

Immediate Exercises versus Late Postoperative Exercises for Onco-Mammary Surgeries: Limitation or Release of Range of Motion?

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Exercícios Imediatos versus Exercícios Tardios no Pós-Operatório de Cirurgias Oncomamárias: Limitação ou Liberação da Amplitude de Movimento?

Ejercicios Inmediatos versus Ejercicios Tardíos en el Postoperatorio de Cirugías Oncológicas Mamarias: ¿Limitación o Liberación de la Amplitud de movimiento?

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Abstract

Introduction: Breast cancer is the most common type among women in the world and in Brazil, it is part of a heterogeneous group of diseases, thus having different signs and behavior. Possible treatments include surgical approaches, chemotherapy, radiotherapy, endocrine therapy, and target therapy. The surgical procedure can lead to several complications and consequences for the patient, so a follow-up process is necessary after this approach, exercises are fundamental to return functionality and quality of life, but there is divergence in the literature regarding the moment of beginning of the execution of the same. **Objective:** To perform a systematic literature review, present studies and analyze the impact of the release of immediate versus late exercises, after onco-mammary surgeries, without associated plastic intervention. **Method:** This is a systematic literature review. To perform the same, a search was made in the database of PubMed, PEDro and SciELO databases using the descriptors: rehabilitation, breast neoplasms, prospective period, prospective care, exercise and their respective ones in the Portuguese language, being these, rehabilitation, breast cancer, postoperative period, postoperative care and exercise. **Results:** For the accomplishment of this study, 48 articles were found, being 12 relevant to the review. **Conclusion:** The studies are divergent, but a literary update emphasizes immediate postoperative exercises of onco-mammary surgeries can be used without increasing the incidence of complications.

Key words: Exercise Therapy; Breast Neoplasms; Postoperative Care; Review.

Resumo

Introdução: O câncer de mama é o tipo mais comum entre as mulheres no mundo e no Brasil, faz parte de um grupo heterogêneo de doenças, tendo assim sinais e comportamento distintos. Os tratamentos possíveis são abordagens cirúrgicas, quimioterapia, radioterapia, endocrinoterapia e terapia-alvo. O procedimento cirúrgico pode levar a diversas complicações e consequências para a paciente, sendo assim é necessário acompanhamento após essa abordagem, e exercícios são fundamentais para devolver a funcionalidade e a qualidade de vida. Porém existem divergências na literatura em relação ao momento de início da sua execução. **Objetivo:** Realizar uma revisão sistemática de literatura, apresentar estudos e analisar o impacto da liberação de exercícios imediatos versus tardios, após cirurgias oncomamárias, sem intervenção plástica associada. **Método:** Trata-se de um estudo de revisão sistemática de literatura. Foi realizada uma pesquisa no banco das bases de dados PubMed, PEDro e SciELO, utilizando os descritores: *rehabilitation, breast neoplasms, prospective period, prospective care, exercise* e no idioma português: *reabilitação, câncer de mama, período pós-operatório, cuidados pós-operatórios e exercício*. **Resultados:** Para a realização deste estudo, foram encontrados 48 artigos, sendo 12 relevantes à revisão. **Conclusão:** Os estudos se apresentam divergentes, porém observa-se uma atualização literária que enfatiza quais exercícios imediatos no pós-operatório de cirurgias oncomamárias podem ser empregados sem trazer aumento na incidência de complicações.

Palavras-chave: Terapia por Exercício; Neoplasias da Mama; Cuidados Pós-Operatórios; Revisão.

