Update on radioguided surgery: from international consensus on sentinel node in head and neck cancer to the advances on gynaecological tumors and localization of non-palpable lesions

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Special collaboration

Update on radioguided surgery: From international consensus on sentinel node in head and neck cancer to the advances on gynecological tumors and localization of non-palpable lesions☆

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ABSTRACT

The aim of this review is to provide an updated perspective on different fields of radioguided surgery. With reference to the sentinel lymph node biopsy in oral squamous cell carcinoma, we present the results of the interactive debate held at the recent Congress of our specialty about the more relevant aspects of the London Consensus. Drainage peculiarities and indications according to the current guidelines on gynecological tumors, endometrial and cervical cancer, are detailed and new scenarios for nuclear medicine physicians are presented; robotic surgery and hybrid tracers, for instance. Moreover, the notable growth in radioguided surgery indications for non-palpable lesions, widely used in mammary pathology, make it advisable to update two procedures which have shown satisfying results, such as the solitary pulmonary nodule and the osteoid osteoma.

Actualización en cirugía radioguiada: del consenso internacional en ganglio centinela de cabeza y cuello a los avances en tumores ginecológicos y localización de lesiones no palpables

Palabras clave:
Biopsia del ganglio centinela
Carcinoma escamoso de la cavidad oral
Cáncer ginecológico
Trazadores híbridos
Cirugía robótica
Cirugía radioguiada

RESUMEN

La presente revisión tiene como objetivo brindar una visión actualizada en diferentes campos de la cirugía radioguiada. En lo que se refiere a la biopsia del ganglio centinela en el carcinoma escamoso oral, se exponen los resultados del debate interactivo llevado a cabo en el reciente Congreso de nuestra especialidad sobre los aspectos más relevantes del Consenso de Londres. En los tumores ginecológicos, cáncer de endometrio y cérvix, se detallan las particularidades del drenaje, las indicaciones establecidas según las guías actuales y se presentan nuevos escenarios para el médico nuclear, como pueden ser la cirugía robótica y los trazadores híbridos. Por otra parte, la notable expansión de las indicaciones de la cirugía radioguiada de lesiones no palpables, ampliamente utilizada en patología mamaria, hace conveniente la puesta al día en dos procedimientos que han demostrado resultados satisfactorios, como son el nódulo pulmonar solitario y el osteoma osteoide.

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Introduction

The very successful 37th Congress of the Spanish Society of Nuclear Medicine and Molecular Imaging (SEMNIM) held in Oviedo, Spain, included a meeting of experts proposed by the Working Group of Radioguided Surgery which had the objective of knowing the most recent advances in three areas of great interest which are selective sentinel lymph node biopsy (SSLNB) in oral squamous cell carcinoma, in gynecological tumors and in radioguided surgery of non-palpable lesions. We requested the collaboration of this Working Group to hereby present a summary of this session in order to learn about these advances from the experts.

The most important prognostic factor in oral squamous cell cancer is involvement of the cervical lymph nodes. The incidence of occult metastasis in patients with clinically negative lymph nodes is high, ranging from 20 to 30%. SSLNB provides a minimally invasive method to avoid unnecessary treatment in three quarters of the patients and minimizes the associated morbidity. However, SSLNB is still not accepted as a standard method in all centers, with important controversial and challenging aspects remaining, such as the biopsy of sentinel lymph nodes (SLN) localized at level I in tumors localized on the floor of the mouth. In this scenario, the upcoming appearance of the new guidelines to update the current 2009 guidelines is welcomed. Thanks to Dr. Valdés Olmos and Vidal-Sicart, in Oviedo we had the opportunity of knowing and voting on the most relevant aspects debated in the Consensus Conference in London. Thus, in the first section we present the current status of this subject and the result of the voting compared with what was obtained in the consensus meeting.

Cervical cancer (CC) and endometrial cancer (EC) are two of the gynecological neoplasms in which SSLNB can be performed, reducing the morbidity associated with pelvic lymph node dissection. The use of SSLNB has been increasing in the last years, although many aspects remain to be investigated. The first aspect is the indications of the technique for adequate validation and clinical validation. The second is the type of injection, which is especially controversial in EC in which different modes of radiotracer administration have been described. Another important aspect is the protocol of image acquisition, with special attention being given to the performance of single-photon emission computed tomography/computerized tomography (SPECT/CT) taking into account the presence of deep drains as well as adequate evaluation of lymphatic drainage zones of greater anatomical complexity. With regard to intraoperative detection, nuclear medicine physicians must adapt to new scenarios[1] which may include robotic surgery and the management of new hybrid tracers. All of this was reported in the Congress by Dr. Paredes and Dr. Fuertes and is summarized in the second section.

On the other hand, at present we know that improvement in the sensitivity of diagnostic imaging techniques, closer follow-up of oncological patients and the increasingly more frequent use of primary systemic treatment in some tumors have led to surgery being performed in patients with very small sized lesions which are difficult to locate during the surgical procedure.

Systemic administration of a radiotracer which specifically accumulates in the lesion to be resected or intralesional injection of a lesion which does not migrate enables the surgeon to localize and resect the lesion, minimizing the invasiveness of the procedure regardless of whether it is diagnostic or therapeutic while also maintaining maximum benefits.

Even less frequent procedures such as the resection of pulmonary lesions by videothoracoscopy or radioguided surgery of osteoid osteoma have shown satisfactory results with a high efficacy in extraction, a reduction in surgical time and complications as well as an increase in the sensation of the safety of the equipment involved. Dr. Danús and Dr. Rayo reported their experience with these two indications in Oviedo and are described here in the third and last section.

