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Continuing Education

Sentinel node approach in prostate cancer

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ABSTRACT

In general terms, one of the main objectives of sentinel lymph node (SLN) biopsy is to identify the 20-25% of patients with occult regional metastatic involvement. This technique reduces the associated morbidity from lymphadenectomy, as well as increasing the identification rate of occult lymphatic metastases by offering the pathologist those lymph nodes with the highest probability of containing metastatic cells. Pre-surgical lymphoscintigraphy is considered a "road map" to guide the surgeon towards the sentinel nodes and to ascertain unpredictable lymphatic drainages. In prostate cancer this aspect is essential due to the multidirectional character of the lymphatic drainage in the pelvis. In this context the inclusion of SPECT/CT should be mandatory in order to improve the SLN detection rate, to clarify the location when SLNs are difficult to interpret on planar images, to achieve a better definition of them in locations close to injection site, and to provide anatomical landmarks to be recognized during operation to locate SLNs.

Conventional and laparoscopic hand-held gamma probes allow the SLN technique to be applied in any kind of surgery. The introduction and combination of new tracers and devices refines this technique, and the use of intraoperative images. These aspects become of vital importance due to the recent incorporation of robot-assisted procedures for SLN biopsy. In spite of these advances various aspects of SLN biopsy in prostate cancer patients still need to be discussed, and therefore their clinical application is not widely used.

El ganglio centinela en el cáncer de próstata

Palabras clave:
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RESUMEN

En términos generales uno de los principales objetivos de la biopsia del ganglio centinela (GC) es identificar el 20-25% de pacientes que presentan enfermedad ganglionar regional clínicamente oculta. Esta técnica minimiza la morbilidad asociada a la linfadenectomía y aumenta también la tasa de identificación de metástasis linfáticas ocultas al ofrecer al patólogo aquel o aquellos ganglios con mayor probabilidad de contener células tumorales. La linfogammagrafía prequirúrgica se considera como un "mapa de carreteras" para guiar al cirujano hacia los GC y para la localización de patrones de drenaje impredecibles. En cáncer de próstata este aspecto adquiere especial importancia debido a su drenaje multidireccional en la pelvis. En ese contexto la inclusión de SPECT/TC aparece como esencial para lograr un mejor índice global de detección del GC, clarificar la existencia y ubicación de ganglios centinelas difíciles de interpretar a las imágenes planares, conseguir una mejor definición de los mismos en localizaciones cercanas a la inyección y entregar puntos de referencia anatómica que puedan ser reconocidos durante la operación para localizar los GC.

La utilización de sondas detectoras de rayos gamma convencionales o laparoscópicas permiten la aplicación de la técnica en cualquier tipo de cirugía. La implementación y combinación de nuevos dispositivos y trazadores permite refinar la técnica, así como la utilización de imágenes intraoperatorias. Estos aspectos han ido adquiriendo especial importancia debido a la incorporación de la biopsia del GC en protocolos que emplean cirugía robótica. A pesar de ello, la aplicación clínica de la biopsia del GC en pacientes con cáncer de próstata todavía sigue incluyendo aspectos a discutir y por ello su aplicación clínica no se ha generalizado.

Introduction

Prostate cancer is predominantly a tumor of older males but it is the most frequent urogenital malignancy, the most common solid neoplasm and the second most common cause of death by

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cancer in males in Europe. Median age at diagnosis is 72 years. In the United States more than 200,000 new patients are diagnosed every year. Age-standardised cases of incidence and mortality per 100,000 population per year were 96.0 and 19.3 in Europe and 96.8 and 15.2 in Spain, respectively.[1]

In the period 1989–2008, in Spain there were 104,955 deaths due to prostate cancer, accounting for 10% of mortality among all male malignant tumors. The prostate cancer mortality pattern was not at all pronounced, indicating, as in the case of breast cancer among women, territorial uniformity in exposure to possible risk factors. A south-north pattern was in evidence during the first three quinquennia. In Andalusia, which had registered lower than expected mortality in the first three quinquennia, a change seemed to be taking place in the period 2004–2008.[2]

The diagnosis of prostate cancer is well established, being based on the determination of the prostate-specific antigen (PSA), rectal tact, transrectal echography and prostate gland biopsy. The performance of a biopsy is guided by the ultrasound suspicious image but should be randomly performed to collect a sufficient number of samples from each lobe.[3]

A majority of the tumors are adenocarcinomas and magnetic resonance (MRI) is the technique of choice for accurate delimitation of extension: capsular infiltration, invasion of the neurovascular bundle and infiltration of the seminal vesicles.

Currently, the most used histologic grading system is the Gleason scale, which recognizes the following categories[4]:

Gx, grade of differentiation cannot be evaluated.
Gleason 2–4 (G1), well differentiated (weak anaplasia).
Gleason 5–6 (G2), moderately differentiated (moderate anaplasia).
Gleason 7–10 (G3–4), poorly differentiated/undifferentiated (marked anaplasia).