Resumen

Introducción: El cáncer de mama es el tipo más común entre las mujeres en el mundo y en Brasil, forma parte de un grupo heterogéneo de enfermedades, teniendo así signos y comportamiento distintos. Los tratamientos posibles son abordajes quirúrgicos, quimioterapia, radioterapia, endocrinoterapia y terapia objetivo. El procedimiento quirúrgico puede llevar a diversas complicaciones y consecuencias para la paciente, por lo que es necesario un proceso de seguimiento después de este enfoque, ejercicios son fundamentales para devolver funcionalidad y calidad de vida, pero existe divergencia en la literatura en relación al momento de inicio de la su ejecución. **Objetivo:** Realizar una revisión sistemática de la literatura, presentar estudios y analizar el impacto de la liberación de ejercicios inmediatos versus tardíos, después de cirugías onco-mamarias, sin intervención plástica asociada. **Método:** Se trata de un estudio de revisión sistemática de la literatura. Para la implementación se trataba de una encuesta en la orilla de las bases de datos PubMed, SciELO, PEDro y utilizando las siguientes palabras clave: *rehabilitación, neoplasias de la mama, del período prospectivo, de cuidado prospectivo, de ejercicio y su en portugués, siendo éstas, la rehabilitación, el cáncer de mama, período postoperatorio, cuidados postoperatorios y ejercicio*. **Resultados:** Para la realización de este estudio se encontraron 48 artículos, siendo 12 relevantes a la revisión. **Conclusión:** Los estudios se presentan divergentes, pero se observa una actualización literaria que enfatiza que los ejercicios inmediatos en el postoperatorio de cirugías onco-mamarias pueden ser empleados sin traer aumento en la incidencia de complicaciones.

Palabras clave: Terapia por Ejercicio; Neoplasias de la Mama; Cuidados Posoperatorios; Review.

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INTRODUCTION

Breast cancer is the most incident in women in the world and in Brazil, excluding non-melanoma skin cancer. Its onset is more common after 35 years old, progressing with ageing, but can also affect younger women. Men are rarely affected¹.

According to Sledge et al.², the treatments for breast cancer have evolved consistently along the story. Treatments as extensive and mutilation surgeries have given place to more tailored and conservative treatments.

The treatment varies according to the disease staging, biological characteristics as well as the patient's conditions of the. The prognosis is contingent upon the extension of the disease (staging) and the characteristics of the tumor³.

It is the healthcare provider responsibility, physician or other to determine the best course of treatment tailored to each patient needs⁴. The treatment usually adopted consists of surgical approaches, chemotherapy, radiotherapy, endocrinotherapy and target-therapy⁵⁻⁷.

Problems like lymphedema, pain, paresthesia, depletion of the muscular strength and reduction of the range of motion (ROM) of the member involved are frequently observed and reported by women breast-operated and are considered the most difficult outcomes of breast cancer because they interfere in the quality of life⁸.

Physiotherapy has a key role in the recovery of these women after the onco-mammary surgery, granting the reclaiming of the functionality and the improvement of the quality of life, in addition to act in the prevention or control of the repercussions of the post-operative complications^{9,10}.

Studies affirm that women followed up by the physiotherapy team present improved adherence rates to the exercises in the first post-operative six months when compared to groups receiving only guidelines and the first is directly connected to better conditions and results for the recovery¹¹.

It is observed that several of the aforementioned complications are related to the restriction of the ROM of the ipsilateral upper member to the surgery; therefore, the assumption for the current systematic literature review concerns the immediate or late release of postoperative exercises of onco-mammary surgeries, analyzing the contribution or the damage made in the process of recovery. Thus, the present study has the objective to compare the results of exercises activities beginning in immediate or late mammary post-operation without associated plastic intervention and discuss the angle used in these exercises.

METHOD

It is a systematic review of the literature that has the objective of analyzing the impact of the immediate ROM *versus* late release postoperatively onco-mammary surgeries without associated plastic intervention.

The research was conducted through a search in the databases: PubMed, PEDro and SciELO. It were used the descriptors in English: *rehabilitation, breast neoplasms, prospective period, prospective care, exercise* and in Portuguese: "reabilitação, câncer de mama, período pós-operatório, cuidados pós-operatórios and exercício".

It were selected exclusively articles of the type *clinical trials* and randomized clinical trials, with only one experimental study of elaboration of protocol. The studies were available cost-free in full, in Portuguese and English and cutoff dates were not determined because of the low quantity of theme-related articles.

The articles were analyzed by title and abstract to obtain pertinent and relevant studies, thus, it were selected as inclusion criteria only those who analyzed and/or cited protocols of exercise in breast cancer early/delayed post-operation. It were excluded those, which approached methods of evaluation of postoperatively complications, without conduct associated or complications caused by other treatments as chemotherapy and radiotherapy.

