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EDITORIAL COMMENTARY

Cost-effectiveness of ^{99m}Tc-MIBI in the evaluation of thyroid nodules for malignancy: a new lease of life for an old radiopharmaceutical?

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In nuclear medicine practice, physicians are often confronted with the problem that formal registration of a specific radiopharmaceutical and the indications for its use are lacking (e.g. the modern ^{68}Ga-labelled somatostatin analogues). If formal registration is available, this registration often only covers a few, specific and predominantly commercially interesting indications even when the radiopharmaceutical can be applied more broadly. A good example of the latter is the case of ^{99m}Tc-methoxyisobutylisonitrile (MIBI).

MIBI was first described in the 1980s [1, 2]. Originally developed for myocardial perfusion scintigraphy for the detection and localization of coronary artery disease, it went on to eventually achieve registration not only for this indication, but also for the assessment of global ventricular function, scintimammography for the detection of suspected breast cancer when mammography is equivocal, inadequate or indeterminate, and localization of hyperfunctioning parathyroid tissue in patients with recurrent or persistent hyperparathyroidism, both primary and secondary, and in patients with primary hyperparathyroidism scheduled to undergo initial surgery of the parathyroid glands [3].

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However, for many years it has been known that MIBI scintigraphy can also be used in the diagnostic work-up of scintigraphically cold and therefore suspicious thyroid nodules in combination with fine needle biopsy (FNB) [4–12]. As Wale et al. show in this edition of the *European Journal of Nuclear Medicine and Molecular Imaging* [13] and Treglia et al. showed recently in a comparable meta-analysis [14], in conjunction with prior ^{99m}Tc-pertechnetate thyroid scintigraphy MIBI scintigraphy can achieve a very high negative predictive value ranging from 88 % to 100 % with a mean of 97 %. Furthermore, the sensitivity of MIBI scintigraphy is similarly good with an aggregate value of 96 %. This indicates that a negative MIBI scan will obviate the need to surgically remove the thyroid nodule for definitive histological clarification in the large majority of patients, as the risk of malignancy in such a nodule is very low.

This of course does have economic implications. Considering that the risk of missing the diagnosis of thyroid cancer is low, and a large number of, in hindsight unnecessary, comparatively expensive surgical procedures can be avoided, it is not surprising that Wale et al. are able to show that the addition of MIBI scintigraphy leads to a considerable saving in costs per patient and per cancer diagnosed while not significantly affecting life expectancy [13].

Of course, the model used by Wale et al. is a theoretical one and any model requires simplification of the sometimes complex individual situations of different patients. For example, the authors did not directly assess the life expectancy of patients scanned with MIBI, but derived these data from unrelated survival analyses of patients with thyroid cancer. This and further notable limitations of the model are mainly due to the lack of data from prospective randomized controlled trials.

Ultimately, only such trials allow a reliable evaluation of the diagnostic and prognostic capabilities as well as the patient-related benefits and costs of MIBI scintigraphy. However, it is well known that due to the slow growth of thyroid cancer, such prospective studies with disease-specific survival as a primary endpoint are nearly impossible to realize and, if realized nonetheless [15], will take a great number of years to reach a conclusion. Therefore, there is currently no alternative but to act upon the best available evidence. A considerable merit of the paper by Wale et al. [13] is the demonstration that, concerning the cost-effectiveness of MIBI thyroid scintigraphy, there is a remarkable amount of evidence in the cited literature that is amended by their own data. Models such as the one presented by the authors are important tools to summarize the available data and, based on this, to draw conclusions on the medical effectiveness and cost-effectiveness of the procedure in question. This has already been performed for several other nuclear medicine procedures [16–18]. Wale et al. deliver additional information that goes well beyond the known literature. They transform empirical data into probabilities which permit more general concluding statements than would be possible based on the individual studies themselves. Moreover, the robustness of the model can be tested by performing sensitivity analyses that permit insecurity in the model assumptions to be taken into account.

Thus the model proposed by Wale et al. makes a strong case in favour of the use of MIBI thyroid scintigraphy, as the alternative, withholding of MIBI, would likely lead to an increase in costs and decrease in patient-related benefits. This is of particular interest for health-care policy makers since most health-care systems worldwide share the problem of decision-making constrained by limited financial resources. Financial savings and patient-related benefits should be a strong argument for the reimbursement of this method.

