Endocrine (2019) 64:203–208
https://doi.org/10.1007/s12020-019-01841-z

REVIEW

F18-choline/C11-choline PET/CT thyroid incidentalomas

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Received: 8 November 2018 / Accepted: 3 January 2019 / Published online: 12 January 2019

Abstract

Introduction Thyroid incidentaloma is defined as a thyroid lesion incidentally and newly detected by imaging techniques performed for an unrelated purpose and especially for a non-thyroid disease. Aim of this review is to evaluate the prevalence and clinical significance of focal incidental radiolabelled choline uptake in the thyroid gland (CTI) revealed by PET or PET/CT.

Methods A comprehensive computer literature search of the PubMed/MEDLINE, Scopus, and Embase databases was conducted to find relevant published articles about the prevalence and clinical significance of CTIs detected by PET or PET/CT in patients studied for other oncologic purposes.

Results Fifteen articles (14 case reports, one retrospective study on a larger population sample) were included in the systematic review. Considering the case reports, 7/14 CTIs were benign and 7/14 malignant. In the retrospective study on a larger population sample, 14/15 CTIs which underwent further investigations were benign.

Conclusion Despite very rare but probably underestimated, CTIs frequently signal in the presence of unexpected lesions in the thyroid that differ from the indicated reason for which the patient was initially scanned, and the risk of malignancy is not negligible.

Keywords Thyroid · Incidental · Thyroid incidentaloma · Choline · PET/CT · Positron emission tomography

Introduction

Fluorine-18 (F18) or Carbon-11 (C11) choline-based PET/CT is a whole-body imaging technique extensively studied for the detection of prostate cancer (PCa) lesions. Choline is the precursor for phosphatidylcholine, a major component of the cellular membrane; it is metabolized and internalized into cells by choline kinase, an enzyme that is over-expressed in certain tumors such as PCa, and its accumulation is observed because of the increased incorporation into the proliferating tumor cell membranes [1]. As tumor cells present an elevated metabolic rate, choline uptake increases in tumor tissue to keep up with the demands of the synthesis of phospholipids in cellular membranes; choline analogues radiolabelled with F18 and C11 (biochemically indistinguishable from natural choline) have been used with similar results showing superiority over Fluorine-18 fluorodeoxyglucose (F18-FDG) in PCa patients; F18-choline has a much longer half-life than C11-choline ($T_{1/2} = 109.8$ vs 20.4 min, respectively), making its use possible in PET centers without an on-site cyclotron; moreover it is slightly more excreted in the urine than C11-choline, making the assessment of the prostatic bed a little bit more difficult [2–4]. Physiologic choline activity is seen in the salivary and lacrimal glands, liver, pancreas, and kidneys. Bowel and bone marrow activity is variable and can be heterogeneous. Low-level uptake is frequently observed in small-volume reactive inguinal, mediastinal, or axillary nodes. Currently, no standardized patient preparation is necessary for radiolabelled choline PET/CT; generally, patients are advised to fast for 4–6 h before scanning to reduce physiologic bowel activity. Imaging acquisition

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starts immediately after injection of C11-choline while after 45–60 min in case of F18-choline.

The diagnostic role of radiolabeled choline PET or PET/CT is well established in the evaluation of PCa, particularly when a biochemical relapse is present [5–8]. However, PET and PET/CT with radiolabeled choline have been largely tested also for a variety of malignancies other than prostate cancer [6, 9, 10]. In particular, radiolabelled choline PET or PET/CT has been used in evaluating many different malignant cancers in different organs such as the liver (hepatocellular carcinoma), breast, brain (in particular gliomas), lung, head and neck, esophagus, urinary bladder, and muscoloskeletal system with encouraging results [10].

Thyroid incidentaloma is defined as a thyroid lesion incidentally and newly detected by imaging techniques performed for an unrelated purpose and especially for a non-thyroid disease. Aim of this review is to evaluate the prevalence and clinical significance of focal incidental choline uptake in the thyroid gland (CTI) revealed by PET or PET/CT.

