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USE OF 125IODINE SEEDS (ROLLIS) FOR INTRA-OPERATIVE LOCALIZATION OF NONPALPABLE BREAST LESIONS: ANALYSIS OF THE IMPLANT OF 338 SEEDS IN 284 PATIENTS

Uso de sementes de iodo-125 (ROLLIS) para localização intraoperatória de lesões impalpáveis da mama: análise do implante de 338 sementes em 284 pacientes

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ABSTRACT

Objective: To analyze the feasibility, efficacy and results of the use of 125Iodine seeds for intra-operative localization of nonpalpable breast lesions. Method: Retrospective review of 284 patients, referred by various breast specialist surgeons, with radiologically detected but clinically nonpalpable microcalcifications or nodules, submitted to pre-operatory 125Iodine seed implant, between July 2012 and September 2016. A total of 338 seeds were implanted in ordinary radiologic departments, supported by ultrasonography or mammography exams, chosen according to the morphologic aspect of the lesion. Radioguided surgical procedure took place on the same day or few days after the implant of the seeds, with the help of a radiation detector called Gamaprobe, which directs the surgeons towards the radioactive seeds and to the lesion to be resected. **Results**: All implants were performed as outpatient procedures, with patients immediately returning to their daily activities. No complications such as pain, bleeding, infeccion and haematoma were recorded. Pathologists had no difficulty in preparing the surgical specimens for histopathologic analysis. Surgical safety margins were considered adequate in all pathologic reports, with no need for re-operations. The healing process was not jeopardized by radiation, and the surgeons were pleased with the improvement on intraoperative lesions localizations and shortening on operatory time. Cosmetic results were well accepted by the patients. **Conclusion**: The 125Iodine seed implant is an effective alternative method for intraoperative localization of radiologically detectable and clinically nonpalpable breast lesions.

KEYWORDS: Breast; iodine radioisotopes; breast diseases; diagnostic techniques, radioisotope.

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RESUMO

Objetivo: Avaliar a exequibilidade e a eficácia do método de implante de sementes de 125Iodo (ROLLIS) para localização intraoperatória de lesões impalpáveis da mama. Método: Trata-se de um estudo retrospectivo, incluindo 284 pacientes com nódulos ou microcalcificações mamárias, visíveis na mamografia e/ou ultrassonografia, porém, clinicamente impalpáveis, submetidas a implantes de sementes de 125Iodo, de julho de 2012 a setembro de 2016, sendo implantado um total de 338 sementes. As pacientes foram encaminhadas por diversos mastologistas que executaram cirurgias radioguiadas com auxílio de detector de radiação denominado Gamaprobe, realizadas no mesmo dia do implante ou vários dias após, seguindo a agenda do centro cirúrgico, da equipe médica e a conveniência da paciente. **Resultados**: Os implantes foram realizados em regime ambulatorial, com imediato retorno das pacientes às atividades cotidianas, não sendo registrada qualquer complicação como dor, hemorragia, infecção ou hematoma. Os patologistas não constataram prejuízo no processamento do espécimen cirúrgico. O processo cicatricial se efetuou normalmente, obtendo-se plena satisfação por parte dos cirurgiões, que referiram maior facilidade na localização intraoperatória das lesões e diminuição no tempo operatório. O resultado cosmético também foi beneficiado, sendo bem aceito pelas pacientes. As margens cirúrgicas foram consideradas adequadas em todos os casos, graças à avaliação feita pelo patologista e às ampliações executadas no momento da cirurgia, dispensando re-excisões. **Conclusão**: O implante de sementes de 125Iodo (ROLLIS) é uma técnica segura e eficaz para localização intraoperatória de lesões radiologicamente visíveis, porém clinicamente impalpáveis, da mama.

PALAVRAS-CHAVE: Mama; radioisótopos do iodo; doenças mamárias; técnicas de diagnóstico por radioisótopos.

INTRODUCTION

Recent media campaigns and dissemination on the prevention of breast cancer, along with the technological advances in radiology, have considerably increased the diagnosis of radiologically visible, though clinically impalpable, breast lesions referred for surgical excision, becoming a major challenge for surgeons[1].

