Scientific Research Publishing

Open Journal of Biophysics, 2024, 14, 1-10
https://www.scirp.org/journal/ojbiphy
ISSN Online: 2164-5396
ISSN Print: 2164-5388

Ambulatory Radio Iodine Therapy in the Management of Hyperthyroidism in Africa: African Systematic Review and Perspectives in Burkina Faso

Ki Thierry Romuald[1*], Mamadou Salif Djigo[2], Gora Thiaw[2], Arsène Sanou[3], Mamounata Zoungrana[1], Mamadou Mbodj[2]

[1]Nuclear Medicine Department of the Yalgado OUEDRAOGO University Hospital Center in Ouagadougou, Ouagadougou, Burkina Faso
[2]Biophysics and Nuclear Medicine Laboratory of the Cheikh Anta DIOP University of Dakar, Dakar, Senegal
[3]Radiology Departement of the Bobo Dioulasso University Hospital Center in Bobo Dioulasso, Bobo Dioulasso, Burkina Faso
Email: *boleki1983@yahoo.fr

How to cite this paper: Romuald, K.T., Djigo, M.S., Thiaw, G., Sanou, A., Zoungrana, M. and Mbodj, M. (2024) Ambulatory Radio Iodine Therapy in the Management of Hyperthyroidism in Africa: African Systematic Review and Perspectives in Burkina Faso. *Open Journal of Biophysics*, **14**, 1-10.
https://doi.org/10.4236/ojbiphy.2024.141001

Received: December 17, 2023
Accepted: January 20, 2024
Published: January 23, 2024

Abstract

Introduction: In hyperthyroidism, selective irradiation of the thyroid gland with radioactive iodine is a radical treatment and an alternative to surgery. The aim of this review is to assess the medium-term efficacy of outpatient treatment of hyperthyroidism with iodine-131 in Africa. **Methods**: We identified the studies carried out in Africa on outpatient radiation therapy between 2016 and 2020. For each article included, we noted the country concerned and the year of publication, the numbers studied, the socio-demographic characteristics of the patients, the indications for radio iodine therapy, the dose administered, the results of the hormonal dosage 6 months after radiation. **Results**: 13 retrospective studies were included to constitute a total population of 925 patients. The average age was 40.77 years, the sex ratio of 1/5.4 with a clear female predominance. The 3 main etiologies of hyperthyroidism justifying outpatient radio iodine therapy were Graves' disease (55.89%), toxic multinodular goiter (22.70%) and toxic adenoma (21.40%). The average dose of iodine 131 administered per course is 13.7 mCi. No short- and medium-term complications were reported. The radio iodine therapy was effective in 86.08% (n = 796) of the patients with extremes of 72% and 100%. **Conclusion**: Radio iodine therapy is effective in Africa. It is simple, inexpensive on an outpatient basis and well tolerated. The introduction of outpatient radio iodine therapy could improve the management of patients with hyperthyroidism in Burkina Faso.

Keywords

Hyperthyroidism, Outpatient Radio Iodine Therapy, Africa

1. Introduction

Hyperthyroidism is a public health problem in Africa. Its prevalence is estimated between 1.2% and 9.9%, with Graves' disease being the most common cause [1]. In 1936, Karl Compton, then president of the Massachusetts Institute of Technology (MIT) and the Thyroid Group at Massachusetts General Hospital (MGH), undertook a joint study that led to the production of small amounts of short-lived radioactive iodine from life (iodine 128, half-life = 25 min). The original intention was to use it for the diagnosis and treatment of thyroid disease. However, their first work was done on rabbits and published in 1938 to explore the underlying thyroid physiology. In 1941, the MGH-MIT team, using mainly 130 iodine, was able to successfully treat a few patients with hyperthyroidism and thus achieved their original goal. The Berkeley group did the same a few months later, using mainly 131 I or iodine 131 [2].

In 2021, the therapeutic approach to hyperthyroidism is intended to be optimal. This optimal approach incorporates patient preferences and specific clinical characteristics such as age, medical history, goiter size… The three therapeutic modalities recommended by the ATA (American Thyroid Association) are synthetic antithyroid drugs (ATS), radiation therapy (IRA) and surgery. Each of the treatment modalities has unique advantages and disadvantages that clinicians should be familiar with in order to best counsel their patients [3]. The successes of outpatient radio iodine therapy in hyperthyroidism and the rich literature that accompanies it should be enough to convince us of the possibility of its implementation.