Selective sentinel lymph node biopsy in tumors of the oral cavity. Technical challenges and currect status according to the 2018 Consensus Meeting in London

As a consequence of the validation of the concept of the SLN in melanoma by Morton et al.[2] in 1992, the use of SSLNB in other malignant tumors has spread quite rapidly over the years.[3] Based on the results of large clinical studies and a rich interchange of criteria in congresses and specialized journals, SSLNB has become a standard modality to stage regional metastatic dissemination in early stages of both melanoma and breast cancer. This has all been accompanied by a process of gradual consensus in relation to its clinical indication, despite some controversy, especially regarding methodology, in breast cancer (injection site, size of colloid particles, etc.) in the first decades of its application.[4] This later generated other discussions as to the indication and clinical management, especially in new categories of patients in whom the SSLNB procedure has been applied in the last years.[5] There has been less controversy related to melanoma, most likely because of the regulatory effect that two Multicenter Selective Lymphadenectomy Trial (MLST) studies have had.[6,7]

With regard to the application of SSLNB in other prevalent malignant tumors, the process of consensus has been more gradual. Thus, for example, following a Delphi survey carried out in different European centers with experience in the SSLNB procedure in prostate cancer,[8] a consensus panel meeting of 16 experts was held in Berlin in 2017. Consensus was obtained on 91 of the 150 statements (61%) discussed and reviewed and after systematic review of the diagnostic accuracy of the procedure in the literature.[9]

The process of consensus of the use of SSLNB in carcinoma of the oral cavity has followed quite a similar path. The final event occurred within the framework of the VIII Conference on SLN in head and neck cancer held in London in April 2018. Prior to the conference, which was organized by the surgeons Mark McGurk and Claire Schilling, a group of experts selected 31 items to be agreed upon in 6 sessions including: eligibiity/selection, surgery, positive SLN, results/management, pathology and Nuclear Medicine. With regard to Nuclear Medicine, the 7 subjects selected had previously achieved consensus in January of the same year in Vienna in a meeting of experts sponsored by the International Atomic Energy Agency (IAEA) and the European Association of Nuclear Medicine (EANM). In this meeting, the practical recommendations for the procedure of radioguided procedures of the SLN in mouth cancer of 2009 were also updated.[10]

During the 37th SEMNIM Congress in Oviedo in June 2018, both the 7 subjects of Nuclear Medicine in Vienna and a selection of the specific items of the London Consensus were discussed in a special session with nuclear medicine physicians who are experts in radioguided surgery. In an interactive session, the nuclear medicine physicians were asked to reach consensus on these items or premises without knowing the London results. Table 1 shows the list of the subjects and the items voted upon as well as the results of London and Oviedo.

In the Oviedo meeting an intermediate category ("perhaps") was included in order to evaluate the margin of doubt. This varied from 25 to 35% in the voting on 4 items, with the greatest margin of doubt being limiting the procedure of SLNB only to patients in adequate physical conditions to support a second intervention in the case of a positive SLN. This item achieved 35% of approval in Oviedo, which is very low, but to a certain degree is in line with the 59% reached in London. The greatest disagreement between Oviedo and London was in the question on whether the presence of isolated tumor

Table 1
Results of the voting in Oviedo for some of the items which had achieved consensus in London.

Subject	Item	London	Oviedo
Eligibility and selection	Only patients in good physical condition are eligible for a second intervention in the case of (+)SLN.	59% yes 41% no	35% Yes 35% perhaps 30% no
Surgery	The rule of 10% and >10 times the background activity is valid to extract radioactive lymph nodes only in the area of the SLN indicated by the preoperative image.	87% yes 13% no	55% yes 30% perhaps 15% no
Positive sentinel lymph node (SLN)	Calculate the rate of false negatives (FN) in relation to the true positives (TP) with the formula: rate of FN = FN/TP + FN, with a minimun of 2 years of follow-up.	87% yes 13% no	74% yes 24% perhaps 2% no
Histology	The presence of isolated tumor cells (ITC) should be considered as a (+)SLN.	83% yes17% no	48% yes 25% Perhaps 27% no

Table 2
Different items achieving wide consensus in London.

Subject	Items
Eligibility and selection	CT, MR, ultrasonographyh + fine needle cytology with application in stage N0. Ultrasonography + fine needle cytology are indicated in suspicious cervical lymph nodes. Biopsies should be made by trained surgeons providing data for audits. Sentinel lymph node biopsy (SLNB) should be considered for staging of the contralateral side. Biopsy of the SLN is of value to evaluate lymphatic drainage in a previously treated neck.
Surgery	The incision site is determined by the SLN and not by possible cervical lymph node dissection. If the SLN is not detected at level I in cancer of the floor of the mouth, perform surgical exploration. Optical tracers complementary to radiotracers can especially be applied in the floor of the mouth.
(+)Sentinel lymph node	A rate of false negative results less than 15% is acceptable. In the case of a (+) SLN the patient should be offered lymph node dissection at levels I–V. Biopsy of the SLN and cervical lymph node dissection should be performed by an experienced surgeon.
Results and clinical management	Ultrasonography of the neck should be a part of the standard surveillance during the following 24 months after treatment. The rate of discapacity attributed to cervical lymph node dissection is the most adequate method for measuring the quality of life after SLN biopsy.

cells (ITC) should be considered as a positive SLN. The low 48% of approval as well as the 25% of margin of doubt in Oviedo can be explained by the fact that for the classical applications of SSLNB, ITC have historically been characterized by a different clinical management between melanoma (in which until only a short time ago the presence of ITC led to emptying of the affected lymph node group) and breast cancer (in which it was the rule to not carry out posterior lymph node emptying).

It should be taken into account that voting in the Oviedo Congress was performed within the framework of a plenary session in which the audience/voters included first year residents and staff devoted to other areas, while the voting in London was made by experts in the field. Therefore, the differences may be due, at least in part, to the different characteristics/expertise/training of the voters.