Methods

Search strategy

A comprehensive computer literature search of the PubMed/MEDLINE, Scopus, and Embase databases was conducted to find relevant published articles about the prevalence and clinical significance of CTIs detected by PET or PET/CT in patients studied for other oncologic purposes. We used a search algorithm that was based on a combination of the terms: (a) "PET" OR "positron emission tomography" AND,(b) "choline", AND (c) "thyroid". No beginning date limit was used; the search was updated until 31 October 2018. Only articles in English language were selected. To expand our search, references of the retrieved articles were also screened for additional studies. All literature studies collected were managed using EndNote web 3.3.

Study selection

All articles reporting CTIs detected by C11- or F18-choline PET or PET/CT were eligible for inclusion. Two researchers (FB and GT) independently reviewed the titles and abstracts of the retrieved articles. Articles were rejected if they were not reporting CTIs. The same two researchers then independently reviewed the full-text version of the remaining articles to determine their eligibility for inclusion.

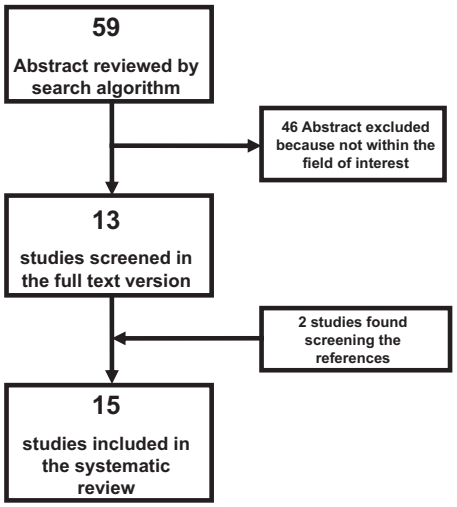

Fig. 1 Flow-chart of the search strategy

Data abstraction

For each included study, information was collected concerning basic study (author names, year of publication, country of origin, and type of study) and PET device used (PET or PET/CT), number of patients evaluated, number of patients who underwent further investigations, and malignancies detected. At last, the main findings of the articles included in this review are reported in the results.

Results

Literature search

The comprehensive computer literature search revealed 59 articles (Fig. 1). Reviewing titles and abstracts, 46 articles were excluded because reported data were not within the field of interest of this review. Twelve articles were selected and retrieved in full-text version [11–22]; one study was available only as abstract, but it was included because it was the only study about CTIs in a large population retrospectively analyzed and not a case report or case series [23]; two additional studies were found by screening the references of these articles and included in the review [24, 25]. Lastly 15 articles were included in the systematic review [11–25].

Qualitative analysis (systematic review) and results

Findings of several studies have shown that radiolabelled choline PET imaging may identify unexpected foci of hypermetabolism within thyroid, many of which have clinical relevance. The characteristics of the studies are presented in Tables 1 and 2. Considering the case reports, 7/

Table 1 Characteristics of studies analyzed

First author	Ref.	Year	N.Pts	Country/study type	Device	Isotope	Thyroid lobe
Hodolic M	11	2014	2	Slovenia/France/C	PET/CT	^{18}F	Left/NA
Paone G	12	2013	1	Switzerland/C	PET/CT	^{18}F	Right
Ciappuccini R	13	2018	1	France/C	PET/CT	^{18}F	Left
Aziz AL	14	2015	1	France/C	PET/CT	^{18}F	Left
Eccles A	15	2013	1	UK/C	PET/CT	^{18}F	Left
Treglia G	16	2014	1	Italy/C	PET/CT	^{18}F	Right
Lalire P	17	2016	1	France/C	PET/CT	^{18}F	Left
Ouattara A	18	2016	1	Belgium/C	PET/CT	^{11}C	Left
Haroon A	19	2015	1	UK/C[a]	PET/CT	^{18}F	Left
Welle CL	20	2016	1	USA/C	PET/CT	^{11}C	Right
Schillaci O	21	2010	1	Italy/C[a]	PET/CT	^{18}F	Right
Thanseer NTK	22	2017	1	India/C	PET/CT	^{18}F	Right
Ruiz-Esponda R	23	2014	30	USA/R	PET/CT	^{11}C	NA
García Vicente AM	24	2012	1	Spain/C	PET/CT	^{18}F	Right
Parvinian A	25	2018	3	USA/C	PET/CT	^{11}C	NA