RESULTS

Initially, it were encountered 50 articles, 39 from PubMed, seven from PEDro and four from SciELO. Of these, two were duplicated in the referenced databases, remaining 48 articles for title reading, of which, 29 were excluded because they failed to meet the criteria determined. Of the 19 selected articles for analysis of the abstracts, seven were excluded, with 12 remaining to be eligible for this study. Upon reviewing the references, no other article was included. At the end of the data search, the review included 12 articles; the flowchart of Figure 1 details all the search procedures through the selected researches to elaborate this review.

DISCUSSION

It was observed a great divergence of conducts in relation to the beginning of the functional rehabilitation of women who went through breast cancer surgical treatment. The divergences revolve around the possible complications that could be related to surgical procedure and functional recuperation of the movements of the ipsilateral shoulder of the surgery.

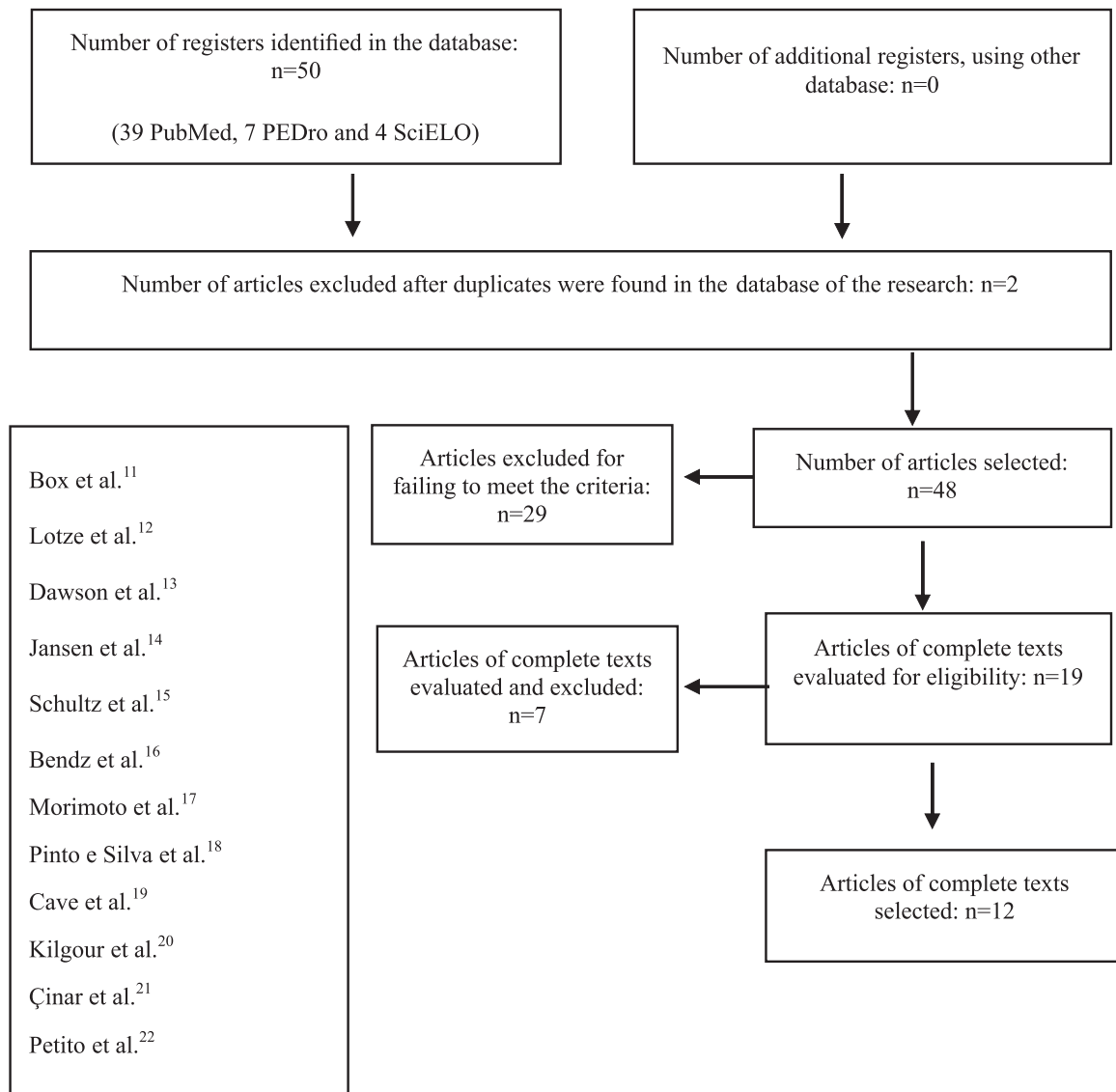


Figure 1. Flowchart of the studies identified

Lotze et al.¹² conducted a study with 36 randomized patients divided in early and delayed group, the first, initiating in the first day post-operation and shoulder limited-ROM to 40°, advancing only towards this range when the late group was released. The delayed group was approved only to perform the exercises after the eight day post-operation, also limited to 40°, also limited to 40° ROM, increasing the range only after the removal of the drain after 12 days of the surgery. This study observed that the early group remained more time hospitalized, developed more infections in the wound and formation of seroma, compared to the delayed group. However, there were no significant differences of the shoulder function in the two groups.

Years later, it was developed another study with a larger sample of patients (100) by Dawson et al.¹³, that also

believed that early exercises of the shoulder post onco-mammary surgeries could have deleterious effects for the recuperation in what concerns scarring and seroma. In his study, the exercise group initiated in the first day post-operation, while the immobilized group had a sling in the first five days. The patients in the exercise group had a higher incidence of seroma and delay of operatory wound. Post-operative infections occurred only in the exercise group. In relation to the mobility of the shoulder, the number of patients with functional loss of more than 15° was slightly major comparing with the immobilized group.

Jansen et al.¹⁴ conducted a similar study to Dawson et al.¹³ where the groups were divided likewise the former study with the difference that the immobilized group remained as such for seven days and initiated the exercises

only in the eight day post-operation. It was seen as well that the incidence of seroma was higher in the group of exercise (early) compared to the immobilized group (delayed). These studies, so forth, provide guidance about the ideal scenario where the patients would keep the ipsilateral shoulder to the surgery immobilized for a

few days just as in the study of Schultz et al.¹⁵. But the authors¹⁵ added the idea that the older age of the patients is more associated to the incidence of seroma than to the early or delayed immobilization itself.

There is no consensus in the literature about the required number of sessions, but it is believed that

