Summary and general discussion

10

Introduction

Since the introduction in the 1970s of the unilateral approach in surgery for primary hyperparathyroidism by Wang [1], authors have increasingly been recommending limited forms of parathyroid surgery [2 3]. Although unilateral explorations reduce operation time and admission days, decrease operative risk and give better cosmetic results, the debate about the best surgical treatment for primary hyperparathyroidism has never been settled. 'Bilateralists' oppose less invasive approaches because they estimate the incidence of multiple gland disease to be as high as 30% [4]. However, in spite of a systematic bilateral exploration of the neck in search of the diseased parathyroid gland, with identification and estimation of the size of all parathyroid tissue, in only 44% of cases are four glands identified, in 37% three, and in 19% less than three [5].

In **chapter 1** we reported an exceptional case of persistent hyperparathyroidism (due to a non-descended inferior parathyroid) after extensive bilateral exploration, illustrating a clinical dilemma that can be encountered in parathyroid surgery. Imaging carried out prior to re-exploration and including, among other methods, ultrasonography and computed tomography, revealed a parathyroid adenoma at the level of the mandibular angle and the hyoid bone. Guided by the imaging results the adenoma was successfully resected by a local direct procedure taking less than 10 minutes.

In general, the main reason an adenoma is not found during exploration is the variability in location, rather than variety in the number of glands. It is therefore of pivotal importance to understand not only the anatomy, but also the embryology of the parathyroid glands. As radiologist John Doppman succinctly stated, 'If you are an experienced parathyroid surgeon and not able to find a tumor, you cannot have looked high enough'.

Since primary hyperparathyroidism can be diagnosed with nearly 100% accuracy and successfully treated in more than 95% of cases, surgery is the treatment of choice. The gold standard in parathyroid surgery has been conventional neck exploration (CNE), and with success rates exceeding 95% and virtually no complications nothing more seemed left to be desired. However, it cannot be denied that there is a discrepancy between the extent of the operation and the size of the offending gland in the majority of patients [6]. Encouraged by the pace of development in methods of imaging (resulting in increased accuracy), combined with the knowledge that primary hyperparathyroidism is caused by a solitary adenoma in at least 85% of cases, and our experience of the relatively simple and quick MIA procedure (**chapter 1**) we wondered whether such a direct, minimally invasive strate-

gy could be utilized for the more common cases of primary hyperparathyroidism as well.

For this purpose we formulated the following hypothesis (**chapter 3**): 'A substantial group of patients with primary hyperparathyroidism can be successfully treated by limited access surgery after preoperative localization studies and may thus be spared unnecessary extensive dissection (conventional neck exploration)'.

Minimally invasive adenomectomy

We prospectively tested this minimally invasive approach as an alternative to CNE. In **chapter 4** we described the results of 110 consecutive patients who underwent parathyroidectomy, 84 of whom were selected for minimally invasive adenomectomy (MIA) and 26 for CNE. Operating time was 20 minutes in the MIA group and 80 minutes in the CNE group ($p<0.05$), and admission days were reduced to 1.7 days (MIA group) from 3.0 (CNE group) ($p<0.05$). MIA was shown to be a safe and effective technique with a success rate of 96%, capable of replacing conventional neck exploration in approximately 75% of patients, with virtually no complications. Several other investigators have proposed less invasive strategies as alternatives for CNE, most of which have focused on unilateral neck exploration [3]. True minimally invasive techniques were reported to be feasible, guided by preoperative ultrasonography, in about 40% of cases [8], while others have reported excellent results using intraoperative sestamibi-technetium99m scintigraphy (Sestamibi) parathyroid scanning with a hand-held gamma probe [9]. Though attractive when the neck has to be reoperated on due to failure of an initial exploration, in our opinion the costs associated with the Sestamibi scanning preclude its routine use, as discussed below. Alternatively, some surgeons have advocated endoscopy to achieve minimally invasive adenomectomy in selected patients [10]. Although conceptually elegant, this technique appears difficult to learn and certainly requires more operating time than the direct approach described in this thesis.