N.Pts cases examined,; *R* retrospective, *C* case report or case series, *NA* not available

[a]a case reported in studies with other aims

14 CTIs who underwent further investigations were benign and 7/14 malignant; papillary thyroid carcinoma (PTC) was the most frequent malignant CTI. Only in the abstract of Ruiz-Esponda et al. [23] a wider population was analyzed; they retrospectively analyzed 1197 patients revealing CTIs in 30; 16/30 patients underwent cytological examination or ultrasound and clinical follow-up to determine benign or malignant nature of the CTIs; the other did not underwent any further diagnostic procedure because of the clinical status and one patient had a non diagnostic fine needle aspiration cytology; the results documented that 14/15 CTIs which underwent further investigations with a definitive diagnosis were benign.

Only Parvinian et al. [25] reported information on the prevalence of CTI: in their study the prevalence of CTI at C11-choline PET/CT in male patients evaluated for PCa only was 0.1% (3/2933). However, the authors did not provide further information on the nature of CTI [25].

Discussion

In patients with known cancer, work-ups often focus on the patient's primary disease, and incidental coexistence of another malignant or benign lesion can be missed. The prevalence of additional primary neoplasms is anything but negligible. F18-FDG PET or PET/CT thyroid incidental focal uptakes have been widely studied in literature [26–29] documenting that they are relatively frequent, most focal uptakes are benign but about one third of focal uptakes are malignant (PTC is the most frequent histology); moreover all the studies suggest that all thyroid incidentalomas need further investigation and clinical evaluation. On the other hand, CTIs are significantly less analyzed in literature, possibly because of the lesser use of radiolabelled choline PET/CT in comparison to F18-FDG PET/CT; moreover the main clinical application setting of radiolabelled choline PET/CT is PCa; this situation effectively excludes the wide use of radiolabelled choline PET/CT in female patients with higher incidence of thyroid diseases. Another point is that the clinical widespread use of radiolabelled choline PET/CT is more recent in comparison to F18-FDG reducing the population of patients globally analyzed. In fact the number of paper concerning CTIs is very low and all the published studies are case reports (or cases reported in articles with other aims) with the exception of the study of Ruiz-Esponda et al. [23], which is a retrospective analysis on a wide number of patients but presented as an abstract at the Endocrine Society's 96th Annual Meeting and EXPO in 2014. If we consider only case report papers the number of benign and malignant lesions among CTIs are similar; including the study of Ruiz-Esponda et al. the number of benign lesions exceeds the malignant ones. Interestingly, considering all malignant lesions, PTC is the most represented type; in fact 7/8 malignant lesions diagnosed among CTIs were PTC. This fact opens new insights about the metabolic behavior of the most frequent histological type of differentiated thyroid carcinoma (DTC); in particular, a lot of studies published in literature have documented that some DTC at the very beginning of the malignant thyroid disease (incidental and in a very early stage) show F18-FDG uptake and this point has suggested the necessity to overcome the so-called "flip-flop phenomenon" dogma; some DTC are F18-FDG avid since the very beginning of their natural history and, in this scenario, CTIs may suggest something more: the

Table 2 Benign or malignant nature of focal choline incidental uptake in the thyroid gland (CTIs)

First author	Ref.	NL	A (S)	PTC (S)	TL (S)	BCN (S)	FT (S)
Hodolic M	11	2	1 (3.3)	1 (NA)	–	–	–
Paone G	12	1	1[c] (NA)	–	–	–	–
Ciappuccini R	13	1	–	1[a] (4.1)	–	–	–
Aziz AL	14	1	1[c] (NA)	–	–	–	–
Eccles A	15	1	–	–	1 (NA)	–	–
Treglia G	16	1	–	–	–	1 (8)	–
Lalire P	17	1	–	1[b] (NA)	–	–	–
Ouattara A	18	1	–	1[a] (NA)	–	–	–
Haroon A	19	1	–	–	–	1 (NA)	–
Welle CL	20	1	–	1 (NA)	–	–	–
Schillaci O	21	1	–	–	–	–	1 (NA)
Thanseer NTK	22	1	–	1 (NA)	–	–	–
Ruiz-Esponda R	23	15/30[d]	–	1 (NA)[d]	–	14 (NA)[d]	–
García Vicente AM	24	1	–	–	–	1 (NA)	–
Parvinian A	25	3[e]	–	–	–	–	–