Staging follows the TNM approach, as depicted in Table 1.

On the other hand, the lymph node status serves as a key predictor for clinically localized prostate cancer. As in many other cancers, lymph node staging is important for both prognosis and therapeutic management.

Prostate-specific antigen (PSA) levels, pathologic stage and Gleason score are predictors for lymph node involvement; the higher these factors, the greater is the probability of nodal involvement. The prevalence of infiltration of the lymph nodes has been shown to be approximately 25% of the patients with prostate cancer with a reduction in 5-year survival of 85% in N0 patients and of 50% in N1 patients.

The presence of lymph node metastatic involvement may lead to the abandon of local curative therapy, such as radio therapy or radical prostatectomy, and subsequently to initiate androgen deprivation therapy. Limited nodal metastases may be treated with extended pelvic lymph node dissection or with external beam radiation therapy combined with long-term androgen deprivation therapy. Currently, none of the available imaging diagnostic modalities provides a reliable assessment of lymph node metastases. Conventional imaging techniques show a low sensitivity in the localization of lymph node disease since the criteria accepted to define pathologic character is size and, on many occasions, involved lymph nodes smaller than 1 cm. Thus, the sensitivity of computerized tomography (CT) varies greatly, being between 25 and 70% and from 75 to 78% for MRI. The sensitivity of these modalities is particularly limited in metastasis smaller than 5 mm. This has contributed to establish the role of extended pelvic lymphadenectomy (EPL) as the gold standard for the identification of lymph node metastases in prostate cancer.[5]

Post-operative pathologic examinations of tissue samples obtained during EPL assess metastatic spread. With an increase in the dissection template and the thorough histopathologic study of those nodes the N1 group has increased in number with improvement of staging.

Table 1
TNM staging.

T: Primary tumor
Tx: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T1: Tumor clinically inapparent, neither palpable or visible using imaging techniques
T1a: Tumor detected as incidental finding in an extension ≤5% of the tissue resected
T1b: Tumor detected as incidental finding in an extension greater than 5% of the tissue resected
T1c: Tumor identified by biopsy puncture (i.e. because of elevated PSA)
T2: Tumor confined within prostate[a]
T2a: The tumor involves half of a lobe or less
T2b: The tumor involves more than half of a lobe but not both lobes
T2c: The tumor involves both lobes
T3: Tumor which extends beyond the prostatic capsule[b]
T3a: Extracapsular extension (uni or bilateral)
T3b: Tumor which invades the seminal vesicle(s)
T4: Tumor is fixed or invades adjacent structures other than the seminal vesicles: vesicle neck, external sphincter, rectum, elevator muscles of the anus and/or pelvic wall

N: Regional lymph nodes
Nx: Regional lymph nodes cannot be evaluated
N0: Regional lymph node metastasis not shown
N1: Metastasis in regional lymph nodes

M: Distant metastasis
Mx: Distant metastasis cannot be evaluated
M0: No distant metastasis
M1: Distant metastasis
M1a: Non regional lymphatic lymph node(s)
M1b: Bone(s)
M1c: Other localization(s)

Adapted from NCCN guidelines 2015. www.nccn.org; accessed 27/2/2015.
[a] Tumor in one or both lobes by needle biopsy but not palpable and visible by imaging, is classified as T1c.
[b] Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.

However, the use of EPL has been found to be associated with various complications (venous thrombosis, lymphocele, lower extremity edema and ureteral injury) and its incidence increases with the number of dissected lymph nodes varying from 10.5% for 1–5 lymph nodes to 24.3% when dissection includes more than 20 lymph nodes.[6]

Predictive nomograms have therefore been developed, among which the most accepted is the Roach formula [(2/3) PSA + (Gleason-6) × 10]. Using this tool patients who are candidates for lymphadenectomy can be selected. However, whether a standard or extended technique should be performed continues to be a controversy, due to the lack of an imaging technique to assist in the localization of lymph node infiltration.[7]

Moreover, the area of EPL has its limits; in most descriptions the common iliac artery is only cleared up to the crossing of the ureter, the external iliac vessels as a rule are the lateral border, and the internal iliac is usually cleared from the bifurcation up to just beyond the superior vesical artery. The EPL area as well includes the obturator fossa that consists of the tissue between the external iliac vein and the obturator nerve. Nowadays, several reports indicate that EPL improves biochemical relapse-free survival, especially in patients with minimal lymphatic dissemination.[8]

As an alternative for the EPL the sentinel lymph node (SLN) biopsy was introduced using open surgery and a gamma probe.[9] Subsequently the procedure was validated for laparoscopy.[10]

SLN biopsy focuses on the identification, subsequent to minimal invasive excision and extensive histopathologic evaluation of the lymph nodes that drain directly from the primary tumor. Assuming the orderly spread of tumor cells through the lymphatic system,