Apart from these aspects interactively discussed in Oviedo, in London a consensus was reached on a series of items, some of which are summarized in Table 2.

In relation to the subject of Nuclear Medicine, consensus was achieved in different aspects ranging from the dose and injection to the elaboration of a nuclear medicine report. A protocol of lymphoscintigraphy was agreed upon which included sequential images based on a dynamic study as well as early and delayed static images. SPECT/CT was defined as being obligatory and should be performed after delayed planar images. The criteria indicating that the radioactive lymph nodes to be surgically extracted should principally be the SLN indicated by the nuclear medicine physician either by cutaneous or digital marking on the SPECT/CT images were also approved. Another aspect which was highlighted was the need for nuclear medicine physicians to incorporate anatomical reference points in their report to facilitate identification by the surgeons in the operating room. These reference points should include the sternocleidomastoid muscle, cervical blood vessels, cricoid cartilage and the hyoid bone. Likewise, the conclusion of the report should include the surgical levels in which the SLN are found. All the innovative techniques currently available in Nuclear Medicine may be applied (hybrid tracers with aggregated fluorescence, high resolution portable gamma cameras, navigation with augmented reality devices, etc.) for the intraoperative detection of the SLN at level I of the neck taking into account the difficulties in finding the SLN in carcinomas of the floor of the mouth presented at this surgical level.[11] These aspects are shown in Fig. 1.

In addition to the updating of the practical recommendations for the radioguided procedure of the SLN in oral cavity cancer, sponsored by the EANM and IAEA and published in 2018, the results of the multidisciplinary consensus in London are being prepared and will be published in the next months with the aim of standardizing the criteria and providing schedules of evaluation of results as well as designing future multicenter studies.

Finally, it can be concluded that the interactive session with telephone voting and statistics of results in real time (Votephone system, Multiversoft S.L.) organized in Oviedo (Fig. 2) by the Working Group of Radioguided Surgery of the SEMNIM has resulted in an excellent method for diffusing, reproducing and directly discussing at a national level the subjects related to the SSLNB procedure for which previous consensus has been reached in international multidisciplinary forums and is a model which should be applied in other areas.

Radioguided surgery in cervical and endometrial cancer. Indications, novelties in the surgical approach and new radiotracers

Indications

Radioguided surgery in gynecological tumors such as CC and EC differs methodologically from the remaining organs due to the localization and, especially, drainage. The uterus is an organ

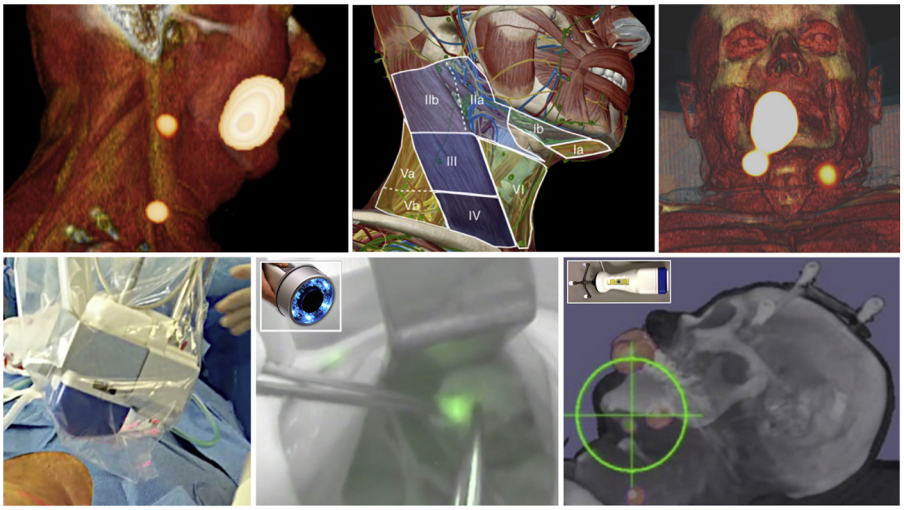

Fig. 1. Upper left, use of SPECT/CT to automatically localize the sentinel lymph nodes (SLN) using the sternocleidomastoid muscle as a reference on the right side of the neck. The localization of the SLN should be reported by the nuclear medicine phyhsician in relation to the surgical cervical levels (center). Special attention should be given to level I in carcinomas of the floor of the mouth (right) because of the difficulty in finding the SLN in this area in the operating room. Bottom left: this supports the intraoperative use of high resolution portable gamma cameras, fluorescence cameras associated with hybrid tracers (center) and navigation with specific systems of augmented reality (right).

Fig. 2. Interactive radioguided surgery session with telephone vote in real time carried out in Oviedo within the framework of the 37th SEMNIM Congress.

situated in the mid-line and presents bilateral pelvic lymphatic drainage. Therefore, in cases showing unilateral drainage in the lymphoscintigraphy prior to surgery, it is necessary to perform a lymph node study of the hemipelvis which does not show drainage.[12] This assertion is well established in CC and has also been extended to EC, although it has not been completely evaluated. However, another peculiarity of uterine drainage is the different lymphatic network presented by the cervix and the uterine corpus. The cervix shows an orderly drainage pattern; first toward the external and obturator iliac chains after having passed the parametrial lymph nodes and then continuing to the common iliac chains and finally reaching the paraaortic and interaortocaval territories.[13] On the other hand, the uterine corpus presents a different drainage according to the segments; the drainage of the lower two thirds is similar to that of the cervix while the upper third can drain directly to the retroperitoneal territory without the need to pass previously through the pelvic territory. This is the reason why it is important to obtain a good lymphoscintigraphic study prior to surgery in order to draw the lymphatic map of the tumor and to perform the injection of the radiotracer into the endometrial corpus and not only the cervix to study the whole organ.

