Strategy in asymptomatic and mildly symptomatic primary
hyperparathyroidism, new arguments for the surgical option

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The widespread use of multichannel serum chemistry autoanalyzers has resulted in a sevenfold increase in the reported incidence of primary hyperparathyroidism (pHPT) [1]. Subsequently physicians have been increasingly confronted with the most common form of pHPT: an asymptomatic or mildly symptomatic disease characterized by mild chronic hypercalcemia with or without subtle symptoms such as fatigue and muscular weakness. It is estimated that approximately 80% of all the patients with pHPT fall into this category [2]. Today it can be calculated that pHPT develops in about 6000 patients each year in the Netherlands.

The serendipitous discovery of asymptomatic and mild pHPT has raised relevant questions about the advisability of treatment in these patients. At the National Institutes of Health (NIH) Consensus Development Conference on Diagnosis and Management of Asymptomatic pHPT in 1990, surgical treatment was advised along the guidelines given in **Table 1** [3]. One could wonder however, why operative treatment is not advised in more patients with pHPT, for surgery is the only curative treatment available, surgery is very successful (return to normocalcemia is achieved in up to 95-99% of cases in experienced hands), surgery has a low morbidity and even with a long follow-up the recurrence rate is very low [4]. Furthermore, after successful surgery the patient is saved repeated monitoring and long term follow-up and there is no chance of developing one of the more severe complications of hypercalcemia.

Table 1 Indications for surgical treatment in primary hyperparathyroidism according to the National Institutes of Health Consensus Statement 1990.

Markedly elevated serum calcium: 2.85 to 3.00 mmol/L (normal range 2.20 to 2.60 mmol/L)

History of an episode of life-threatening hypercalcemia

Reduced creatinine clearance: reduced by 30% compared with age-matched normal persons

Confirmed 24-hour urine calcium excretion > 10 mmol (normal range 2.5 to 7.5 mmol/24 hr)

Substantially reduced bone mass: more than two standard deviations below age-, gender-, and race-matched controls

In addition:

Patient requests surgery

Consistent follow-up is unlikely

Coexistent illness complicates management

Patient is below the age of 50 years

The standard operation for pHPT is a systematic bilateral neck exploration in which all four parathyroid glands are sought and when identified, the macroscopically enlarged glands are removed. It is understandable that there is some reservation towards this surgical option. After all, there is a discrepancy between the extent of the operation and incision versus the median size of the causative parathyroid adenoma weighing in general no more then 200-300 mg. Although surgical exploration is attended with a low morbidity, when complications do occur they are serious. There is a small risk of permanent hypoparathyroidism (ranges between virtually zero and four percent) and damage to the recurrent laryngeal nerve leading to hoarseness and a reduced voice volume in less than one percent of the cases [2]. Also persistent hypercalcemia postoperatively, signaling a failure of the operation, has to be considered as a complication [5].

It has to be realized that pHPT is a solitary gland disease in at least 85-90% of the patients, meaning that in the majority of patients only one enlarged gland is causing the disease and consequently that removal of that one enlarged gland cures the patient. Why then is an extensive bilateral neck exploration still the gold standard when surgery is indicated ? The reason lies in the fact that preoperative localisatory techniques have up till now not yielded satisfactory results in attempts to replace the systematic bilateral neck exploration with a less extensive operation, although unilateral operations have been advocated by some [6 7 8]. The overall sensitivity of techniques like ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), thallium-201/technetium-99m scintigraphy and technetium-99m sestamibi imaging ranges from 40 to 90%, with specificity reported from 65 to 95% (**Table 2**) [9]. Ultrasonography is undoubtedly operator-

Table 2 Sensitivities and specificities of parathyroid imaging in patients without previous neck surgery.