The most commonly used method for the surgical localization of these lesions, since its creation in 1979, it is the insertion of a metallic wire with an arrow-shaped tip (Kopans Wire) into the lesions, guided by radiological images[2]. Although practiced universally for many years, this technique includes several drawbacks[3]. Literature studies[1,4] show that this method leads to high rates of positive surgical margins, ranging from 20 to 70%, requiring reoperations, with high levels of local recurrence, in cases of malignancy. This is an important factor, since the main objective of any given procedure to locate a lesion is to facilitate a complete surgical excision in a single event, discarding new interventions. Another drawback of the metallic wire is its displacement in the preoperative period or during surgery, with reports of its migration into the pleural cavity[5], the miocardium[6], pulmonary hilum[7], abdominal cavity[8], in addition to cases of bending and rupture both before and during surgery[9,10]. Surgeons complain that the tip of the metallic wire is difficult to be felt in palpation during the operative event, impairing the complete excision of the lesion with adequate safety margins[11]. The insertion point of the wire into the skin is usually located in an area far from the ideal incision position, requiring an extended surgical area in order to identify the wire and for the lesion to be removed[1,11]. Another disadvantage of this method is the need to perform the surgery on the same day of the wire implant, once its exteriorization through the skin requires dressings, immobilization maneuvers, protection and care by the patients. In addition, complications such as pain, bruises and infections are reported in 8 to 10% of cases[12]. Due to the many drawbacks mentioned, researchers were encouraged to find another method for intraoperative localization of impalpable breast lesions. Then, there was the idea of using radiation emitted by radioactive isotopes as a guide to surgical targets[13].

In 1999, Luini et al.[13] published a new technique called radioguided occult lesion localization (ROLL), using colloidal albumin marked with 99m-technetium as a radiotracer, which, when injected directly into the lesions, under mammography or ultrasonography guidance, allows the localization of nodules and microcalcifications by means of gamma-type radiation emitted by the radioisotope and detected through a device called Gamaprobe. Several subsequent studies demonstrated the advantages of the ROLL technique in comparison to the metallic wire, observing inferior levels of inappropriate surgical margins, reducing the need for re-excisions and reducing the volume of breast parenchyma removed in the operative specimen[14-16]. Despite the advantages of this method over the metallic wire, some drawbacks related to difficulties and limitations to its use have been found. The≈colloidal albumin marked with 99m-technetium is not radiopaque, making it difficult to be visualized in radiological tests, impairing the confirmation of its positioning within the lesions. Also, it has a rather short half-life (six hours), which requires the execution of the surgery on the same day of the implant. Due to its liquid form, its diffusion through neighboring

tissues after being injected is unavoidable, making it rather difficult to perform the surgery by producing ill-defined margins and thus generating insecurity in the surgeon, who is forced to withdraw greater amounts of breast parenchyma, which interferes negatively on the cosmetic result[17].

Due to the inconveniences described, the search for a method with lesser difficulties continued. In 2001, Gray et al.[18] published a new technique using radioactive seeds of 125Iodine (ROLLIS), which, due to its small dimensions, concentrates the radiation within the target lesion (unpalpable lesion), facilitating the surgeon's work, by making it easier to be found through radiation. Subsequent publications[19-21] demonstrated many advantages to this method, such as reduced occurrence of compromised margins, reduced amounts of breast tissue removed, reduced surgical time due to easier location of the lesion and better cosmetic result, when compared to wire and 99m-technetium[20,21]. The external capsule of the 125Iodine seed is made of titanium, which, being radiopaque, is easily visible during mammography and ultrasound. This is a very important characteristic, once it allows verifying, at the moment of the implant, the position of the radioactive source within or near the lesion to be resected. Another advantage of 125Iodine is its prolonged half-life (60 days), allowing the surgery to be carried out up to 2 months after the implant, with no need of being performed on the same day or the day after the procedure. This flexibility to schedule the surgery facilitates the organization of the medical team, the surgical center and the patient, providing everyone involved with comfort and tranquility. Another favorable finding for the use of the seed is the absence of displacement and migration of the marker to other areas but the area of interest, despite surgical manipulation and free movements of the patient[22].

Due to 125Iodine radioemission, doubts arose regarding the doses absorbed by the patient and by the medical team. According to Pavlicek et al.[23], the maximum dose deposited in the residual breast that received the seed implant is rather low, around 2 cGy, equivalent to the dose of two X-ray incidences of a routine mammography. A survey on the amount of radiation received by the surgical team showed that no one received a dose higher than the environmental level[24], proving the absence of risk to the medical staff, to the patient and to the general population.