The utility of SSLNB in CC has been widely evaluated in multicenter studies.[14] The current indications in CC include the IA1 stage with vascular lymphatic invasion and IA2 of the International Federation of Gynecological Oncology (FIGO).[15,16] These tumors are of at least 2 cm in size and are confined to the cervix without parametrial or vaginal invasion. Initially the technique was performed in tumors with parametrial invasion (IIB), however, the percentage of drainage is lower and the rate of false negative results may increase.[17,18] Tumors between 2 and 4 cm in size confined to the cervix (stage IB1) present a lower percentage of drainage and a higher rate of false negative results, and therefore, the European guidelines suggest completing lymph node studies with lymph node dissection,[15] with a grade of recommendation of B. In this way the benefits of ultrastaging of SSLNB are obtained without obviating the histological analysis of any of the lymph nodes of the pelvic chains. Nonetheless, with this therapeutic strategy the benefit of a reduction in morbidity provided by SSLNB is lost. Some studies[19] have compared the percentage of lymph node drainage and bilaterality among tumors of less than 2 cm and between 2 and 4 cm in size, being higher for the small tumors, albeit without statistically significant differences. Thus, SSLNB is also useful in stages IB1,[20] adding this clinical situation to the list of indications of SLN detection: IA1 + IVL, IA2 and IB1.

There is a great deal of controversy regarding the indication of SSLNB in EC. At present, the American guidelines of the NCCN include the indication of SSLNB in low risk endometrial tumors.[21] The stratification of risk is determined by the histology of the tumor (the histology of high risk involves serous carcinoma, clear cell carcinoma and carcinosarcoma), the histological grade (G1 or G2) and myometrial infiltration less than 50%. The classification of tumors of intermediate or intermediate-high risk has been modified over time. However, tumors of low risk are defined as small sized, well or moderately differentiated (G1–2) tumors confined to the uterine corpus. In routine practice tumors of high risk are accompanied by pelvic and paraaortic lymph node dissection for staging, while no additional lymph node study is performed in tumors of low risk. Lymph node study in tumors of intermediate risk depends on the protocols of each unit. SSLNB was introduced into the clinical guidelines in 2014[22] with the aim of ultrastaging patients with high risk tumors. In this subgroup, the percentages of drainage (74%) and bilaterality (19%) are not sufficiently optimum to avoid lymph node dissection as a staging technique.[23] At present, most groups apply SSLNB in patients with low risk tumors, performing cervical injection because of its accessibility and greater success

Fig. 3. The Da Vinci robotic surgery system includes a master console (upper left), control table (upper right) the slave robot (lower left). The new Da Vinci SP (Single Port) model is shown below on the right.

of drainage and achieving a detection rate of 87% and bilaterality of 60%.[24] Although this has been recommended in the American guidelines since 2017,[21] the last consensus meetings also recommend the use of this technique in high risk tumors accompanied by paraaortic lymph node dissection, since with cervical injection only drainage to the pelvic chains is guaranteed.[24] According to stratification – high, low and intermediate risk – the use of the SSLNB will be determined by prospective studies in the different populations.

In gynecology, radioguided surgery has evolved with the technological innovations available, with the development of robotic surgery and radiopharmaceuticals, thanks to the introduction of fluorescent and hybrid tracers.

Da Vinci robotic surgery

In 1999, the development of a robotic system of surgery was completed and commercialized by Intuitive Surgical Inc., which launched the first robotized surgical system called Da Vinci. This system was approved for surgical use by the Food and Drug Administration (FDA) in 2000.[25]

The Da Vinci system is a master–slave robot, that is, it does not have the capacity of autonomous movement and is absolutely dependent on the orders of the surgeon, thereby being dependent on the judgment, knowledge and skills of the physician. The system has the following elements (Fig. 3): 1. Master Console: this is the control table situated at a distance from the operation table and where the surgeon performs the hand movements in 3 dimensions which are identically formed by the arms of the robot. The surgeon observes the operative field through binoculars which provide high resolution 3D vision which ensures greater vision of the surgical field with real perception of depth. The arms of the surgeon are placed on armrests which provide stability and comfort, increasing physical resistance. The console controls and checks each of the motors of the robot and verifies the position of the surgical instrument being used, eliminating the possibility of producing erroneous movements. The software is designed so that if the surgeon makes a brusque movement, the robotic arms automatically brake, and in addition, an infrared light source disactivates the arms whenever surgeons withdraw their eyes from the binocular system. 2. Slave robot: in the current models it is made up of 4 arms, one of which contains the manipulator for the camera and the other 3 have the manipulators of articulated instruments which reproduce the movements of the hands of the surgeon made from the master console. The slave robot is set up on a mobile support (patient cart) which can be installed next to the operating table. 3. Instruments: special instruments are used with a small mechanical articulation system called EndoWrist. The computer of the robot transmits the movements of the hands of the surgeon to the articulated point of the instruments which are reproduced in the same direction, eliminating the "Fulcrum" effect or inverse movement, providing 7 grades of freedom of movement in each hand, and thereby conferring great skill. As a final effect, this articulated instrument can use any standard and conventional surgical instrument such as scissors, scalpel, different types of forceps, hooks, dissectors, needle holders, etc. and can be interchanged during surgery with the help of an instrumentalist and surgeon's assistant. In the field of surgery there is also a 12 mm laparoscopic trocar which is manipulated by the assisting surgeon which can place the laparoscopic gamma prove to detect the SLN and extract the lesions resected. 4. Vision cart: in the latest models (Da Vinci Xi) the screens are tactile and more ergonomic.

