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Review

Minimally invasive radioguided parathyroid surgery: A literature review

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ABSTRACT

The minimally invasive approach to parathyroid glands represents an important field of application of radioguided surgery. As always happens, in all cases pertaining to hyper-specialized skills, scientific production has long been the prerogative of a few Authors, but the ever increasing technological diffusion, combined with excellent results often achieved, increases the interest in this technique. This is particularly true in the era of minimally invasive surgery. The Authors realize a review of the existing literature to allow an overall view of current knowledge on this particular topic and to guide future research.

1. Introduction

During the last 30 years radioguided surgery (RGS), as well as its related technologies, has been spreading and improving, thus influencing the management and surgical therapy of malignancies such as breast cancer [1–4], melanoma [5–7] and other cutaneous tumors [8–13], gastro-oesophageal cancer [14,15], colo-rectal cancer [16,17], anal cancer [18], head and neck malignancies [19–24], gynecologic malignancies [25,26], urologic malignancies [27–32], thoracic malignancies [33,34], neuroendocrine tumors [35–37] and others. The first description of RGS, involving a gamma detection probe (γ-probe), was provided by Harris et al., in 1956 [38] and it was about a patient with thyroid cancer: using a handheld scintillation detector device as γ-probe, they succeeded to localize and resect an area of residual thyroid tissue. The first application of RGS to a parathyroid adenoma (PA) has been provided in 1984 by Ubhi et al. [39]: they used 201Tlthallous chloride and a γ-probe to identify a mediastinal PA. In 1989, Coakley et al. [40] reported that 99mTc-sestamibi (MIBI) was taken up and retained in abnormal parathyroid glands and, in 1995, Martinez et al. [41] first described the use of MIBI for intraoperative detection of a parathyroid gland. Two years later, in 1997, Norman and Chheda published the first series of fifteen consecutive patients with primary hyperparathyroidism (HPT) who underwent a "minimally invasive parathyroidectomy facilitated by intraoperative nuclear mapping" [42]. Since then, excluding radioguided sentinel lymph node biopsy for breast cancer and melanoma, parathyroid surgery has been one of the largest area of application and study of minimally invasive RGS through the use of γ-probes and many Authors have published their contribution to the field [22,43–61].

2. Materials and methods

A literature search, using the Medline/PubMed database for full-length papers, was performed up to 31 January 2015. Entry terms were: minimally invasive, radioguided surgery, parathyroid, hyperparathyroidism, γ (gamma) probe, 99mTc-sestamibi, SPECT. Out of the retrieved records, those pertinent to the objective of the

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present review were selected. The corresponding full-length articles were examined carefully and those articles with relevance were considered for analysis. Review articles on minimally invasive radioguided surgery of parathyroid glands were also analyzed and critically reviewed.

3. Discussion

3.1. Forms of hyperparathyroidism

Hyperparathyroidism (HPT) results from the excessive secretion of the parathyroid hormone (PTH) by at least one hyperfunctioning parathyroid gland: it usually leads to hypercalcemia.

Primary HPT is characterized by autonomous hyperactivity with hypersecretion of PTH by one or more enlarged parathyroid gland and is caused mainly by a single adenoma, in 85–90% of the cases [62]. Dual adenomas are present in approximately 4% and multiglandular hyperplasias (HPl) are present in approximately 10%–15% of cases [63–65]; frequently parathyroid carcinoma causes excessive secretion of PTH and can lead to hypercalcemic crisis [66]. Primary HPT affects 1 in 700 individuals [64] and some evidences showed that its incidence is increasing and prevalence approaching 1% in elderly women [67].

Secondary HPT usually results from parathyroid gland HPl related to chronic renal failure and for this reason is often defined “renal HPT”. The pathophysiology is dependent on a combination of hyperphosphatemia and reduced renal production of vitamin D causing hypocalcemia and, as a result, excessive secretion of PTH [68]. About 90% of patients with chronic renal failure develop this disease by the time hemodialysis is initiated [69]. Other causes of secondary HPT include osteomalacia, rickets, and malabsorption [68].

Tertiary HPT is an entity most commonly occurring in patients with secondary HPT who, after receiving a renal transplantation, show persistent elevated PTH levels. This condition is observed in up to 30% of kidney transplant recipients [70] and is classically caused by HPl of all 4 glands that, after correction of the renal impairment by transplant, fails to resolute and continues to oversecrete PTH [70,71].