Asymptomatic and mildly symptomatic patients

The 1990 National Institute of Health (NIH) Consensus Development Conference arrived at a consensus on the indications for surgical intervention in asymptomatic primary hyperparathyroidism [10]. Among their findings, the panel concluded that the diagnosis of primary hyperparathyroidism does not mandate referral for operative intervention in all cases. Conscientious surveillance was thought to be justified in asymptomatic patients whose calcium levels are only mildly elevated (to < 3.0 mmol/L; normal 2.20-2.60), and whose renal and bone status are close to normal (creatinine clearance reduced not more than 30% and bone mass not more than two standard deviations below those of controls matched for age, sex, and ethnic origin.

Nevertheless, patients with primary hyperparathyroidism have significant functional health status impairment independent of the level of serum calcium [11]. In addition, our experience with MIA has provided us with new arguments for making it the surgical option of choice in asymptomatic and mildly symptomatic patients. In **chapter 5** we advised the following strategy for the asymptomatic or mildly symptomatic patient. When a patient has biochemically proven hypercalcemia with inappropriate levels of parathormone (PTH), localization of the adenoma has to be attempted by Doppler-ultrasonography and computed tomography. When test results unequivocally indicate a solitary adenoma the patient is advised to undergo a minimally invasive procedure. However, if the test results are equivocal or indicate the possibility of multiglandular involvement a conservative policy is advocated. If the disease advances, major symptoms develop and/or the patient fulfills the NIH-guidelines, parathyroid imaging should be repeated before whichever form of operation is indicated.

Imaging

Before the introduction of imaging-guided, minimally invasive parathyroid surgery, the general opinion about preoperative localizing studies was that imaging before initial surgery was not worthwhile. This objection to the routine use of localizing tests was based on 1) inferior sensitivity rates in localizing studies (reaching 85% maximum) when compared with success rates in conventional neck exploration (over 95%); 2) the reduced accuracy of localizing studies in multiglandular disease; 3) an unjustified economic burden because of lack of evidence for the cost effectiveness of imaging studies; and 4) the possibillity of misleading less experienced surgeons [10 12 13 14]. Now, a decade after the NIH meeting, some of these argu-

ments may be viewed critically.
Firstly, most of these studies were carried out retrospectively and none followed a strict protocol. Modern, state-of-the-art imaging modalities and prospective adherence to a strict protocol gives, in our experience, good results. Furthermore, a team approach with a dedicated radiologist and an experienced endocrine surgeon has contributed considerably to the success of direct adenomectomy. In our series ultrasonography gave a sensitivity of 78%, a specificity of 78% and a positive predictive value of 96% (**chapter 6**). Despite the fact that the combined results of ultrasonography and computed tomography moderately improved the sensitivity to 84% (**chapter 4**), the diagnostic use of spiral computed tomography was advised with caution, because of the associated costs and risks of radiation (**chapter 6**). Nevertheless, the routine employment of both techniques can be justified because 1) computed tomography produces an operator-independent roadmap, and 2) with the use of 'cine-loop' reconstruction at the computer work-station, additional information and an essential three-dimensional view are available, helping the surgeon in planning the operation.
Secondly, imaging (in our series ultrasonography combined with computed tomography) was shown to be beneficial in preoperative planning for the treatment of primary hyperparathyroidism since, with its aid, we were able to select approximately 75% of patients for minimally invasive adenomectomy.
Thirdly, economic evaluations were limited in number and, if available, mostly based on bilateral explorations.

On the basis of our personal favorable results we adhered strictly to the use of ultrasonography combined with computed tomography. However, this does not preclude the use of other modalities in the treatment of primary hyperparathyroidism. Parathyroid scanning using radioisotopes has evolved over the years and is able to localize adenomas in approximately 90% of cases [15 16]. The use of a hand-held gamma probe (Sestamibi) to guide the surgeon to the parathyroid adenoma has been advocated as being useful in reoperations on the neck [17]. Moreover, excellent cure rates have also been reported with the use of a gamma probe in initial surgery, simultaneously decreasing operating time and hospital stay, resulting in significant cost reduction without compromising patient safety [9 18]. Conventional scintigraphy (thallium201-technetium-Tc99m pertechnetate scanning) is, in our opinion, not suitable for selecting patients for MIA because of the relatively poor image resolution and anatomical information obtained. Sestamibi, has been reported to give sensitivity rates up to 100% in solitary disease [14], but, in our opinion, it should be restricted to a selected group of patients because of its high costs (+/- € 680). The modest increase in accuracy using Sestamibi does not justify the disproportionate rise in cost.
Other imaging modalities consist of magnetic resonance imaging (MRI) and selective venous catheterization for measurement of PTH levels. Although MRI (sensitiv-