The system for image acquisition is very similar to the system used in laparoscopic surgery but in real third dimension. Likewise, the last models present the Firefly fluorescence system which can visualize indocyanine green (ICG) which is activated from the console of the surgeon.

Limitations of laparoscopic surgery

Laparoscopic surgery has important limitations, the most notable being the loss of sensation of depth, tactile sensation and strength and natural eyes–hands coordination, with the subsequent reduction in manual skill. The loss of sensation of depth is due to the two plane vision provided by observing the operative

field through a monitor. In addition, a mirror image is also produced in the movement of the surgical instruments, which makes it necessary to move in the opposite direction to what we wish to make. This situation is known as the "fulcrum effect" or inverse movement and leads to a loss of ability and skill. In laparoscopic surgery, long, rigid, non-articulated instruments are used with great restriction of movement. All these circumstances make surgeons adopt rigid and uncomfortable positions with the subsequent appearance of fatigue, which further increases tremor and unwanted movements, limiting surgical maneuverability and skill. The development of robotic surgery has the objective of solving these limitations.

Benefits of robotic surgery in gynecological surgery

The advantages of robotic surgery compared to traditional or laparoscopic surgery are:

1. Surgeons: (a) excellent visualization of the anatomical points of reference and tissular planes. The system provides tridimensional vision (3D), which can also perform rapid zooming of the zone and a panoramic view of the surgical field; (b) it facilitates access to complicated anatomies, enabling the surgeon to perform maneuvers which, without this system, would be impossible in some cases. All of this provides greater surgical safety; (c) greater oncologic radicality.[26] Taking into account the previously described advantages, the resection of a greater number of lymph nodes has been reported with robotic surgery compared to other modalities[27]; (d) greater accuracy with a limited number of small incisions, increasing control and reducing hematic losses[26,28]; (e) greater reconstructive accuracy, guaranteeing better postoperative functionality and rapid functional recovery, and (f) elimination of functional tremor.
2. Patients: (a) small incisions with better estetic results; (b) reduction in postoperative complications,[26,27] lesser need for transfusions; (c) less pain; (d) reduction in hospital stay,[26,27] and (e) more rapid return to normal, social and occupational activity.[28]

Limitations of robotic surgery

(a) Additional surgical training; (b) increase in surgical costs; (c) limitations of instrumentation, although the last models have specific material such as vessel sealers, mechanical staplers and vascular clips; (d) increase in the time of placing the robot before use and little flexibility in maneuvers once anchored if there is a change in surgical strategy due to technical problems. However, in the last models the placement time is reduced since the new patient carts enable changing the work area without having to move the patient; (e) the large size of the robot, although the latest models are smaller and more manageable.

Benefits of the new Da Vinci Xi system

(a) Fluorescence: in CC and EC this system enables visualization of the lymph nodes and, therefore, the SSLNB by injection of ICG. This allows pelvic and paraaortic lymph node dissection to be performed more safely, and the SLN can also be resected with greater safety even in zones of difficult access; (b) vessel sealer: more rapid and safer dissection with fewer complications derived from bleeding; (c) multiquadrant access: possibility of having access to multiple quadrants without the need to move the patient, thereby reducing the length of surgery. It has an adjustable rotating platform and a rotatory head allowing access to the 4 quadrants without repositioning the surgical cart. The new cart can be placed anywhere around the patient in order to avoid conflictive areas such as the head and legs and provides more flexible configuration of the operating room.

Indications for robotic surgery approaches in gynecology

Any type of surgery that can be performed by laparoscopy is indicated for robotic surgery: hysterectomy in benign and malignant disease, endometriosis, myomectomy, oophorectomy, sacrocolpopexy, salpingo-oophorectomy and tubal reanastomosis. Nonetheless, the greatest advantages of robotic compared to laparoscopic surgery are in: (a) nerve-sparing radical hysterectomy; (b) paraaortic lymph node dissection in any gynecological cancer; c) hysterectomy + double adnexectomy ± pelvic lymph node dissection in obese women.

Future

The Da Vinci SP (Single Port) model has a single cannula of 2.5 cm which controls 3 fully-wristed, elbowed instruments and the endoscopic camera (Fig. 3). It can reach up to 24 cm deep and triangulate the instruments at the distal tip. It can access any anatomy within 360° from the location of the port.

New radiotracers. Detection with hybrid tracers (ICG-^{99m}Tc-albumin nanocolloid)

With respect to other classical radiotracers such as methylene blue or radiotracers in some pelvic tumors such as prostate cancer, CC or EC, ICG has become the only radiotracer used. It is based on excitation with light and the detection of its emission in the spectrum of near-infrared light. ICG has no ionizing radiations, and therefore, its use enables injection and direct management by the surgical team, simplifying the detection of SLN to a mere surgical action. This simplicity implies the loss of a preoperative lymphatic map which the radiotracers provide. Thus, in the last decade hybrid tracers have been developed (ICG-^{99m}Tc-albumin nanocolloid) which combine the advantages of both compounds – the ease of intraoperative detection of the fluorescent emitter and the lymphatic map of the radiotracers. In gynecology, SSLNB with ICG provides excellent results in the detection of pelvic lymph nodes in EC, with 95% of global detection and 66% of bilaterality, similar to the radiotracers which achieve 93% and 71%, respectively.[24] In a metaanalysis including 538 patients, the utility of ICG was evaluated compared to the combined technique of a radiotracer with a dye such as methylene blue in CC and EC.[29] No significant differences were observed in global detection, but the use of ICG was favored in the detection of bilaterality.