	sensitivity %	specificity %	references
Ultrasonography	34-92	75-96	9 11 12 17 18
Computed Tomography	41-86	62-94	9 11 12 18
Magnetic Resonance Imaging	57-90	75-91	9 12 17 18
Thallium 201/technetium-99m scintigraphy	25-74	68-93	9 11 12 17 18
Technetium-99m sestamibi iodine 123 imaging	60-88	97-100	19 20 21 22

dependent whereas, not surprisingly, the sensitivity of all procedures declines when the weight of the enlarged gland drops below 500 mg [9 10 11 12]. These techniques are also less accurate after previous neck surgery. Combining tests has yielded somewhat better results: up to 87% using scintigraphy in combination with US [8]. The combination of three or more techniques has not increased the success rate [10].

In general the results of preoperative imaging have not been good enough for a substantial change in surgical policy. According to most authorities a bilateral neck exploration is still the procedure of first choice when surgical treatment is indicated [4 13 14]. In this respect one of the most cited remarks is that of the prominent American radiologist Doppman 'The only localizing modality required in the patient who has not had any previous neck surgery is to localize an experienced parathyroid surgeon'.

So, seven years after the NIH consensus meeting, nothing much seems to have changed. The indication to operate in patients with pHPT is, in the group fulfilling the NIH criteria and/or suffering from major symptoms such as nefrolithiasis and severe bone-pain, no matter of debate. For the majority of patients, that is the group which is asymptomatic or only mildly symptomatic, most physicians understandably still prefer a conservative attitude.

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However during these years changes have occurred as well in surgery as in radiology and these changes might be relevant for patients with pHPT. The most prominent change in surgery more recently has been the development and implementation of minimally invasive techniques best exemplified by procedures such as laparoscopic cholecystectomy and laparoscopic inguinal hernia repair. This in turn has led more and more patients to request the least invasive technique possible, also in other areas of surgery. Progress in technology has greatly affected radiological imaging. This improvement contributes considerably to the imaging quality of the radiological techniques as US and CT, creating new possibilities for more reliable localisatory procedures in pHPT.

Looking for a less invasive procedure in parathyroid surgery, encouraged by the improvement of the radiological techniques and aware of the very high incidence of solitary adenoma in pHPT, the subjoined hypothesis was born. If it would be possible to localize the parathyroid adenoma preoperatively with high accuracy, an adenomectomy by a local procedure instead of the conventional neck exploration would be a potential option, resulting in less morbidity, reduction of operation and admission time, and leaving a surgical scar of about 1.5 cm instead of at least 10 cm length.
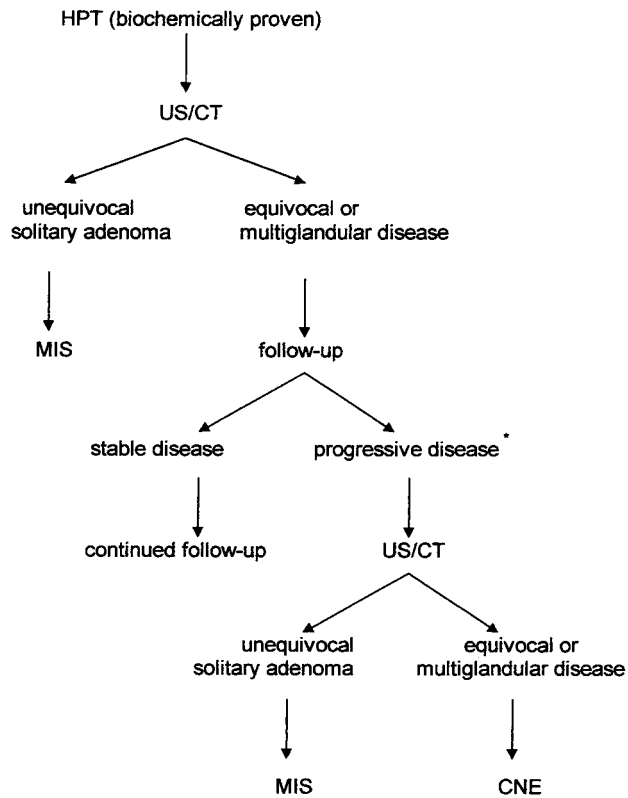
Using Doppler assisted US and spiral CT for preoperative parathyroid imaging the feasibility of a minimally invasive approach was tested by us originally in 15 symptomatic patients [15]. From the successful results it could be calculated that minimally invasive surgery would probably suffice in at least 70% of patients with pHPT,