ity 57-90%) is only marginally more accurate than computed tomography (sensitivity 41-86%) [13 19], MRI avoids the need for use of contrast medium and shoulder artifacts are circumvented, we prefer computed tomography for reasons of availability and cost. Finally, since selective PTH sampling requires an expert radiologist, is invasive and associated with high costs, its use should be restricted to reoperations.

Parathormone assay

The clinical utility of rapid PTH measurement in parathyroid surgery was first reported in 1988, using a modified intact PTH immunoradiometric assay [20]. The authors concluded that intraoperative measurement of PTH would be helpful to the surgeon. The combination of more accurate preoperative localization studies and the ability to predict the postoperative serum calcium would facilitate limited explorations [3]. The use of non-radioactive kits transportable on a trolley has allowed the rapid assay to be performed in or adjacent to the operating theatre. These commercially available portable kits measure PTH within 15 minutes with sensitivity rates reaching 96%, specificity of 100% and overall accuracy of 97% [21 22]. Although it cannot be denied that these tests are highly effective providing true intraoperative results, the preliminary procedures (e.g. instrument performance check, generating calibration curves and assay quality control prior to surgery), and their substantial cost preclude their widespread introduction. In a search for a less costly alternative rapid PTH assay, we studied the reliability and applicability of a non-portable rapid PTH assay to predict successful surgical treatment of primary hyperparathyroidism (**chapter 7**). In that chapter we described the results of the first 35 patients measured with a rapid PTH assay (modified Immulite Regular assay) providing results within 70 minutes. Once the results were shown to agree fully with both conventional PTH measurements and postoperative serum calcium levels, we included the Immulite Regular assay in our protocol. We also tested three other non-portable PTH assays (Immulite Turbo, Advantage Regular and Advantage Turbo assays), which are described in **chapter 8**. All these methods were concluded to be useful to ascertain the success of an exploration. The Immulite Regular and Immulite Turbo assays, however, were believed to be more accurate than the Advantage Regular and Advantage Turbo assays when used according to our protocol (a decline in PTH of >50%, measured 8 minutes after resection, predicting normocalcemia).

Costs

Minimally invasive adenomectomy has definitely entered the therapeutic regimens for primary hyperparathyroidism, and therefore it is important to study the economic burden. We cost-analyzed a prospective series of 164 patients to obtain information on the relative costs of MIA and CNE (**chapter 9**). To observe the effect of changing appreciable variables, multiple sensitivity analyses were carried out. The mean cost of MIA was calculated as € 1,288 and that of CNE € 2,106 ($p<0.0005$). The reason MIA is so much cheaper than CNE is the differences in operating time (median 20 minutes in MIA versus 75 minutes in CNE) and admission days (2 days in MIA versus 3 days in CNE). Sensitivity analyses showed that an increase in total average costs of 63%, an increase in operating time to 272 minutes, prolongation of admission from 2 to 4.5 days, or an initial operation failure rate of 54% in the MIA group would result in MIA costs equaling those for CNE. Such extreme examples are clearly unrealistic, but admission time remains a variable that is highly dependent on 'local' logistics, and may be amenable to reduction. In particular, day care surgery will shortly become possible for MIA, provided a safe protocol for the management of postoperative hypocalcemia can be designed (and adhered to).

The future

The ongoing technical developments of imaging modalities presage an increase in discriminating capacity and increasing accuracy of various techniques, making MIA possible for even more patients. The possibility of day-care MIA, using intravenous sedation combined with local anesthesia, will further liberalize the indications for this method.

Conclusion

In conclusion, minimally invasive adenomectomy is a safe and effective alternative to conventional neck exploration, able to replace it in approximately 75% of cases. It is not only associated with a very low complication rate, comparable to that of conventional neck exploration, but is also cheaper than conventional exploration. In the future, additional savings may be anticipated when day-care MIA becomes possible.

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