The hybrid tracer was developed in animals in 2010[30] and was quickly used in humans with application in prostate cancer with excellent results similar to those of the radiotracers. It has 5 main advantages: (1) ICG reduces the "shine-through" effect of the radiotracers in the detection of SLN close to the injection point, thereby increasing the detection rate; (2) ICG provides visual feedback to the surgeon which facilitates intraoperative detection with less tissue dissection and a shorter surgical time; (3) on the other hand, radiotracers (Fig. 4) provide the lymphatic map of each individual tumor; (4) the hybrid tracer more rapidly and accurately identifies the first localization of the SLN, identifying the lymph node territory in which tissue should be dissected, and lastly, (5) it provides flexibility in surgical programming since with this tracer a one or 2 day protocol can be performed.[31] However, there is scarce scientific evidence in gynecology. In a pilot study in CC[32] it was found that both components of the hybrid tracer obtain similar results in the global detection of the SLN (100%) and bilaterality, with no significant differences between ICG and radiotracers. Nonetheless, differences in detection were observed

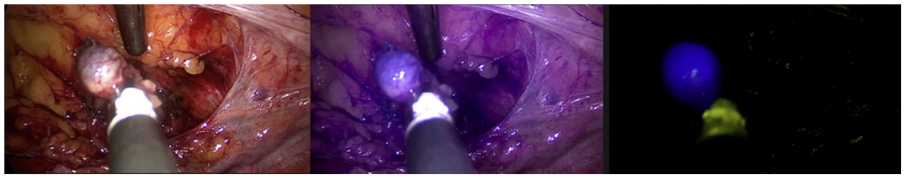

Fig. 4. Intraoperative detection with hybrid tracer of a left external iliac lymph node. Detection of tracer using gamma detector probe and white light (left), detection of the fluorescent component of the indocyanine green using near-infrared optics (right) and fusion of white light with near-infrared light (middle).

between ICG or radiotracers and methylene blue ($p = 0.0015$ and $p = 0.0013$, respectively), which only allowed the detection of the SLN in 85.7% of the cases. Another interesting aspect which is an advantage of the hybrid tracer compared to each of its components separately is that *in vivo* detection of some SLN is, in some cases, performed thanks to the exclusive detection of one or another component, but not both, which supports the use of the hybrid tracer.

Experience in EC is limited to publications in specific congresses in which there seems to be a similar trend to that observed with CC, in which each of the components, especially of the radiotracer, is better than the vital dye This finding might be explained by a higher body mass index, and therefore, of fatty tissue around the pelvic lymph node chains hindering visualization of the dyes. The detection rate with myometrial injection of the hybrid tracer has reached 80% with a bilaterality of 40%. The identification of any two components allows *in vivo* detection of the SLN, thereby increasing not only the number of lymph nodes biopsied but also the number of territories affected.

Localization of non-palpable lesions. Expansion of radioguided occult lesion localization (ROLL)

ROLL in solitary pulmonary nodules

The evolution of the diagnostic techniques available makes it increasingly easier to detect lesions and treat the disease earlier. These small sized lesions are mainly benign. Due to their small size, even the usual percutaneous biopsy techniques are not, on some occasions, diagnostic requiring the need for surgical biopsy. On being a non-palpable lesion the localization should be anatomical requiring resection of a quantity of the parenchyma above the lesion.

It is already known that in surgery there are situations in which it is necessary to localize non-palpable lesions. In view of this, different solutions to this problem have been developed.

Non-isotopic techniques include the introduction of metallic materials such as the wire and coil, labeling with radioopaque substances such as cyanocrylate, barium and lipiodol, and labeling with contrasts such as blue dye. Most of the techniques require a scope, and therefore, a specific operating room is necessary. The use of percutaneous injection blue dye presents rapid diffusion of the injection point with possible contamination of the pleural cavity, and it is not useful for visualizing deep lesions. It also presents the risk of anaphylaxis. Radioopaque contrast (such as lipiodol) may diffuse outside the nodule and enter the pulmonary lymph nodes possibly leading to infarction because these agents are not hydrosoluble. Percutaneous insertion of the wire can cause pneumothorax in patients with marked emphysema, air embolism and movement of the fixation point perioperatively.[33]

Another technique is intraoperative ultrasonography the main convenience of which is the occupation area of the lung with bad image transmission, making the experience of the person performing the ultrasonography an even more important limitation. Lastly, other techniques such as intraoperative pleural marking have been developed. However, this is a complex technique and only marks lesions of little depth.

Nuclear medicine provides a solution already applied in other localizations, that is radioguided occult lesion localization (ROLL). The use of ROLL was first described by Chella et al.[34] in 2000, and since then multiple articles describing the experience of different groups have been published.

The pulmonary ROLL technique is based on the marking of the lesion to be resected using different radiotracers according to accessibility: human serum albumin microspheres labeled with ^{99m}Tc (^{99m}Tc-SAM), ^{99m}Tc-colloid, ^{99m}Tc-phytate, and ^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA). Only one experimental study on radiotracer selection by Daniel et al.[35] compared ^{99m}Tc-MAA, ^{99m}Tc-sulfur colloid and pertechnetate, showing the best results with the first radiotracer.

The dose administered is variable, ranging from 5 to 1110 MBq, with the most frequent dose being 10 MBq. The volume used varies between 0.2 and 2.5 ml of radiotracer. Some groups add iodine contrast for better location of the zone where the dose is administered, adding 0.1 or 0.2 ml of the contrast to the dose of the radiotracer.

The administration of the dose is made with the same technique as pulmonary biopsy. On review of the literature all the studies describe the use of 22 G needles. The volume to be administered should be calculated according to the needle used in each center. All are of 22 G, but not all are of the same length.

The radiologist places the needle in contact with the lesion or as close as possible. The needle is fixed at the height of the surface of the skin with a Kocher needle holder to avoid mobilization of the needle during administration of the dose of the radiotracer. It is necessary to control breathing during the administration of the dose.