so that conventional neck exploration can be avoided. These good initial results were further corroborated in a subsequent large prospective evaluation study including all consecutive patients who presented with an indication for operative treatment [16]. This series again proved the correctness of the original hypothesis. A total of 66 patients (54 female, 12 male) with a median age of 60 years and a median serum calcium of 2.90 mmol/L (2.55-3.60) were studied. Fifty-one of these patients underwent a minimally invasive approach which was successful in 49. In two patients conversion to a conventional neck exploration -in the same operative session- was necessary. A conventional neck exploration was primarily carried out in the other 15 patients because of equivocal results of preoperative imaging. The median operation time in the minimally invasive group was 15 minutes (10-35), that in the group which underwent the conventional neck exploration was 75 minutes (60-120). All 66 patients became normocalcemic postoperatively. Except for one patient who suffered a transient unilateral vocal cord paralysis no complications were registered. Overall the combination of preoperative Doppler US and spiral CT-scanning made a successful minimally invasive approach of pHPT possible in 74% (49/66) of patients.

The data presented above leave us in no doubt that minimally invasive surgery definitively has entered the treatment of pHPT. This certainly applies to the patients with symptomatic disease, but it could well have consequences also for the large group of patients with asymptomatic or only mildly symptomatic pHPT. Suppose a patient with asymptomatic or only mildly symptomatic pHPT undergoes parathyroid imaging, preferably by US and CT (based on our personal favourable experience), and imaging shows a definite adenoma suited for the minimally invasive approach then this patient could be definitively cured by a small operation and with a low chance of recurrence of disease this obviates the need for frequent out-patient follow-up, and for repeated blood testing and prevents any anxiety that symptoms will occur or will worsen.

In other words, experience with the minimally invasive approach of pHPT in symptomatic patients has given us new arguments for the surgical option in asymptomatic or mildly symptomatic pHPT patients. We therefore tentatively propose a new strategy. If a patient presents with a biochemically proven asymptomatic or mildly symptomatic pHPT decision-making according to the following algorithm is advised (**Table 3**). Localization of the enlarged gland should be attempted by means of doppler US and spiral CT. The examinations should be performed systematically under guidance of a dedicated radiologist and the results discussed with the surgeon in charge. When the test results unequivocally indicate a solitary adenoma the patient is advised to undergo a minimally invasive procedure. When the test results are equivocal or indicate the possibility of multiglandular disease a conservative policy is advocated. When the disease should progress in time or the patient develops major symptoms and/or fulfils the NIH-guidelines, parathyroid

Table 3 Algorithm in asymptomatic/mildly symptomatic pHPT.

HPT (biochemically proven)

↓

US/CT

unequivocal solitary adenoma   equivocal or multiglandular disease

↓   ↓

MIS   follow-up

stable disease   progressive disease *

↓   ↓

continued follow-up   US/CT

unequivocal solitary adenoma   equivocal or multiglandular disease

↓   ↓

MIS   CNE

pHPT	primary hyperparathyroidism
US	doppler assisted ultrasonography
CT	spiral computed tomography
MIS	minimally invasive surgery
CNE	conventional neck exploration

*progressive disease is defined as the development of signs according the NIH-criteria which were previously absent and/or the development of major symptoms.

imaging procedures should be repeated preceding the then indicated operative treatment.

Implementation of such a strategy could be of considerable benefit to a substantial number of patients with asymptomatic or only mildly symptomatic primary hyperparathyroidism.

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