The ROLLIS technique proved to be easy to learn, intuitive and learning-curve-free, a fact proven by the constant results found during all the years of its execution[1].

MATERIAL

This study was approved by the Ethics Committee of the *Hospital Pró-cardíaco – Esho Empresa de Serviços Hospitalares/Hospital Pró-cardíaco* (HPC), CAAE registration No. 47149315.4.0000.5533. It is a cohort, retrospective, observational study, consisted of 284 patients with impalpable breast lesions, submitted to 125Iodine seed implants.

Indication to the use of seed in this work include radiologically visible, though clinically impalpable lesions, which would be submitted to excisional biopsy for histopathological diagnosis, and lesions which already had a pathological report and would be treated by surgery. Before the implant, patients were given detailed explanations on the method, for full knowledge and authorization for the procedure.

1. Seed:
   125Iodine seeds are capsules containing salts of titanium-coated 125Iodine, measuring 5 x 0.8 mm, with a half-life of 59.4 days, low-energy gamma emission (27 keV), acquired through the Institute of Energy and Nuclear Research (*Instituto de Pesquisas Energéticas e Nucleares* – IPEN), loaded with radioactive material ranging between 0,2 and 0,9 mCi, sterilized and handled according to the safety guidelines of the National Nuclear Energy Commission.
   125 Iodine seed
   The emission of low-energy photon radiation causes the radiobiological effect in neighboring tissues to be of negligible intensity, without harming the histopathological analysis of the surgical specimen nor the healing process. Also, there is no need for sophisticated and expensive radioprotective measures, although it is necessary to adopt the established care for the manipulation of radioactive material.
2. Needle:
   The seed are implanted through stainless steel needles, with centimetric marking, echogenic tip and shear bevel, visible during ultrasound and on X-ray films. They measure 20 cm in length and 18 Gauge in diameter and are supplied sterilized, being discarded after use. They have a metallic plunger, which pushes the seed into the lesion. Due to the rigidity of the stainless steel, they easily penetrate the breast tissue, moving toward the predetermined targets without deviations, curves or ruptures, implanting the seed with great precision and little trauma.
   Needle and 5 seeds
3. Gamaprobe:
   It is the low-energy gamma radiation (27 Kev) detector, measuring the radiation emitted by the 125Iodine seed, consisting of a radiation recording compartment, connected to a sensor through a flexible probe, with suitable weight and dimensions for an easy displacement. The device used is made by Johnson & Johnson, Neoprobe 2000 model, capable of also detecting gamma radiation of 140 Kev emitted by the 99m-technetium phytate, which makes it able to differ the radiation released by the seed from that emitted by the sentinel lymph node, in the same procedure.

METHODS

Implanting the seed

The implant of the seed is carried out in a conventional radiological center, by a radiologist assisted by the radio-oncologist. The choice between mammography and ultrasonography as an auxiliary radiological method is made by the radiologist, based on the morphological characteristics of the lesion. In general, nodular lesions are implanted using ultrasonography, while microcalcifications are best seen during mammography with biplanar or stereotaxic methods. After positioning the patient in the selected device, the asepsis is performed, followed or not by local anesthesia. All cases implanted during ultrasonography are subsequently radiographed in craniocaudal and profile incidences, in order to confirm the perfect positioning of the seed. After the implant, the patient is immediately released and may return to their daily routine activities, discarding special care, dressings or any limitation to their routine.

Surgical procedure

The preoperative procedure is the same of any surgical breast intervention, planed conventionally, and may be performed on the same day of the implant or up to 60 days after it, to the convenience of the medical team, the surgical center and the patient, without any urgency or pressure on any of the parties involved. The surgical center is chosen by the surgeon and has no need for sophisticated radioprotection equipment. The surgery is radioguided by the Gamaprobe sensor, which shows the position of seed and lesion by emission of a sound signal directly proportional in intensity to the amount of radiation detected. Based on this information, the surgeon defines the position and type of incision, guiding the dissection to the seed and the target-lesion with the aid of the Gamaprobe noise. After having the parts and the surgical margins analyzed by the pathologist, the surgical wound is closed, and the patient is discharged at the appropriate time, remaining in ambulatory supervision until complete healing. Since it contains radioactive material, the seed must be handled with special attention in order to avoid being lost when wrapped in compresses, gauze or by suction of the aspirator.