After the administration of the dose confirmatory planar images or tomographic images are performed. With the planar images we only know if the dose is in the lung and if it has diffused or not to the pleural cavity or has migrated to the hilar lymph nodes, which may sometimes occur. In our center, confirmation is performed with SPECT/CT because we not only want to know whether the dose is inside, which is very important, but also, overall if thoracoscopic surgery is performed, we want to know the exact relation of the dose with the nodule to be studied since it is sometimes not possible to puncture the lesion itself. SPECT/CT can be performed in a hybrid machine or in two machines and then fuse the studies with some points of reference. These points should be visible, but both CT and the gamma camera and fusion applications are used for evaluation.

On some occasions there may be dispersion of the dose into the pleural cavity. In this case, if the lesion is punctured and there is contamination in the cavity, and if the pleural dose is troublesome, lavage can be performed during the surgery. Another situation is hilar drainage, although ^{99m}Tc-MAA is injected, drainage is possible and may be an artifact for detection according to the localization of the lesion.

Different approaches may be used during surgery: thoracotomy, videothoracoscopy or thoracoscopy. It is recommended to use a thoracoscopic probe independently of the approach carried out since the characteristics of the surgery require that the instrument be easy to manage in the thorax.

The thoracotomy approach can localize lesions rapidly and accurately. The thoracoscopic route requires two trocars of at least the diameter of the probe since it is necessary to be able to track the pulmonary surface from different view points in order to correctly identify the zone to resect. Once the lesion has been localized, it helps to delimit the margin of the lesion. The lesion is resected and the margins of both the piece and the surgical bed are checked (video available at https://youtu.be/hEMCDd66t_8).

At present, the margins can be checked in the operating room with hybrid portable gamma cameras, thereby helping evaluation of the resection of the region marked.[36]

In conclusion, the pulmonary ROLL technique is useful for not only non-palpable but also palpable lesions and enables closed surgery to be performed. Important coordination is necessary between the Departments of Radiology, Nuclear Medicine and Thoracic Surgery. Benefits of the technique include both correct identification of the lesion as well as a reduction in postsurgical morbidity.

Radioguided surgery of osteoid osteoma

Diagnosis and treatment

Osteoid osteoma (OO) is a tumor which is not frequently found, representing 3% of primary bone tumors and 11% of benign osseous tumors. It is third in frequency among the latter. It is more prevalent in the second decade of life and in males, with a 1.5:1 proportion compared to women. The most common localization is the cortex of the long bones followed by the spinal column.[37] The most characteristic symptom is important, predominantly nocturnal, inflammatory pain which can be alleviated with salicylates and other non-steroidal antiinflammatory drugs.

Histologically, the lesion is characterized by a nidus of up to 1.5 cm with highly vascularized mesenchymal tissue which produces osteoid that calcifies in the central zone and is surrounded by dense sclerotic bone. Pain is associated with the presence of unmyelinated nerve fibers, and the role of prostaglandins as a vasodilator agent which increases intralesional pressure is under debate.

X-rays is the first imaging procedure to be performed, being complemented with a CT and/or MRI. Four-phase selective bone scintigraphy (vascular, blood-pool, delayed and at 24 h) shows an increase in activity in all the phases.[38] SPECT/CT obtains an anatomical-functional image of the lesion.

Osteoid osteomas can spontaneously evolve to disappearance and remission of the pain. They have a wide range of therapeutic options which vary from traditional open surgery (OS) with block excision of the nidus to minimally invasive techniques such as laser photocoagulation, percutaneous cryoablation or CT-guided percutaneous radiofrequency ablation (RFA).[39] The inconveniences of OS are larger incision, the need for fixations or bone grafts, the risk of postoperative fractures and longer hospital stay. At present, RFA is the technique of choice because of its good results, although the appearance of complications is possible including cutaneous necrosis, vascular and neurological damage and the risk of osteonecrosis. A recent study[40] compared OS and RFA in OO of the spinal column, obtaining a rate of complications of 19% and 8%, respectively. On the other hand, other authors[41] have reported 16% of recurrences in the treatment with RFA, which were significantly correlated with the size of the nidus.

At the beginning of the 1980s radioguided surgical techniques began to be successfully developed, and in 1981 they were applied for the first time in the biopsy and resection of suspicious bone lesions. Radioguided surgery of bone lesions ranges in efficacy from 97 to 100%, obtaining a rate of complications of close to 0%.[42] From 30 to 70% of the lesions biopsied by radioguided surgery are found to be malignant.[43]

Preoperative diagnosis

In the era of molecular imaging, bone scintigraphy with bisphosphonates labeled with ^{99m}Tc (^{99m}Tc-MDP) continues to be one the nuclear medicine techniques most frequently used due to its elevated sensitivity and diagnostic yield in the early detection of changes in vascularization and bone metabolism.

Three-phase bone scintigraphy enables obtaining images of the incorporation of the radiotracer in the zone evaluated. The images of the first phase (vascular or blood flow) and the second phase (early or blood-pool) provide information of the vascular and inflammatory component that characterizes the OO. The third phase (delayed or bone itself) shows a zone of intense uptake centered in a more diffuse halo and with less uptake which appears as a lighthouse in the fog, also called the double intensity sign. Tomographic studies (SPECT) increase the already high sensitivity of the test, and SPECT/CT hybrid studies can not only correctly localize the lesion and determine its size but also define well delimited lesions, with low attenuation, surrounded by a dense sclerotic reaction, and can observe foci of calcification in the interior of the nidus and vascular channels around the lesion. All of these findings can establish the differential diagnosis with stress fractures, Brodie abscess and toxic or inflammatory synovitis in the case of intraarticular OO.