Table 1. Description of eligible articles of systematic review

Title/author	Sample studies	Beginning of the exercises	Type of exercises	Range of the movement adopted	Results
<i>Early versus delayed shoulder motion following axillary dissection a randomized prospective study</i> Lotze et al. ¹²	36 patients	The early group initiated in the 1st day post-operation and the delayed group was only released in the 7th day post-operation	The early group initiated flexion and abduction of the shoulder and the delayed group was only released for flexion in the 8th day post-operation. The early group did not progress beyond 40° of abduction until the 7th day, while the delayed group waited until 12 days or until the removal of the drain	The early group initiated flexion and abduction of the shoulder up to 40°, progressing only after the 7th day post-operation	The early group showed more volume of drainage of the operative wound, delay of cicatrization and more time of hospitalization. Nearly all the patients of both groups of the study reached the functionality because of the early involvement of the physiotherapist to maintain the articular mobility until the cicatrization and drainage, which lead to the progression of the rehabilitation of ROM
<i>Effect of shoulder immobilization on wound seroma and shoulder dysfunction following modified radical mastectomy: a randomized prospective clinical trial</i> Dawson et al. ¹³	100 women randomized in 2 groups. Group exercise (51 patients) and group immobilized (49)	The group exercise initiated the exercise in the 1st day post-operation In the group immobilized, the ipsilateral arm was held with sling for 5 days	Not informed	Not informed	The drained volume of the group exercise was 15% greater than the immobilized. The seroma was more frequent in the group exercise and extended delay of the operative wound, compared to the immobilized group. Infections were present only in the group exercise. The number of patients with functional loss of more than 15% was slightly high in the group immobilized
<i>Immediate versus delayed shoulder exercises after axillary lymph node dissection</i> Jansen et al. ¹⁴	144 patients were divided in group 1 with 78 women (immediate beginning of exercises), group 2 with 66 women (delayed)	Group 1 executed active exercises from the 1 st day post-operation, group 2 initiated in the 8 th day post-operation, with the arm immobilized until the 7 th . day	Not informed	Not informed	The high incidence of seroma was higher in group 1. In group 1, there were more volume of drainage of the operative wound (14%) compared to group 2. No difference was encountered in the functionality of the shoulder after immediate or delayed exercises in the shoulder
<i>Delayed shoulder exercises in reducing seroma frequency after modified radical mastectomy: a prospective randomized study</i> Schultz et al. ¹⁵	Total of 163 patients, 89 in early group and 74 in delayed group	The early group initiated the exercises in the 1st day post-operation and the delayed group, in the 7th day	Patients were instructed to execute active exercises to recover total ROM of the shoulder, mainly abduction, flexion and external rotation, three times a day	Not informed	Seroma was more frequent in the early group (38%) compared to delayed (22%). There were no significant difference between the early and delayed group in relation to shoulder rehabilitation