NL number of lesions citologically/histologically documented,; *S* SUVmax, *NA* not available, *A* adenoma, *PTC* papillary thyroid carcinoma, *TL* thyroid lymphoma, *BCN* benign citology (hyperplastic or not better specified), *FT* focal thyroiditis

[a]Follicolar variant

[b]Oxyphilic variant (in this patient was also diagnosed a medullary thyroid carcinoma)

[c]Oncocytic/Hurtle cell adenoma

[d]Sixteen patients with cytological or ultrasound and clinical follow-up to determine benign or malignant nature of the CTIs, the other did not underwent any further diagnostic procedure because of the clinical status, 1 patient had a non diagnostic fine needle aspiration cytology

[e]Not available information on the nature of CTI

hypothesis that not only some DTC and in particular PTC are F18-FDG avid since the very beginning of their natural history but also that they could be choline avid; this insight could be a pioneer for future clinical and diagnostic implications, uses and applications of the choline PET/CT. The study of Wu et al. [30], in which C11-choline PET/CT has been proposed in the detection of thyroid carcinoma and its metastases, performing better than F18-FDG in a preliminary series of four patients [30], moves in this direction. On the other hand, the significant number of benign findings after further investigations or follow-up makes the risk of pitfalls in the interpretation of CTIs not negligible; the axiom "CTI means malignancy" cannot exist and further investigations are always necessary.

Moreover, since 2012, incidental radiolabelled choline uptakes due to parathyroid adenomas have been reported in patients undergoing PET/CT for prostate cancer assessment; preliminary studies showed that radiolabelled choline PET/CT may localize hyper-functioning parathyroid glands both in primary and in secondary hyperparathyroidism. This should be another point to take into account in the interpretation of CTIs and the necessity of further investigations of these findings [31].

Unfortunately, considering the very low number of reports and patients analyzed, no high quality evidence could be drown about the real prevalence and clinical significance of CTIs; further studies and prospective protocols are desirable to clarify the real meaning of CTIs, their nature, clinical significance, and the possible role of radiolabelled choline PET/CT in the diagnostic flow-chart of DTC.

Conclusion

Despite being very rare but probably underestimated, CTIs frequently signal in the presence of unexpected lesions that differ from the indicated reason for which the patient was initially scanned, and the risk of malignancy is not negligible. This emphasizes the importance of further investigations of these incidental findings as well as for F18-FDG incidental uptakes, preferably to the point of tissue confirmation, to avoid missing a malignant lesion. Contrary to other imaging techniques which are usually limited to smaller body segments, radiolabelled choline PET/CT is a whole-body imaging technique, which provides important

informations above and beyond that for which the scan was ordered. Further studies are desirable to clarify the real meaning of CTIs, their nature, clinical significance, and the possible role of radiolabelled choline PET/CT in the diagnostic flow chart of DTC.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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References