On performing the fourth scintigraphy phase at 24 h after the administration of the bisphosphonate, persistence of the radiotracer can be observed in the lesion. This physiopathological characteristic may be of great help in surgical radiolocalization of OO in the spinal column or the upper third of the femur, both of which are localizations that are very close to zones of radiotracer uptake and physiological elimination such as the kidneys and bladder.[44]

In addition, the data obtained in the diagnostic phase of scintigraphy of OO is of great use in the programming of the surgical intervention: localization and relation with adjacent structures, lesion/background index, surgical time and lesion lavage, etc.[42]

Preoperative localization

Between 2 and 4 h before the intervention 4–25 mCi of ^{99m}Tc-MDP are intravenously administered, although low doses of radiotracer are sufficient for good radiolocalization of the lesion, reducing the dosimetry of the surgical team. If the administration of ^{99m}Tc-MDP is done the day before (20–25 mCi), this further reduces the dosimetry of the personnel and interference with renal or vesical activity. It is recommended to obtain informed consent and correct fulfillment with the same (identification and signature of the patient and physician, including the date).

In the preoperative unit the zone of maximum uptake is localized by probe or portable gamma camera and the skin is marked with indelible ink.[42]

The previous diagnostic images are also reviewed and the zone marked on the skin, with the surgical team determining the most adequate approach to facilitate extirpation of the lesion and minimize surgical trauma.

Intraoperative localization

Following preparation of the surgical field and the radioguidance surgical equipment, an incision is made at the zone with the greatest uptake or as close as possible to this zone when the adjacent neurovascular structural make this difficult. It is usually sufficient to make a small incision of 3–6 cm to expose the bone structure. Then the zone of maximum uptake is localized which usually has a lesion/background index ranging between 1.2 and 10. In order to avoid errors, it should be taken into account that OO is located on a bone structure which also has radiotracer uptake and

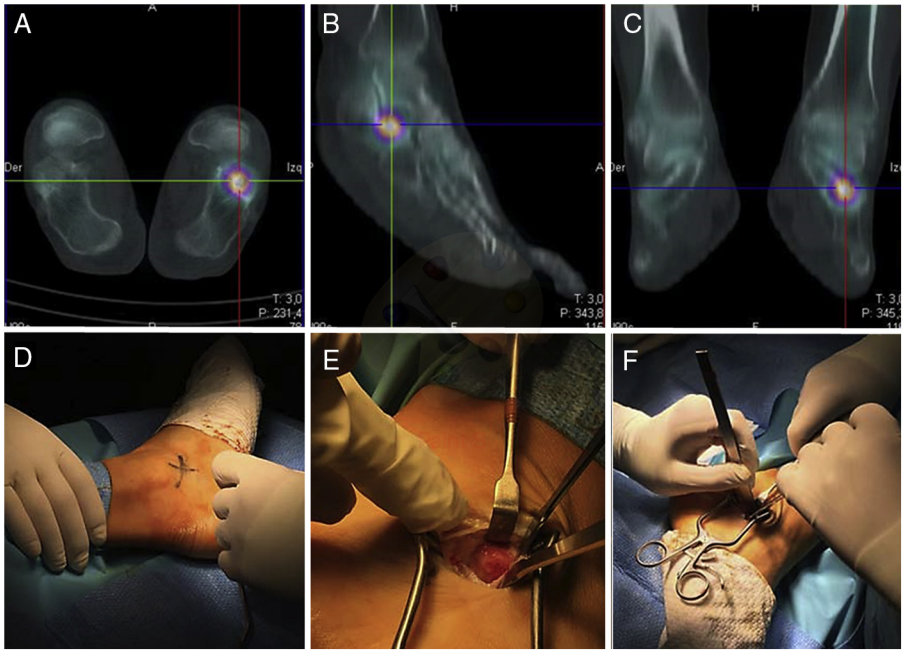

Fig. 5. Above, transaxial (A), sagittal (B) and coronal (C) slices of SPECT/CT of the scintigraphy with ^{99m}Tc-MDP obtained in a patient with an osteiod osteoma localized in the left calcaneus. Below, marking of skin with indeleble ink (D), localization with gamma detector probe (E) and surgical approach of the lesion (F).

that organs such as the bladder or kidneys may increase the background activity. It is essential for the nuclear physician to be skillful in probe orientation and movement.

Once the lesion and its extension have been localized, drilling of the lesion is performed, or failing that, the nidus is resected in block. In the latter case, radioguided surgery reduces the size of the block to a minimum. The excisional limit is defined by the activity of the radiotracer and/or changes in bone structure (Fig. 5).

Histological study

The definitive proof that the nidus has been localized is obtained by the histological study, but this does not prove that the nidus has been completely excised. Since bone uptake is the expression of physiopathological changes caused by the OO, normalization indicates a guarantee of an adequate result. It is especially important in the case of the use of drilling since the type and quantity of sample obtained can show a negative histological result in 18–23% of the patients, meaning that the nidus has not been completely resected.[45] In this case, the evolution of the patient and the disappearance of pain are indicative of successful surgery.

Conclusions

The advantages of radioguided surgery in OO compared to the other techniques available are:

1. It guides the intervention in real time, avoiding failure in the localization and approach in compromised neurovascular zones.
2. It accurately delimits the nidus which enables adequate excision of the lesion without excessively wide margins, avoiding weakening of the bone structure or the need to use bone grafts.
3. It can obtain histological information about the lesion which is not possible with other techniques such as RFA.
4. It allows orthopedic surgeons from hospital centers which do not have CT-guided RFA to treat these patients.
5. It reduces the morbidity and surgical complications, facilitating the return of the patient to the workplace.

Conflict of interest

The authors declare that there are no conflicts of interest.

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