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Running title : Intrathoracic goiters and chest X-rays

Key words: chest X-rays; thyroid surgery; intrathoracic goiters; cervico-mediastinal goiters; mediatinal nodules.

Abstract

Background

Intrathoracic goiters (IG), classified in cervico-mediastinal goiters (CMG) and independent mediastinal nodules (MN), must be detected before thyroid surgery in order to anticipate potential sternotomy and to avoid reoperations for "missed" MN.

Precise characterization if IG is no longer done by Chest XRay (CXr), but it is nowadays done by computerized tomography (CT) or magnetic resonance imaging (MRI). But, in order to screen a population for unsuspected IG, CT and/or MRI cannot be used because of their cost.

We hypothesized that CXr remained useful to detect some IG during the preoperative check up in patients referred for thyroid surgery.

Methods

This prospective study was conducted on 2,554 patients undergoing thyroidectomy during a 7 years period. CXr usefulness was evaluated in relation with patients complaints, clinical examination, neck ultrasonography (neck US) anatomical and surgical findings.

Results

CMG (n = 67) and MN (n = 42) were symptomatic in 10 and 5 patients, respectively. Clinical examination or neck US suspected their existence in 25 and 13, and 45 and 17 patients, respectively. Among the 50 IG detected by CXr (42 CMG and 8 MN), 5 CMG and 2 MN had not been diagnosed by clinical examination or neck US. CXr failed to detect IG in 59 patients (54% of false negatives): 25 CMG (37 %) and 34 MN (80%). A total of 28 IG (9 CMG and 19 NM) were discovered only during surgery. False positive images were observed by CXr in 88 out of 2445 patients without IG (3.5% false positives). CXr potentially saved 2 patients from reoperation (= a maximum saving of 6160 €) and the total cost of CXr being 54,895 €.

Conclusions

CXr should not be used routinely for the preoperative of IG: the screening showed mediocre performance and it was not cost effective. Surgeons may preferably screen for IG by clinical examination or neck US and perform directly CT scan when a mediastinal extension is suspected.

Introduction

The presence of thyroid tissue in the mediastinum occurs in 2 to 19% of patients who undergo thyroidectomy (1). These intrathoracic goiters (IG), also called retrosternal, substernal, cervico-mediastinal or mediastinal goiter, can be connected to the thyroid, like in cervicomediastinal goiters (CMG) or disconnected from the thyroid body, resulting in independent thyroid mediastinal nodules (MN).

There are two caveats in the surgery of IG: (a) surgical difficulty during the cervical approach which may need sternotomy (b) risk of missing a MN and the need of reoperation (2). Therefore, it is mandatory to detect IG preoperatively. This can be challenging since these lesions are asymptomatic in 20 to 30% of cases (3, 4) and develop in an area not easily accessible to clinical examination or neck ultrasonography (US).

In the past, chest X-ray (CXr) was the reference for the preoperative diagnosis of IG. Nowadays, computerized tomography (CT) scan and magnetic resonance imaging (MRI), are the accurate tools for the characterization of IG (8, 9). But CT and MRI are not used to screen for IG, because of their cost (10).

We hypothetized that CXr could remain a good screening test to detect IG unsuspected by clinical examination and neckUS and to select patients who should benefit from further assessment (by CT or MRI) for an appropriate surgical strategy. We could not find any prospective study that confirmed (or infirmed) that hypothesis.

In this report we describe the results of a prospective study (in 2,570 patients referred for thyroidectomy during a 7-year period) aimed at evaluating the usefulness of a systematic screening by CXr (as a complement of clinical examination and neck US) for the detection of IG before thyroidectomy.

Materials and Methods

This prospective study included 2,570 patients referred to the Endocrine Surgery Department of Paul Desbief Hospital, Marseilles, France during a 7-year period (2005-2011) for surgery of thyroid goiters. For the entire group of patients, the age ranged between 13 and 86 years with a mean (± SD) of 50.4 ± 14.0 years. The female/male ratio was 4:1 (2,074/496).

Population characteristics (demographics and pathology) are described in table 1.

Preoperative investigations included anamnesis, clinical examination looking for mediastinal extension and/or compression with specific attention to patients' complaints (dyspnea, dysphagia, hoarsness), physical signs (lower pole of the gland not palpable, tracheal deviation, signs of venous thoracic compression), neck US (access or not to the lower pole of the gland) and CXr (posterior-anterior CXr performed with both arms over the head). The CXR abnormalities revealing mediastinal thyroid extension were classified as anterior, lateral and latero-tracheal deviation and mediastinal opacities.