Table 1. continue

Title/author	Sample studies	Beginning of the exercises	Type of exercises	Range of the movement adopted	Results
<p><i>Shoulder movement after breast cancer surgery: results of a randomized controlled study of postoperative physiotherapy</i></p> <p>Box et al.¹¹</p>	<p>65 women randomly divided in treatment and control group</p>	<p>The group treatment received daily, immediate, supervised intervention of the physiotherapist with a protocol of exercises; the group control received guidance for self-administered exercises in post-operation. Both groups initiated or were guided to initiate the exercises immediately (within the 1st month), but there is no information in the study of how many days exactly post-operation</p>	<p>Not informed the protocol of exercises. It only cites that the protocol had the objective of recover all the movements of the upper limb submitted to operative procedure, except external rotation of the shoulder</p>	<p>Not informed</p>	<p>The programme of supervised exercises by physiotherapists resulted in improved recuperation of the ROM of the shoulder after breast cancer surgery. The supervision facilitates the early intervention, ensuring the women continue to evolve until its full recovery</p>
<p><i>Evaluation of immediate versus delayed shoulder exercises after breast cancer surgery including lymph node dissection — A randomized controlled trial</i></p> <p>Bendz et al.¹⁶</p>	<p>Two groups: immediate exercise, group A, 101 patients; delayed shoulder exercise, group B, 104 patients</p>	<p>Group A initiated the shoulder exercises in the 1st day post-operation; group B waited 14 days, received instructions to use the arm as comfortably as possible, but it was recommended to not execute ample movements and lift weight</p>	<p>Group A included isometric exercises with the hand with a ball, flexion and extension of the elbow, pronation and supination in supine with the arm laying in a pillow. From the 3rd day post-operation: the exercises evolved to elevation and abduction of the shoulder at 90° with flexion of the straight elbow in sedestation. From the 8th day of post-operation: elevation and abduction of the shoulder at 90° with straight elbows, internal rotation with the hands in the back, attempting to reach as high as possible. After 14 days, both groups received the same programme of exercises</p>	<p>90° elevation and abduction of the shoulder in the first 14 days. After this period, evolved to 180°</p>	<p>The differences among the groups were not significant. Group A recovered the mobility significantly earlier than group B</p>