However, 70 years after its beginnings, radio iodine therapy is a reality in the Maghreb, South Africa, Mauritius, Madagascar, Ethiopia, Uganda, Kenya, Cameroon, Nigeria, Ghana, Senegal. The other African countries have still not taken the plunge despite the installation over the past twenty years of nuclear medicine services in many African countries.

To answer this question, we undertook to study the data of the African literature on ambulatory radio iodine therapy published between 2016 and 2020. The objective was to demonstrate its feasibility and effectiveness in developing countries in order to expand its practice in Africa.

2. Methodology

Data used in the study in the form of full text and abstracts were obtained by a multi-source search strategy. The search terms were used in the following databases: Medline (PubMed), Embase, Cochrane, Scopus, Sciences direct, according to the thesaurus of each of the databases, the abstracts published during congresses as well as the national scientific research work such as a master's or doctorate, the World Health Organization database and "Google scholar" as well as a manual search.

2.1. Item Selection

Relevant articles published between January 1, 2016 and January 1, 2021 were

selected. Articles were excluded: 1) dealing with radiation therapy in hospitalization, 2) not providing post-radiation T4 assay, 3) published before January 1, 2016.

The relevant articles were selected on the following criteria: 1) original articles or clinical cases on the topic of outpatient radiation therapy, 2) African populations studied, 3) estimation of the T4 dose at 6 months post-radiation. The analysis of the 43 references identified made it possible to identify a total number of 13 relevant articles (Figure 1).

2.2. Article Analysis

Three reviewers extracted and evaluated the data independently and then the agreement between the three reviewers by the statistical coefficient Kappa (k). For each article included, we noted the country concerned and the year of publication, the numbers studied, the socio-demographic characteristics of the patients, the indications for radio iodine therapy, the dose of radioactive iodine administered, the results of the hormonal dosage at 6 months post radio iodine therapy. Radio iodine therapy was considered effective if it resulted in euthyroidism or hypothyroidism 6 months after irradiation. There is the failure of the radio iodine therapy in the opposite case (persistent hyperthyroidism 6 months after radiation).

2.3. Analysis of Collected Data

The data collected was collated on a Microsoft Excel® sheet and analyzed using Random software version 2.13 for Windows®. The frequencies from the qualitative variables were compared using the Chi-square test; means and medians using Student's T-test. Differences were considered significant when the p-value was less than 0.05.

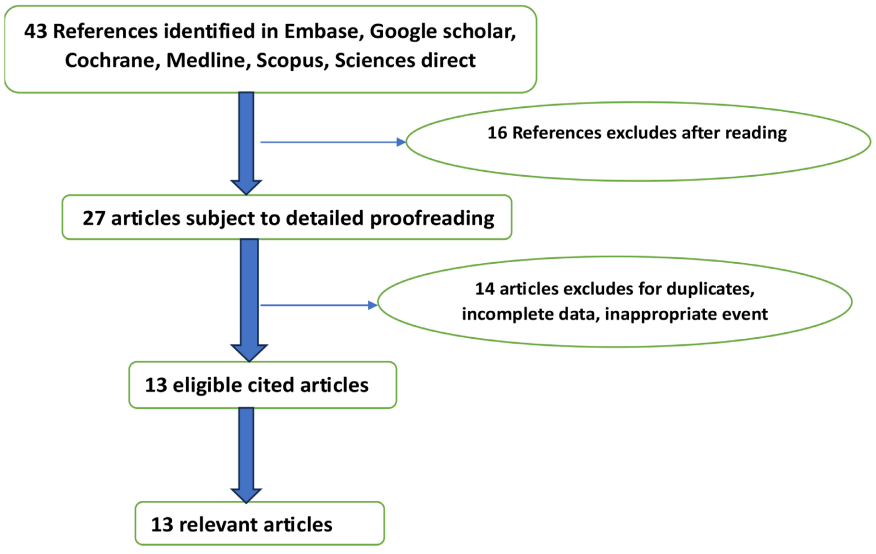

Figure 1. Flowchart of the article selection process.

3. Results

3.1. Descriptive Study

❖ **Characteristics of the articles included in the review**

13 studies mainly retrospectives were selected to constitute a total population of 925 patients. Table 1 shows the characteristics of the articles included.

❖ **Description of the study population**

The total number of all series combined was 925 patients. The average age was 40.77 years with extremes ranging from 10 to 88 years. The sex ratio is 1/5.4 with a clear female predominance (84.40%). Table 2 represents the general characteristics of the population studied.

Table 1. Characteristics of articles included in the review.