When mediastinal extension was found (lower thyroid lobe margins extending below the sternal manubrium), they were described in the anatomical charts: IG were separated into CMG (with parenchymal continuum between the cervical and mediastinal thyroid gland) and MN (lined by its own capsule and disconnected or attached with only a thin fibrous tissue to the cervical thyroid gland). The size of the thoracic portion of the IG, and the distance between MN and the thyroid where noticed. Clinical, imaging and surgical characteristics were compared between CMG and MN. At the end of the operations, visual examination and palpation of the superior mediastinum were routinely performed, searching for occult MN. The majority of thyroidectomies were performed by the same surgeon (AD).

Statistical analysis was performed with the Graph Pad Prism 5 software (La Jolla, CA). The χ^2 test was used for categorical variables and the Mann-Whitney U test was used for continuous variables. A *P* value less than 0.05 was considered significant.

Results

2,554 patients were included in the study since CXr was not interpretable in 16 of them.

Anthropometric results

Patients with CMG were significantly (P = 0.0126) older than those with NM (61.3 ± 12.5 *vs.* 54.3 ± 16.4 years, respectively). There was no significant difference in the female/male ratio between the two groups (2.52 and 5.14, P = 0.1457, for patients with CMG or NM, respectively)

Anatomical characteristics of CMG and MN (table 2)

IG were found in 109/2,554 patients (4.3 %). As indicated, CMG (n=67) showed a parenchymal continuum between the cervical and mediastinal portion of the thyroid gland. MN (n=42) were independent (n = 35) or connected to the cervical thyroid by a thin fibrous tissue (n = 7). The distance between MN and main thyroid varied from 0 cm (contiguous MN) to 3 cm (complete intrathoracic nodule, n = 7). No difference was observed in the size of the thoracic portion of CMG and MN. Partial sternotomy (manubriotomy) was necessary in 2 cases of NM. No total sternotomy was performed.

Preoperative findings

As shown in table 3, CMG and MN were symptomatic in 10/67 (14.9 %) and 5/42 (11.9 %) patients, respectively. Physical examination suspected their presence in 25/67 (37.3 %) and 13/42 (30.9 %) patients, and neck US suspected them in 45/67 (67.2 %) and 17/42 (40.5%) patients, respectively. Overall, clinical examination combined to neck US allowed suspicion of 54/67 CMG (80.6 %) and 21/42 MN (50.0 %).

Performance of CXr

2,554/2,570 CXr were interpretable. CXr detected the mediastinal thyroid extensions in 50/109 patients (45.9 % of **true positives**): 42/67 CMG (62.7 %) and 8/42 MN (19.0 %). CXr

was the only tool that allowed the detection of IG in 6/109 (6.4 %) patients: 4 CMG and 2 MN, which have not been detected by clinical examination and neck US. The 4 CMG had a mediastinal portion of 7, 6, 2 and 2 cm, respectively. One MN detected only by CXr measured 6 cm; it was located 1 cm from the inferior pole of the thyroid and was connected to the thyroid by a fibrous bridge. The other MN measured 3 cm and was disconnected, separated from the thyroid by a 3 cm distance. No manubriotomy was necessary in these 6 patients.

CXr failed to detect IG in 59/109 patients (54.1 % of **false negatives**) separated into 25/67 (37.3 %) CMG and 34/42 (80.9 %) MN. A total of 28 IG (9 CMG and 19 NM) were undetectable by clinical examination, neck US or CXr and discovered only during surgery. Among the 9 CMG, the mediastinal extension measured less than 3 cm in 8 cases and 4 cm in one case. None of them was difficult to remove surgically. Three out of the 19 NM discovered during the operation have been difficult to visualize. In this study, 2 patients were reoperated for MN since it had not been detected during the first operation. Clinical examination and neck US were positive in 31 (16 CMG and 15 MN) of the 59 patients (52.5 %) negative for CXr.

False positive images were observed by CXr in 88 out of 2445 patients without IG (3.5% false positives). The false positive for CMG (n=88) were separated into curved tracheal deviations (n = 50), straight deviations of the whole trachea (n = 24) and “bayonet-like” deviations (n = 4). The false positives for MN include mediastinal opacities (n = 10). All 88 patients had strict cervical goiter; in 11 cases, the inferior limit of the goiter reached the superior limit of the thoracic inlet without crossing it.

In the present study, the specificity of CXr was good (96.8 and 95.3 % for for CMG and MN, respectively) but its sensitivity was low (62.7 and 19.0 % for CMG and MN, respectively).