Table 1. continue

Title/author	Sample studies	Beginning of the exercises	Type of exercises	Range of the movement adopted	Results
<i>Evaluation of a new rehabilitation program for postoperative patients with breast cancer</i> Morimoto et al. ¹⁷	72 patients, 39 with mastectomy and 33, conservative surgery	The exercises were executed since the 1st day post-operation	Active exercises to increase ROM, stretching and activities of the daily life. Divided per post-operative day. Patients were instructed to perform the exercises 3 or 4 times a day after the surgery	It mentions only 90° angle of elbow flexion to perform the exercises in the first days post-operation	90% of the patients have returned to their regular daily activities (RDA) 4 weeks post-operation. The rehabilitation programme soon after the surgery is effective to reach the functional recuperation of the breast cancer post-operation
Post-operation movement of the shoulder after breast invasive carcinoma surgery: Controlled, randomized, prospective study of free exercises versus limited exercises at 90° post-operation Pinto e Silva et al. ¹⁸	59 patients divided randomly in 2 groups, group 1 with 30 women who performed free shoulder exercises up to the possible limit and another group with 29 women who performed limited ROM shoulder exercises in the first 15 days post-operation	Exercises initiated in the 1st day post-operation	After the surgery, the patients were submitted to a supervised 19 exercises protocol. Free-active, assisted-active, stretching in several positions and supine, with 3 exercises initiated in the 1st day post-operation in the hospital; after 48 hours, the exercises were performed in the ward along 40 minutes, 3 times a week during 6 weeks	A group initiated ROM free and the other, limited ROM to 90° until 15 days post-operation	Free ADM exercises since the first day post-operation granted good recovery of the functional capacity of the shoulder with no increase of seroma or dehiscence
<i>Physiotherapy improves shoulder function after treatment in women with early breast cancer</i> Cave et al. ¹⁹	139 women divided in groups: standard post-operative treatment and standard post-operative isolated	Group: standard post-operative: the treatment with physiotherapy beginning after 6 or 8 weeks post-operation Isolated standard post-operation group: initiated therapy intervention after 26 weeks post-operation	Group: standard post-operative treatment, 2 sessions per week during 60 minutes for 6 weeks with guidelines for exercises (not specified) and metabolic exercises	Not informed	Long run physiotherapy implemented immediately after the post-operative recovery, improving the function of the shoulder in women after breast cancer surgery
<i>Effectiveness of a self-administered, home-based exercise rehabilitation program for women following a modified radical mastectomy and axillary node dissection: a preliminary study</i> Kilgou et al. ²⁰	27 women divided randomly in group of experimental post-operative rehabilitation (n = 16) and the group of habitual care (n=11)	From the 3rd day post-operation	The group of habitual care received all the usual information and standard information (written and verbal) and one guide of free exercises in a leaflet. The group of rehabilitation with home-based exercises, in addition to the same material of the group of habitual care, watched a video of free exercise program. The video informed the progression of the exercises from one week to the other. Active exercises with multi-articular exercises in several directions, isometric contraction to keep muscular activity and stretching	It were provided recommendations to attempt to perform free ROM activities until painless ROM twice a day	The group of rehabilitation with home-bases exercises showed more growth of ROM in comparison with the group of habitual care. Both groups increased strength of the shoulder and gripping, not presenting significant differences among them in the study. The video programme could be handed over to women in post-onco-mammary surgery because it is more comprehensive and informative

Table 1. continue

Title/author	Sample studies	Beginning of the exercises	Type of exercises	Range of the movement adopted	Results
<i>The effectiveness of early rehabilitation in patients with modified radical mastectomy</i> Çınaret et al. ²¹	57 patients were evaluated, randomly divided in group of treatment: 27 patients and group of exercises home-based: 30 patients	Group of treatment: exercises in the 1st day post-operation. Group of exercises home-based: Exercises initiated only after the removal of the drains	Group of treatment: after the removal of the drains, 15 individual therapy sessions were carried out, performed home-based exercises for the next 8 weeks. Active, isometric exercises for the range of the abduction, flexion, internal and external rotation of the shoulder, pendulum, stretching. Group of home-based exercises: received an informative handout with guidelines to perform the exercises	In the group of treatment, the shoulder was positioned at 65° flexion, from 45° to 65° of abduction and 65° internal rotation over a wedge pillow in the first day post operation	The early rehabilitation programme (group of treatment) compared to the group of home-based exercises had a better recovery of the mobility of the shoulder and of the functional capacity, without causing adverse effects as infections, seroma or increase of the drained liquid. It demonstrated that a close follow up increased the opportunity of adaptation and adherence to the early beginning of exercises program
Application of the program of exercises at home for the rehabilitation of the shoulder breast cancer post-surgery Petito et al. ²²	64 women	Exercises initiated in the 1st day post-operation	Programme with 9 exercises with 10 repetitions	Free ROM since the 1st day post-operation until the limit of the patient discomfort	The proposed programme of exercises was efficient for the recovery of the movements of flexion, abduction and extension of the shoulder, further to being beneficial the early beginning of the functional rehabilitation, continuously until, at least, three months post-surgery

the follow-up in the medium and long run can bring additional benefits²³. Rett et al.²⁴ demonstrated additional gains in until six months and verified that early initiated physiotherapy is able not only to improve the function of the shoulder, but also the quality of life and pain of these patients.

Studies like Bendz et al.¹⁶ advocate the idea that the early post-operative intervention of onco-mammary surgeries do not increase the chance of complications for these patients as Morimoto et al.¹⁷, that confirmed that a program of early exercises is effective to achieve the functional recovery of these patients without deleterious effects.