3.2. Parathyroid anatomy and parathormone

Normally, there are 2 pairs of parathyroid glands in adult humans. Each gland measures approximately 6 × 4 × 2 mm and weighs approximately 30–50 mg [72–74]. Autopsy examinations showed that in 84% of cases there's a normal anathomy with four glands, the percentage of cases with three parathyroid glands is 3% and supernumerary glands are present in 13% of cases [74]. The anatomic distribution has high constancy but parathyroid glands sometimes might exist in ectopic sites such as in thyroid gland, in carotid sheath or at the level of the carotid artery bifurcation, behind the trachea, in the mediastinum, in the thymus [75]. PTH is a single-chain polypeptide with a molecular weight of 9500 Da, composed of 84 amino acids, although only the first 34 amino acids are required for full biological activity, namely control of ionized calcium level in blood and in the extracellular fluid [72,73]. The biologic half-life of secreted PTH is very short, just 2–3 min, because it is rapidly metabolized by the liver (70%) and the kidneys (20%) [76].

3.3. Classic approach to parathyroid surgery

After the first successful parathyroidectomy was performed on rat with bilateral neck exploration (BNE) in 1925 [77], Mandl established, in 1933, the basic rules for surgery of the parathyroid gland in human [78]. This conventional surgical treatment consists of a cervicotomy, which is generally achieved via a Kocher incision at the neckline and bilateral exploration of all four parathyroid glands with subsequent resection of the enlarged parathyroid glands [65,78]. Those principles have not been changed substantially since that time and have remained the standard treatment of HPT for many years [79–81]. Clearly, with this approach, success depends on the surgeon's knowledge of normal anatomy, and its variations, because an especially challenging aspect of parathyroid surgery is to distinguish a PA from HPl: a distinction that can be difficult not only intraoperatively, but also histopathologically [82].

In general, most experienced surgeons trust their skill to evaluate size, shape, and color of the parathyroid glands at surgery, in order to distinguish normal glands from abnormal ones [82]. Usually, if one gland is enlarged and the others are perfectly normal visually, surgeons lean towards diagnosis of PA [82]. Several surgical protocols also included biopsy of the normal-sized glands in order to discover possible glandular HPl [83]. Definitely, in the hands of an experienced endocrine surgeon, BNE approach yields a 95% success rate with minimal morbidity [79,84–88]. However there is evidence that BNE may increase the risk for injury of the laryngeal recurrent nerve [89] and the risk of hypoparathyroidism, as well as the rate of recurrences [90], especially when biopsy of normal-sized glands is applied or when re-operation is required for persistent/recurrent HPT. Moreover, for at least 85% of all cases, a single PA is responsible of primary HPT so the use of BNE could seem over treatment in such cases [91,92]. Basing on this rationale, Tibblin first described in 1982 the possibility to perform a unilateral neck exploration (UNE) based on PA removal and biopsy of the ipsilateral parathyroid gland, to discover possible HPl [93]. But, at that time, the insufficient accuracy of preoperative imaging techniques for the localization of hyperfunctioning enlarged parathyroid gland constituted the major limitation encountered in performing UNE [79,80,94].

3.4. Evolution of imaging technologies

Several relevant technological advances in preoperative parathyroid imaging techniques have strongly favored the development of limited neck exploration approaches. First of all MIBI scintigraphy [40,95–107] and ultrasonography [98], but also CT-scan, MRI, SPECT.

Parathyroid ultrasonography has a sensitivity for PA identification that ranges between 70 and 80% [98,108] whereas the sensitivity for volume increase has a much wider range, between 30 and 90% [47]. The overall localization accuracy of ultrasound imaging can reach 40–80% when a high-resolution technology is used [109].

The sensitivity of CT scans ranges from 45 to 75%, and is lower in previously operated patients [110]. CT-scan can localize PAs in the retrotracheal, retroesophageal, and mediastinal spaces better than US but it doesn't perform well for ectopic lesions located in the lower neck at the level of the shoulders and lesions close to or within the thyroid gland [111–113]. Moreover, CT-scan performs worse in discriminating upper from lower parathyroid glands [113,114].

On MRI examination, enlarged parathyroid glands display a medium intensity on T1-weighted images, but have considerably increased intensity on T2-weighted and proton density images [115,116]. MRI sensitivity seems to be slightly better (50–80%) than that of CT scans [116,117].

The introduction of MIBI scintigraphy has improved the ability to identify preoperatively abnormal parathyroid gland(s) [118,119] and the overall accuracy of this technique in detecting PAs is very high, around 90% [120,121]. For this reason at the moment MIBI scan is considered the most accurate technique in selecting patients