Surgical part

In cases of previously confirmed malignancy, the excision of the sentinel lymph nodes may be carried out at the same time as the removal of the mammary lesion, due to Gamaprobe's ability to differ low-energy radiation released by 125Iodine seeds (27 KeV) from high-energy radiation (140 Kev) released by 99m-technetium phytate. In these cases, the seed is implanted into the lesion, followed by an injection of 99m-technetium phytate in the same region or in the periareolar area, noting the surgery must be performed within 12 hours, at most, once the half-life of the phytate is of only 6 hours.

RESULTS

This analysis included 284 patients, and a total of 338 seeds of 125Iodine were implanted. Patients were referred by 20 different mastologists, and the complete acquisition of data was not possible in all cases. However, the material collected allow the surveying of clinically important results, capable of making this method an effective alternative for intraoperative localization of clinically impalpable breast lesions.

All breast lesions were successfully resected, with no records of pre- or perioperative incidents caused directly by the presence of the seeds.

The age of patients ranged from 25 to 85 years old, with average 56 years of age and confidence interval of 95% (95%CI) 54.4–59.0.

According to the radiological aspect of the lesions, the images were classified as a nodule in 110 cases, and as microcalcification in 49 of them.

Pathologists did not report any damage to the processing of the operative specimen, and the surgical parts were considered malignant in 90 patients, and benign in 50 patients. The search for sentinel lymph nodes was performed in 57 patients, being metastatic in 8 and not compromised in 49.

As definition of appropriate free margins, the value of 2 mm was adopted as the minimum distance between lesion and the borders of the surgical specimen. Based on this concept, the margin was considered insufficient in only one case, in which the patient only remained in observation, once it was a benign lesion.

The number of seed implanted in each patient ranged from 1 to 4 (Table 1), being applied to both breasts in 20 cases.

The ultrasonography was the radiological method used in 167 implants and the mammography, in 66. All implants performed with the aid of ultrasonography were immediately submitted to a mammography in two orthogonal incidences, in order to confirm the perfect positioning of the seed.

Although the half-life of 125Iodine (60 days) allows the surgery to be performed up to 6 to 8 weeks after the implant, 97 patients were submitted to surgery within 24 hours, 66 of them on the same day of the implant. Only 6 patients were operated 14 to 28 days after positioning the seed, due to their being on neoadjuvant chemotherapy.

In one patient, a seed was used to mark a right axillary lymphadenomegaly, later resected by surgery; and two patients received neoadjuvant chemotherapy in order to reduce the size of the tumor, aiming for a more conservative surgery.

Table 1. Seeds per patient.

Number of seeds	Number of patients
1	239
2	38
3	5
4	2

Adverse events recorded consisted of: accidental movement of the needle plunger by a patient while being positioned at the mammography, thus injecting the seed other than in the planned site; and implantation of a seed far from the lesion due to failure in evaluating the coordinates of the mammograph.

Although no procedure for millimetric evaluation of seed positioning was adopted, surgeons did not record significant displacement of the radioactive source, confirming its presence within or close to the lesions, despite free movements and manipulation of the patients.

No influence of the learning curve was observed in this method, with consistent and reproducible results obtained from its beginning, in July 2012, to 2017, proving it to be easily understood and applied.

The total financial cost of this procedure, including material and staff, was somewhat higher when compared to traditional methods, without, however, causing any objection from paying sources.

DISCUSSION

This work analyzes the feasibility and efficacy of a new method of intraoperative localization of radiologically visible, but clinically impalpable, mammary lesions, using 125Iodine seeds, implanted with the aid of ultrasonography and/or mammography. Survey made of material provided by 20 mastologists allowed the analysis of histopathological aspects of surgical parts and their complications, enabling the comparison of this technique to the traditional methods of metallic wire and 99m-technetium. From July 2012 to September 2016, 338 seeds were implanted in 284 patients, in ambulatories in different radiological services in the city of Rio de Janeiro. In order to facilitate the presentation of the evidence, the comparison of the seed technique (ROLLIS) with the metallic wire will be presented first, and next, the 99m-technetium (ROLL) comparison will be described.