According to Bendz et al.¹⁶, the greatest limitation of ROM is seen in the first two weeks after the surgery. In this study, it were compared groups of immediate and delayed exercises post onco-mammary surgery; after 14 days, both groups were given a program of exercises with abduction, elevation at 180°, internal and external rotation of the shoulder. A conclusion was reached, that showed that differences between the gripping strength and volume of the operated limb were minimal among the groups. But, the immediate exercises group had better recovery of the mobility.

Another aspect to be argued and is quite controversial is about postoperative free or restrained ROM. As quoted by Bendz et al.¹⁶, who initiated their intervention with

exercises of the immediate group with limitation until 90°, there are but a few studies that describe what would be the ideal angle of the movement to initiate the rehabilitation of these patients.

Pinto e Silva et al.¹⁸ carried out an intervention to compare free and limited exercises, where the group of free exercises initiated the rehabilitation in the first day post-operation, doing movements until the possible limit and/or uncomfortable while the other group were limited to 90° in the first 15 postoperative days. The study concluded that free ROM since the first postoperative day granted the patients a fairly functional recovery of the shoulder without any additional complication as seroma and dehiscence, considering that it is likely that the incidence of seroma is related to other factors as surgical technique, infections and lymph nodes affected.

Based in these results, Petito et al.²² conducted a study where patients initiated the exercises in the first postoperative day, free-ROM to the possible limit and these exercises were intensified and toughened gradually. It was confirmed the benefit of the early initiation of the functional rehabilitation that must continue until at least three months after the surgery.

The surgical techniques have evolved in time, which also interferes in the incidence of postoperative complications of breast surgeries²⁵.

Independently of the surgical approach, complications may occur, but less aggressive surgeries grant a reduction and control of the postoperative complications. Thus, the complications are more frequent in women who undergo radical mastectomy and/or total axillary emptying²⁵⁻²⁷.

Brito et al.²⁸ affirm that less invasive surgeries, classified as B for level of evidence, have faster recovery compared to more invasive surgeries and ROM takes more time in radical surgeries.

In the study by Nascimento et al.²⁹, the most frequent surgery was radical mastectomy, followed by quadrantectomy, 52%. Of the 707 women included in the study, 513 (72.6%) adhered to the Program of Rehabilitation. In the first postoperative year, 460 (65%) of the operated returned to evaluation. Of these, 62% presented some complaint or complication. In the second year, only 168 women (23.8%) returned to the Physiotherapy Department, of which 83.3% presented some complaint or complication.

A study by Gosselink et al.³⁰ included 76 patients submitted to mastectomy or conservative surgeries, both with axillary dissection. The mobilization of the shoulder was initiated in the postoperative second day supervised by a physiotherapy. This study demonstrated great importance in relation to the type of surgery and the recuperation of these patients, the most conservative the better.

It is important to emphasize that the role of physiotherapy is essential for the recovery of these patients through constant supervision, orientation and reassessment during the process of rehabilitation; therefore, the odds of possible complications are minimized and, if they occur, will also be treated early. Therefore, physiotherapy allows, most of the times, the total recovery of these patients with the reclaiming of the quality of life.

CONCLUSION

It was conducted a systematic review of the literature where it was observed that there is not a consensus in literature in relation to the practice of the exercises, late or immediate, in postoperative onco-mammary surgeries. Older studies believe that the approval of early exercises could damage post-operation. However, as surgical techniques evolved, more recent studies show that to limit these patients to late exercise can provoke mobility and functionality-related damages of the upper limb approached surgically and that the early intervention does not influence the incidence of the complications; in addition, some authors are already bringing free-ROM studies in the first post-operation day.

CONTRIBUTIONS

Amanda Estevão and Adrielle Fontes Mendes contributed substantially in the elaboration, conception and/or design of the study, obtaining and analysis and interpretation of the data as well as in wording and final approval of the published version. Mariana Lopes da Silva, Patrícia Lima Ventura, Alessandra Cristina Biagi and Márcia Cristina Bauer Cunha contributed substantially to the elaboration of the study, critical review and final approval of the published version.

DECLARATION OF CONFLICT OF INTERESTS

There are no conflict of interests to declare.

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