is 9 months.

There are statistically significant differences between the two curves (Sig = 0.001).

DISCUSSIONS

The preoperative diagnostic endeavor is important because the term Phyllodes tumor includes a wide spectrum of pathological entities. At one end of the spectrum lie the malignant tumors which are characterized by a rapid growth but especially by the capacity to metastasize, thus needing wide resections with safety margins. At the other end however, we talk about benign Phyllodes tumors for which a simple tumorectomy can be enough or even more, which can behave like a usual fibroadenoma and seemingly be treated in a non-surgical way. Furthermore, natural evolution can be unpredictable, studies mentioning the presence of relapses and metastasis, even for tumors histologically found as benign. (3)

Until not long ago, mastectomy represented the standard procedure for the treatment of every kind of Phyllodes tumor. (13,14) In the meantime, studies demonstrated the fact that radical mastectomy does not bring any beneficial results concerning survival in spite of higher incidence regarding local relapses found after breast sparing procedures, and for that reason nowadays conservative surgery is used more often. On the other hand, it is also clear that tumorectomy with margins very near the tumor is not an acceptable solution because such a procedure can be followed by a high rate of recurrence.

Nowadays ESMO and NCCN guidelines recommend (in case of a preoperative diagnosis) an excision with a safety margin of minimum 1 cm for the treatment of borderline or malignant Phyllodes tumors. (15-17) This is also considered to be the most important predictive factor for the evolution of the Phyllodes pathology.

When the tumor reaches an extent of over 10 cm (gigantic), most of the times, the tumor/glandular volume ratio makes the conservative excision almost impossible or useless, thus paving the way to a radical approach.

The appearance of local complications such as bleeding or superinfection, even in the context of a disseminating disease, can represent an indication for a palliative mastectomy.

For cases that were initially considered to be fibroadenomas and which were not accompanied by a confirmation of the pre or intraoperative diagnosis, it is highly recommended to perform a reoperation for the re-excision of the tumoral bed and to obtain safety margins. Using an alternative based on adjuvant radiotherapy does not show to have a proven efficacy for this pathology and is reserved only for the cases where a reoperation cannot be performed. Margins close to the tumor are accepted only in the case of benign Phyllodes tumors, studies pinpointing a relapse rate at 5 years of only 4%. (18) There are some controversies regarding margins invaded by tumors, some authors opting for a re-excision, while others for a regular close monitoring. (7)

In the situation where a preoperative diagnosis cannot be confirmed, the routine dissection of axillary nodes is not necessary because Phyllodes tumors metastasize preferentially via the blood route. Complex studies show a rate of ganglia invasion discovered in less than 10% of patients. (7,19, 20)

However, the procedure is indicated if clinical or imagistic lymphadenopathies are present, especially when the anatomopathological examination is not performed. If the preoperative diagnosis is obtained, the sorting method for patients who may benefit from a lymph dissection might be a preoperative axillary ultrasound and a percutaneous biopsy of the morphological suspect lymph nodes.

The selective lymph dissection of the sentinel lymph node was demonstrated in the case of epithelial tumors of the breast and offers benefits by lowering the number of axillary lymph dissections and the morbidity determined by these procedures. However, most studies followed cases involving tumors of less than 2 cm and do not indicate the technique in case of large tumors or if clinical lymphadenopathies are present. (21)

The local recurrence risk is high for the histologically malignant tumor types. In a study with a population of 51 patients treated using conservatory surgery, Salvadori et al report that relapse was found in 14 cases. (6)

Local relapse in Phyllodes tumors depends on two sets of factors: tumor biology and the amplitude of surgical excision.

The aggressive and recurrent character of these tumors is associated with a series of histologic characteristics such as: mitotic activity, tumor margin (compressive or invasive) and stromal cell atypia. For some cases, depending on breast size and tumor localization, mastectomy might
be required even for tumors with a diameter less than 5 cm. (5, 22)

For the management of gigantic Phyllodes tumors, a complete excision of the lesion is required in order to minimize the recurrence risk. Tumor invasion of the thoracic wall may necessitate a partial excision of the pectoral muscles. The use of adjuvant radiotherapy may be recommended in cases where the tumor is adherent to the thoracic wall due to a high probability of an incomplete microscopic resection. (2, 23)

In cases where one can anticipate that radiotherapy is not necessary, an immediate reconstruction of the breast can follow the performed mastectomy. Singh et al published a series of articles regarding 7 patients diagnosed with Phyllodes tumors who suffered a mastectomy and an immediate reconstruction and who had a follow-up of 40 months with a local relapse detected in only case. Other authors consider that an immediate reconstruction after a mastectomy is a safe alternative for cases where conservative surgery cannot obtain a secure R0 excision. They also underline the advantage given by such a procedure in reducing emotional trauma and the potential difficulties encountered in the process of monitoring and detecting local recurrences. (24-26)

CONCLUSIONS

Recognizing morphological features which have an important prognostic value and adapting protocols to these features can improve the treatment and the outcome of this particular pathology. Some authors who are preoccupied by this certain pathology, propose the founding of senology centers, because an emphasis on this pathology might allow the standardization of obtained data, the trigger for consistent prospective studies, the inclusion of patients in radio or chemotherapy multi-centric protocols and thus improving disease awareness and the obtained results.

REFERENCES