Certainly the use of MIBI in the further clarification of suspicious thyroid nodules is not new, as the oldest publication on this topic dates back 20 years [4]. Considering the wide range of countries from which publications on the subject originate, widespread acceptance can be assumed. Unfortunately, delving more deeply into the studies summarized by Wale et al., shows that several practical problems still hinder the true adoption of thyroid nodule MIBI scintigraphy.

As summarized by Wale et al. in their Table 2 [13], there is no standardization of acquisition times: different studies have acquired a different number of images at different timepoints after tracer injection using widely divergent acquisition duration times and injected activities. Also, there is no consensus on interpretation: some physicians will only give a positive reading for a nodule that takes up more MIBI than the surrounding thyroid tissue, whereas others will give a positive reading for a nodule that is cold on ^{99m}Tc-pertechnetate scintigraphy but shows uptake that is not different from the surrounding tissue on MIBI scintigraphy.

Most importantly, however, MIBI is not registered for use in scintigraphic evaluation of thyroid nodules. This will hinder the large-scale use of this procedure in that in many countries, health insurance companies largely limit reimbursement to proven, registered pharmaceuticals. Furthermore, the use of MIBI for thyroid scintigraphy invokes the additional responsibilities given to physicians for off-label use. Even though the risks and side effects of MIBI scintigraphy are largely negligible, it does pose an extra burden on the physician in terms of informing patients and obtaining informed consent (although the administrative formalities will strongly differ between countries). It is indeed somewhat disappointing that MIBI still has not been registered for the clarification of suspicious thyroid nodules, considering that in recent years MIBI has not been used, for example, for the registered indication of scintigraphic breast evaluation nearly as often as for thyroid scintigraphy. On the other hand, considering the cost involved in registering an old pharmaceutical which no longer carries patent protection for a new indication, we should perhaps not be all that surprised.

The work by Wale et al. further shows signs of an interesting trend which can also be observed in other countries: the evaluation of thyroid nodules by scintigraphy alone. Nearly a fifth of patients included in the authors' cohort did not undergo FNB evaluation, and management instead apparently relied on (negative) MIBI scintigraphy alone. Furthermore, the authors describe performing MIBI scintigraphy on the same day as ^{99m}Tc-pertechnetate scintigraphy without waiting for the results of FNB. This trend towards management of patients with a thyroid nodule by MIBI scintigraphy alone can also be observed in clinical practice elsewhere. A likely explanation for this trend is that, in spite of all the divergence in procedures and interpretations, MIBI thyroid scintigraphy is nowhere near as operator-dependent as FNB, in which both the skill and experience of the physician performing the biopsy and the skill, experience and especially professional motivation of the pathologist assessing the specimen play a major role in the standard of the results achieved. Considering that many physicians are not particularly skilled in thyroid FNB, and a lot of pathologists are neither extensively experienced nor particularly motivated for interpretation of thyroid FNB cytology, it may be no surprise that, in spite of all its drawbacks, a considerable number of hospitals and physicians are reverting to relying on the less operator-dependent assessment modality, even if, strictly speaking, this goes against many guidelines which explicitly state that the primary assessment modality of a suspicious thyroid nodule is FNB. Moreover, FNB generally causes a much higher level of distress for the patients who often feel very uncomfortable during the procedure, whereas MIBI scintigraphy is usually well tolerated.

Considering this trend, perhaps it may be worthwhile evaluating a reversed strategy for evaluation of thyroid nodules. The strength of MIBI scintigraphy lies in the combination of a high negative predictive value and a high sensitivity. In contrast the strength of FNB lies in a combination of a high positive predictive value and a high sensitivity. Therefore these two modalities should be considered complementary. However, the data presented by Wale et al. show that in fact FNB is associated with twice the cost of MIBI scintigraphy. It would therefore likely be even more cost effective to select patients for thyroid surgery by first performing MIBI scintigraphy, and then further evaluating the small fraction of patients who show a positive scan by FNB.

Of course, as described above there are still several issues that need to be resolved, most importantly the matter of registration. As all literature on this topic has thus far been retrospective, good prospective studies showing the diagnostic effectiveness of thyroid MIBI scintigraphy are needed to achieve such registration. As it is unlikely that such studies will be initiated by industrial parties considering that MIBI no longer has patent protection, the nuclear medicine community will need to take matters in its own hands. If successful, however, it could return nuclear medicine to the forefront of thyroid diagnostics, and give both nuclear medicine and an old radiopharmaceutical a new lease of (thyroidological) life.

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