1. R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2016. CA Cancer J. Clin. **66**, 7–30 (2016)
2. F. Podo, Tumour phospholipid metabolism. NMR Biomed. **12**, 413–439 (1999)
3. M. Picchio, C. Messa, C. Landoni, L. Gianolli, S. Sironi, M. Brioschi, M. Matarrese, D.V. Matei, F. De Cobelli, A. Del Maschio, F. Rocco, P. Rigatti, F. Fazio, Value of [11C]choline-positron emission tomography for re-staging prostate cancer: a comparison with [18F]fluorodeoxyglucose-positron emission tomography. J. Urol. **169**, 1337–1340 (2003)
4. T.R. DeGrado, R.E. Reiman, D.T. Price, S. Wang, R.E. Coleman, Pharmacokinetics and radiation dosimetry of 18F-fluorocholine. J. Nucl. Med. **43**, 92–96 (2002)
5. A. Chiti, M. Picchio, The rising PET: the increasing use of choline PET/CT in prostate cancer. Eur. J. Nucl. Med. Mol. Imaging **38**, 53–54 (2011)
6. K. Mertens, D. Slaets, B. Lambert, M. Acou, F. De Vos, I. Goethals, PET with (18)F-labelled choline-based tracers for tumour imaging: a review of the literature. Eur. J. Nucl. Med. Mol. Imaging **37**, 2188–2193 (2010)
7. M. Picchio, E. Giovannini, C. Messa, The role of PET/computed tomography scan in the management of prostate cancer. Curr. Opin. Urol. **21**, 230–236 (2011)
8. G. Bauman, T. Belhocine, M. Kovacs, A. Ward, M. Beheshti, I. Rachinsky, 18)F-fluorocholine for prostate cancer imaging: a systematic review of the literature. Prostate Cancer Prostatic Dis. **15**, 45–55 (2012)
9. C. Nanni, D. Rubello, S. Fanti, Could choline PET play a role in malignancies other than prostate cancer? Eur. J. Nucl. Med. Mol. Imaging **35**, 216–218 (2008)
10. G. Treglia, E. Giovannini, D. Di Franco, M.L. Calcagni, V. Rufini, M. Picchio, A. Giordano, The role of positron emission tomography using carbon-11 and fluorine-18 choline in tumors other than prostate cancer: a systematic review. Ann. Nucl. Med. **26**, 451–461 (2012)
11. M. Hodolic, V. Huchet, S. Balogova, L. Michaud, K. Kerrou, V. Nataf, M. Cimitan, J. Fettich, J.N. Talbot, Incidental uptake of (18)F-fluorocholine (FCH) in the head or in the neck of patients with prostate cancer. Radiol. Oncol. **48**, 228–234 (2014)
12. G. Paone, G. Treglia, M. Bongiovanni, T. Ruberto, L. Ceriani, L. Giovanella, Incidental detection of Hürthle cell adenoma by 18F-choline PET/CT scan in a patient with prostate cancer. Rev. Esp. Med. Nucl. Imagen Mol. **32**, 340–341 (2013)
13. R. Ciappuccini, C. Jeanne, S. Bardet. Incidental focal thyroid uptake on 18F-Choline PET-CT: need to rule out thyroid cancer. Endocrine.(2018). https://doi.org/10.1007/s12020-018-1705-2.
14. A.L. Aziz, F. Courbon, L.O. Dierickx, O. Pascal, S. Zerdoud, Oncocytic adenoma of thyroid incidentally detected by 18F-fluorocholine PET/CT. J. Nucl. Med. Technol. **43**, 133–134 (2015)
15. A. Eccles, A. Challapalli, S. Khan, T. Barwick, S. Mangar, Thyroid lymphoma incidentally detected by 18F-fluorocholine (FCH) PET/CT. Clin. Nucl. Med. **38**, 755–757 (2013)
16. G. Treglia, E. Giovannini, P. Mirk, D. Di Franco, L. Oragano, F. Bertagna, A thyroid incidentaloma detected by 18F-choline PET/CT. Clin. Nucl. Med. **39**, e267–e269 (2014)
17. P. Lalire, M. Zalzali, C. Garbar, C. Bruna-Muraille, D. Morland, Incidental detection of oxyphilic papillary thyroid carcinoma by 18F-fluorocholine PET/CT. Clin. Nucl. Med. **41**, 512–513 (2016)
18. A. Ouattara, T.R. de Oliveira, S. Holz, H. Van den Bossche, D. Strybol, C. Assenmacher, W. Everaerts, G. De Meerleer, S. Joniau, Incidental detection of occult thyroid carcinoma with 11C-choline PET/CT for high risk prostate cancer. Curr. Urol. **10**, 217–220 (2017)