Réf	Country	Year	Study population	Eff	Dosimetric protocol	Limitations of the study
4	Tunisia	2016	Hyperthyroids under 19 years old.	33	NS*	Exclusively pediatric study
5	Ghana and Nigeria	2016	Hyperthyroid patients from two Ghanaian and Nigerian public hospitals.	94	Before 2010: single fixed dose of 10 mci. After 2010: fixed dose according to hyperthyroidism.	Change of dosimetric protocol
6	Morocco	2017	Graves disease	50	Empirical dose according to UTV, age, socioeconomic level.	Basedow alone
7	Morocco	2017	Hyperthyroidism of all etiologies	77	Ablative fixed dose	No mid-term hormonal assessment
8	Tunisia	2017	Graves disease	70	Ablative fixed dose	No short-term evaluation (3 months).
9	Morocco	2019	Hyperthyroidism of all etiologies	208	NS*	
10	Tunisia	2017	Post-ARI evaluation of two groups of hyperthyroid patients: Basedowian subjects and toxic nodules.	78	NS*	Excluding GMNTs
11	Morocco	2018	Evaluation of the therapeutic response after ARI	78	Ablative fixed dose	Selection bias (Basedow only)
12	Algeria	2019	Description of clinical cases	02	Empirical dose according to UTV	Selection bias
13	Cameroon	2019	Review of 4 years of ARI and selection of patients who received ablative doses	74	Empirical dose according to UTV	Consideration of ablative doses
14	Senegal	2020	Population of hyperthyroid patients who received an ablative dose	66	Fixed dose	Preliminary study
15	Tunisia	2020	Hyperthyroidism secondary to Graves' disease	54	Fixed dose	Exclusion of ATs and GMNTs
16	Tunisia	2020	Hyperthyroid patients with analysis of predictive factors for the result of the ARI	41	NS*	Dosimetric protocol not defined

Ref: Reference; Eff: Effective; NS*: Not Specified; UTV*: Ultrasound Thyroid Volume.

Table 2. General characteristics of the population studied.

African studies published from 2016 to 2020	Age		Gender		Effective of series
	Average	Ext*	F*	M*	
Rezgani C. *et al.* in 2016 in Tunisia [4]	16.87 ± 2.2	NR*	29	4	33
A. Yetunde *et al.* in 2016 in Nigeria and Ghana [5]	47.38 ± 12.34	20 - 74	80	14	94
M. Ben Souda *et al.* in 2017 in Morocco [6]	41.8	21 - 57	45	5	55
H. Aschawa *et al.* in Morocco in 2017 [7]	NR*	NR*	NR*	NR*	70
El Feleh E. *et al.* in 2017 in Tunisia [8]	40.5	NR*	63	15	70
I. Rezgani *et al.* in 2017 in Tunisia [9]	45.11 ± 15.81	13 - 80	64	10	78
S. Choukry *et al.* in 2018 in Morocco [10]	12	10 - 14	2	0	2
JF Nwatsock *et al.* in 2019 in Cameroon [11]	55	19 - 82	175	33	74
T. Bounab *et al.* in Algeria in 2019 [12]	43.5	18 - 75	57	9	66
F. Fokoue *et al.* in 2019 in Morocco [13]	38.33 ± 12.7	20 - 79	NR*	NR*	54
E. H. A. L. Bathily *et al.* in 2020 in Senegal [14]	NR*	NR*	34	7	41
A. Sellem *et al.* en 2020 in Tunisia [15]	38.33 ± 12.7	20 - 79	NR*	NR*	54
A. Grassa *et al.* en 2020 in Tunisia [16]	NR*	NR*	34	7	41

NR* = Not specified; F* = Women; M* = Men; Avg*: Average; Ext*: Extremes.

3.2. Analysis of the Modalities of Iratherapy

❖ **In which hyperthyroidism?**

The 3 main etiologies of hyperthyroidism that motivated outpatient radio iodine therapy in all series were, in increasing order of frequency: toxic adenoma (21.40%), toxic multinodular goiter (22.70%), Graves' disease (55.89%). Figure 2 represents the main etiologies that justified radio iodine therapy in our context.

❖ **Place of iratherapy in the therapeutic strategy**

In 61.11% of cases, radio iodine therapy was administered as a second-line treatment after ATS treatment. In these cases, it occurred after a failure of 18 months of medical treatment with ATS, desire for pregnancy, and side effects of treatment with synthetic antithyroid drugs. In the other cases (38.89%) the radio iodine therapy was administered as the first or third intention. The separate proportions (1st and 3rd intentions) could not be combined.