Since in 2 patients, CXr revealed a MN that could have remained undetected, we assumed that CXr saved a maximum of 2 patients from second surgery, which means a maximum saving of 6160 € (3080 € being the cost of an operation for mediastinal lesions resection, as it is evaluated by French Social Security). The total cost of CXr in this study was 54,895 €.

In this series, the irradiation cumulated dose was very low (55 mSv for 2570 CXR).

Discussion

Among 2570 patients referred for thyroid surgery, our series include 109 IG separated into 67 CMG and 42 MN, based on their anatomical characteristics, in the continuum of the cervical thyroid for CMG and independent or attached only by a thin fibrous tissue to the cervical thyroid for MN. Among these 109 IG, 75 (54 CMG and 21 MN) have been suspected after clinical examination and neck US; 6 further cases (4 CMG and 2 MN) have been detected after CXr. In 29 cases, clinical examination and imaging failed to detect IG which was discovered during the first surgery in 27 patients (9 CMG and 19 MN). 2 MN were missed during first surgery and removed after reoperation. Although the diagnosis performance of CXr was low (56% of false negatvie), this procedure was useful in 6 cases (6% of the IG but 0,02% of the thyroidectomies).

In France and in many other countries, routine preoperative CXr, is not recommended any more for all non-cardiac non-thoracic surgeries (11). It is even not systematically reimbursed by the French health insurance since 2012, except if the indication for CXr (like "search for Ig", for instance) is clearly noticed (11). However, CXr is still described as a diagnostic tool in reference textbooks (4) and in recent studies on the management of large descending goiters (12-15). The usefulness of CXr in thyroid surgery, as in many other types of surgery, has been questioned in several studies. In two studies, tracheal deviation detected

by CXr was not correlated to any difficulty of intubation (16, 17). In our series, although its performance in the screening for IG was mediocre, CXr added some useful information to the preoperative investigations, especially in the CMG. Indeed, CXr allowed the diagnosis of 4 cases of CMG and 2 cases of MN unsuspected by clinical examination and US (Both MN would have probably been missed in the absence of CXR).

In this study, CXr was not useful to predict the need for sternotomy or thoracotomy. Classically, predictive factors for sternotomy are the extension below the carina or the aortic arch posterior mediastinum extension and the presence of mediastinal nodule or conical shape of the goiter in which the thoracic inlet becomes a ring of constriction (17-20). Our series include 2 manubriotomies: one for a "snowman-shaped" MN with two contiguous parts separated by a tight, quasi-non-existent collar, the largest part being intrathoracic and one for a CMG descending no more than 1 cm below the thoracic inlet but with strong adherence to the trachea.

Concerning false negative of preoperative studies, all of the 9 CMG that were found during operation were small and they were not difficult to extract. However, it was not the case with the 27 MN. Three MN were discovered by the surgeon during systematic inspection and palpation of the superior mediastinum following thyroidectomy. In this series, 2 MN were missed and needed reoperation. These 2 cases were revealed by ^{131}I fixation during ira-therapy for thyroid cancer. One cannot exclude that more MN have been missed.

False positive CXr signs of tracheal deviations may be artefactual and the consequence of slight deviations of X-rays during imaging. Some mediastinal opacities, especially those situated in the upper part of the mediastinum, may also be explained by the different positions of the patients when CXr and surgery were performed.

In our series, we have also attempted to classify IG on the basis of anatomical characteristics. The IG are usually separated into primary or secondary, depending on their

site of origin (21, 22). Primary IG are rare, less than 1% of all IG; they arise from "ectopic" mediastinal thyroid without connection with the cervical thyroid and they receive their blood supply exclusively from mediastinal vessels. Secondary IG which account for most cases develop through the downward growth of the cervical thyroid. Based on the literature and our experience, we have separated IG into two subgroups: CMG with a continuum between the cervical and mediastinal portions and MN separated or connected only by a thin fibrous tissue to the cervical thyroid. MN may develop through the extension of a nodule arising in the lower pole of a thyroid lobe. The nodule follows a path of least resistance into the mediastinum and its attachment to the cervical thyroid is broken or reduced to a thin fibrous tissue. Alternatively, they may correspond to the rare primary IG with their blood supply originating exclusively from mediastinal vessels. Our results do not allow the distinction between both origins for MN. The MN have been described under different names: aberrant thyroid adenoma found in 32/88 IG (7), ectopic nodules in 4/108 IG (23), grades III and IV thyrothymic rests (24) or the complete intrathoracic goiter as opposed to the partial intrathoracic goiter (25). For these authors, the percentage of complete IG is higher before than after 65 year-old (17/58 vs 12/94). As reported by Cohen and Cho (26), the MN did not receive sufficient recognition although they may be the source of unsuccesful thyroidectomy reported by several authors under the name of forgotten thyroid (27-31).