19. A. Haroon, L. Zanoni, M. Celli, R. Zakavi, M. Beheshti, W. Langsteger, S. Fanti, M. Emberton, J. Bomanji, Multicenter study evaluating extraprostatic uptake of 11C-choline, 18F-methylcholine, and 18F-ethylcholine in male patients: physiological distribution, statistical differences, imaging pearls, and normal variants. Nucl. Med. Commun. **36**, 1065–1075 (2015)
20. C.L. Welle, E.L. Cullen, P.J. Peller, V.J. Lowe, R.C. Murphy, G. B. Johnson, L.A. Binkovitz, ^{11}C-Choline PET/CT in recurrent prostate cancer and nonprostatic neoplastic processes. Radiographics **36**, 279–292 (2016)
21. O. Schillaci, F. Calabria, M. Tavolozza, C. Cicciò, M. Carlani, C. R. Caracciolo, R. Danieli, A. Orlacchio, G. Simonetti, 18F-choline PET/CT physiological distribution and pitfalls in image interpretation: experience in 80 patients with prostate cancer. Nucl. Med. Commun. **31**, 39–45 (2010)
22. N.T.K. Thanseer, S.K. Bhadada, A. Sood, A.S. Parihar, D. Dahiya, P. Singh, R.K. Basher, A. Das, B.R. Mittal, Dual pathologies of parathyroid adenoma and papillary thyroid cancer on fluorocholine and fluorodeoxyglucose PET/CT. Nucl. Med. Mol. Imaging **52**, 154–158 (2018)
23. R. Ruiz-Esponda, V.J. Lowe, D.S. Dean. Clinical significance of incidental thyroid uptake on 11Ccholine PET/CT. Endo. Rev. **35** SUPPL (2014).
24. A.M. García Vicente, A. Núñez García, A.M. Soriano Castrejón, G.A. Jiménez Londoño, J.M. Cordero García, A. Palomar Muñoz, Pitfalls with 18F-choline PET/CT in patients with prostate cancer. Rev. Esp. Med. Nucl. Imagen Mol. **32**, 37–39 (2013)
25. A. Parvinian, E.L. Martin-Macintosh, A.H. Goenka, J.M. Durski, B.P. Mullan, B.J. Kemp, G.B. Johnson, 11)C-choline PET/CT for detection and localization of parathyroid adenomas. Am. J. Roentgenol. **210**, 418–422 (2018)
26. G. Treglia, F. Bertagna, R. Sadeghi, F.A. Verburg, L. Ceriani, L. Giovanella, Focal thyroid incidental uptake detected by ^{18}F-fluorodeoxyglucose positron emission tomography. Meta-analysis on prevalence and malignancy risk. Nuklearmedizin **52**, 130–136 (2013)
27. G. Treglia, L. Giovanella, F. Bertagna, D. Di Franco, M. Salvatori, Prevalence and risk of malignancy of thyroid incidentalomas detected by (18)f-fluorodeoxyglucose positron-emission tomography. Thyroid **23**, 124–126 (2013)
28. F. Bertagna, G. Treglia, A. Piccardo, E. Giovannini, G. Bosio, G. Biasiotto, K. Bahij el, R. Maroldi, R. Giubbini, F18-FDG-PET/CT thyroid incidentalomas: a wide retrospective analysis in three

Italian centres on the significance of focal uptake and SUV value. Endocrine **43**, 678–685 (2013)
29. F. Bertagna, G. Treglia, A. Piccardo, R. Giubbini, Diagnostic and clinical significance of F-18-FDG-PET/CT thyroid incidentalomas. J. Clin. Endocrinol. Metab. **97**, 3866–3875 (2012)
30. H.B. Wu, Q.S. Wang, M.F. Wang, H.S. Li, Utility of ^{11}C-choline imaging as a supplement to F-18 FDG PET imaging for detection of thyroid carcinoma. Clin. Nucl. Med. **36**, 91–95 (2011)
31. S. Grimaldi, J. Young, P. Kamenicky, D. Hartl, M. Terroir, S. Leboulleux, A. Berdelou, J. Hadoux, S. Hescot, H. Remy, E. Baudin, M. Schlumberger, D. Deandreis, Challenging pre-surgical localization of hyperfunctioning parathyroid glands in primary hyperparathyroidism: the added value of 18F-Fluorocholine PET/CT. Eur. J. Nucl. Med. Mol. Imaging **45**, 1772–1780 (2018)