The literature shows that the metallic wire has high levels of compromised surgical margins, ranging from 20 to 70%[1,4]. A review of the pathological reports provided by the laboratories showed appropriate surgical margins in almost 100% of the cases, with only one exception. It should be noted that the histological evaluation of lesions and margins is a routine procedure performed by a pathologist during the surgery in order to ensure the quality of the surgical specimen. Testimonies from surgeons prove seeds were within or close to the lesions in all cases, which is not the case with the metallic wire, which may be displaced and even migrate to further areas, hampering the complete removal of the target-lesion[5-8]. The difficulty in identifying the tip of the wire by palpation during surgery is widely known, which may compromise the safety of the surgical margins and the complete excision of the lesion. This difficulty is not a reality with the use of radioactive seeds, which are easily located thanks to the detection, by Gamaprobe, of the radiation released[11]. Another disadvantage of the wire regards its insertion point in the breast, sometimes positioned far from the lesion, resulting in extensive operative area and surgical trauma, compromising the final cosmetic result. This does not happen in ROLLIS, once the seed is introduced directly into or next to the lesion, being easily visible in the mammography and/or ultrasound carried out at the moment of the implant, due to its radiopacity[1,11]. Patients who receive the wire as pre-surgical marker should be operated as soon as possible, due to the presence of dressings and movement limitation, which may cause unpleasant discomfort. With the use of seeds, these inconvenients do not happen, since there is no need for dressings nor restrictions to routine activities, so patients may return immediately to their daily activities. Studies show complications such as pain, bruises and infection in 8 to 10% of the cases using metallic wire[12], which was not reported, to date, by any patient submitted to the seed technique.

Due to the drawbacks mentioned, the metallic wire is being progressively replaced by the 99m-technetium, which had some advantages and better results[14-16], but which also does not fully satisfy the needs of surgeons and their clientele. Unfortunately, the 99m-tehcnetium is not radiopaque, and thus, its visibility is hindered during mammography and ultrasound, making it rather difficult to ensure its perfect positioning within or close to the lesion. The 125Iodine seeds are coated by titanium, which makes them easily identifiable in any of the radiological methods used, allowing for high precision during implantation. Due to its liquid state, the 99m-technetium diffuses through neighboring tissues, making it difficult to identify their borders and forcing the surgeon to extend the resection limits, with excessive removal and unnecessary amount of mammary parenchyma. On the other hand, the seed are solid and have small dimensions (5 x 0.8 mm), constituting a source of radiation with well-defined limits, facilitating the intraoperative location of the lesion, contributing to more rewarding cosmetic results[17]. Another advantage of the seed, when compared to the 99m-tehcnetium, is related to the half-life of these elements. The technetium has a half-life of only six hours, which forces the surgery to be carried out shortly, inputting great psychological pressure upon the whole medical staff, the surgical center and the patient, allowing no space for unforeseen events which would require the postponement of the surgery. Since the half-life of 125Iodine is very long (60 days), this urgency is unnecessary, allowing the surgeon to schedule the intervention according to their own availability, the surgical center's as well as the patients themselves' availability. In case of unforeseen circumstances, the operation may be postponed to any given date within 60 days, free of pressure and distress of the personnel involved. The half-life of the seed also

allows it to be used as a marker of malignant tumors to be treated with neoadjuvant chemotherapy for the reduction of tumor volume, allowing a more economical surgery. If, by any chance, there is a complete tumoral response, the surgeon will have no parameters to guide them during surgery, forcing more extensive resections[22]. Thus, two patients in this sample were under chemotherapeutical treatment, having received seed implants weeks before the surgery, in order to mark the area to be removed in case there was full response of the tumor to the neoadjuvant chemotherapy. Thanks to the different gamma radiation emitted by iodine (27 Kev) and by technetium (140 Kev), it is possible to perform a lesion excision, marked with seeds, and of a sentinel lymph node, marked by technetium, in the same operation, which is of hard execution when using only the technetium as a radiomarker, for the detector cannot distinguish the radiation originated in the lesion from the one emitted by the lymph node.

There are no significant differences in the financial cost of the three marking methods evaluated in this work, being accepted without further questioning by the paying sources.

No model of evaluation for cosmetic results was used in order to form a scientifically based opinion, however, both doctors and patients seemed satisfied with the aesthetic result achieved by the use of seeds. It was not possible to find, in the literature consulted, a comparison of the cosmetic result between the three processes described in this work.

CONCLUSIONS

The use of radioactive seeds of 125Iodine for intraoperative localization of clinically impalpable breast lesions is a safe, efficient and highly accurate alternative method, presenting numerous advantages over the conventional methods of the metallic wire and the 99m-technetium. The seeds may be adopted in the practice of Mastology, once they facilitate the work of surgeons, without any harm to the pathologist and with several benefits for patients.

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