In our series, preoperative CXr helped to alert the surgeon from potential surgical difficulty in 4 cases (and in one of the cases, CXr itself allowed the detection of the thyroid problem). In 2 other patients, CXr revealed a MN that could have remained undetected. Therefore, CXr saved 2 patients from second surgery, which means a maximum saving of 6160 €. The total cost of CXr in the study being 54,895 €, CXr screening was clearly not cost effective, although the over cost represents less than 1% of the minimal cost of thyroidectomy (21€ vs. 2356 €).

Furthermore, if a CT scan (which costs 266 €) or an MRI (406 €) were performed in every one of the false positive patients, this would have led to an additional unnecessary cost of 88 x 266 € or 88 x 406 € respectively (=23408 or 35728 € respectively).

In conclusion, systematic screening by CXr in order to detect IG had mediocre performance (50% true positive) and, although 6% of IG were suspected by CXR only, and although CXr potentially avoided reoperation in 2 patients, it was not cost effective. CXr may therefore reasonably be abandoned in routine use for the preoperative screening for IG before thyroid surgery. Surgeons may preferably rely on clinical examination or neck US and perform directly CT scan when a mediastinal extension is suspected. However, they may be aware that unsuspected IG may be found during surgery in 34/2570 (1%) patients.

Author Disclosure statement

The authors of this manuscript have no commercial or competing financial interest to disclose.

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Tables

Table 1- Description of the population (n=2750)

Sex ratio	2074 female / 496 male (4:1)
Age (yr)	50.4 (13-86)
Benign disease	2029
Multinodular disease Solitary thyroid nodule Solitary toxic nodule Toxic multinodular disease Grave's disease Thyroiditis Amiodarone induced hyperthyroidism C cell Hyperplasia	1138 484 35 112 218 28 1 13
Malignant disease	524
Papillary Follicular Variant Papillary Follicular Hurtle cell Medullary Poorly differentiated/ Anaplastic Lymphoma Metastases Parathyroid cancer	363 99 22 19 12 3 1 Hodgkin/ 1 thyroid lymphoma 2 kidney/ 1 breast 1
Tumor of undetermined prognosis	17

Table 2 Anatomopathological characteristics of cervico-mediastinal goiters (CMG) and mediastinal nodules (MN).

	n (%)*		
Anatomopathological parameters	CMG (n = 67)	MN (n = 42)	*P* value†
Location			
anterior	11 (16.4)	21 (50)	0.0002
antero-lateral	17 (25.4)	4 (9.5)	0.0412
lateral	39 (58.2)	17 (40.5)	0.0056
Intrathoracic size (cm, mean ± SD)	2.76 ± 2.18	1.79 ± 1.23	0.0251 ‡
Distance from cervical thyroid (cm, mean ± SD)		1.28 ± 1.41	
Differentiated cancer	6 (8.9)	1 (2.4)	0.173

*All data are presented as numbers (%) except when indicated otherwise

† *P* values for differences between CMG and MN were calculated using the χ^2 test except when indicated otherwise

‡ *P* value for differences between CMG and MN was calculated using the Mann-Whitney U test.

Table 3: Efficiency of different diagnostic procedures in the evaluation of cervico-mediastinal goiters (CMG) and mediastinal nodules (MN)

	n (%)*		
Diagnostic procedures	CMG n = 67	MN n = 42	*P* value†
Patients complaints	10 ‡ (14.9)	5 ‡‡ (11.9)	0.6559
Physical examination	25 (37.3)	13 (30.9)	0.4976
Neck US	45 (67.2)	17 (40.5)	0.0062
Physical examination + Neck US	54 (80.6)	21 (50.0)	0.0008
CXr	42 (62.7)	8 (19.0)	< 0.0001
Physical examination + Neck US + CXr	58 (86.6)	23 (54.8)	0.0002
Intraoperative finding	9 (13.4)	19 (45.2)	< 0.0001
Postoperative finding	0	2 (4.8)	0.0714

Neck US: Neck ultrasonography, CXr: chest X-ray.

*All data are presented as numbers (%)

† *P* value for differences between CMG and MN was calculated using χ^2 test.

‡: dyspnea, n = 7; dysphagia, n = 3; venous compression, n = 2; syncope, n = 1.

‡‡: dyspnea , n = 4; dysphagia, n = 1; dysphonia, n = 1.