❖ **The dose administered**

The average dose administered is 13.7 mCi. The dose was fixed in 50% of the studies. The dose calculation was empirical in 21.42% of the studies. The protocol was not specified in the other studies.

❖ **Evaluation at 6 months post radio iodine therapy**

No short- and medium-term complications were reported in any series combined. The efficacy of all series combined was 86.08%.

The performance of the radio iodine therapy at 6 months is shown in Figure 3.

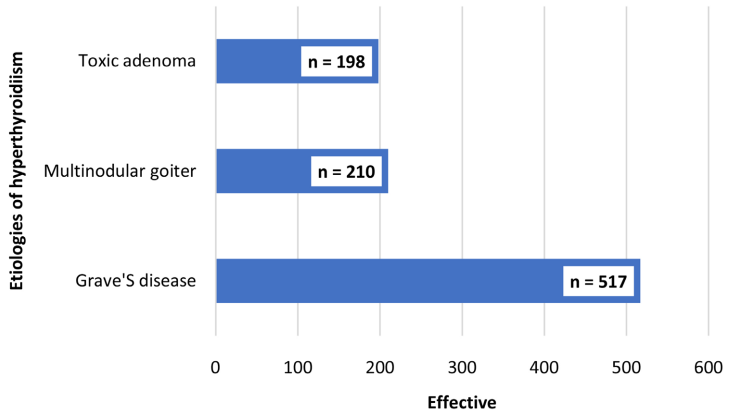

Figure 2. Etiologies of hyperthyroidism.

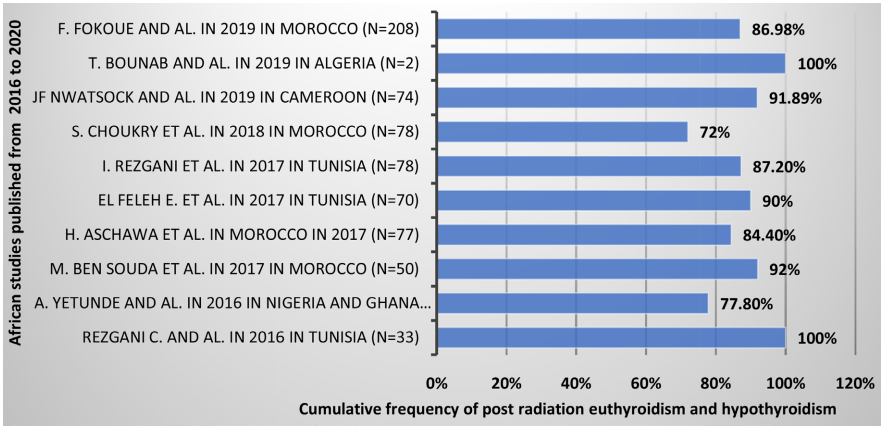

Figure 3. Performance of radio iodine therapy in Africa from 2016 to 2020.

4. Discussion

In the medical field, the progression of knowledge is due not only to the reception of new data but also and above all to the assimilation of old ones. A single study can never truly answer a research question posed by practice, whereas all of the studies that already exist will perhaps make it possible to gradually approach a truth, at least to define the hypotheses and objectives of new studies that will contribute to this [17].

4.1. Limitations of the Review

Selection bias is inherent in this review as all included studies were retrospective. In wanting to provide recent data, we have voluntarily selected studies published between 2016 and 2020. This has systematically eliminated several data from countries where the interest in ambulatory radio iodine therapy no longer needs to be demonstrated and whose data are more than 5 years old. These are mainly Egypt and South Africa.

4.2. Studies Included

As of July 31, 2021, our research databases have recorded 13 studies published

over the past 5 years (January 1, 2016 to December 31, 2020) on outpatient ARI in Africa. The distribution of studies is as follows: Senegal: one study; Cameroon: one study; Ghana and Nigeria: a joint study; Morocco: four studies; Algeria: a study; Tunisia: five studies. In order to limit the heterogeneity of the different series, we excluded the South African study by Onimode A. *et al.*, which was specifically male. [18] The South African study looked specifically at radio iodine therapy in male patients with Graves' disease.

4.3. Comments

The aim of our review was to present what has been done over during the 5 years in terms of outpatient radioiodine therapy in Africa.

On an outpatient basis, treatment with radioactive iodine is done by oral administration of a capsule or a solution of iodine 131 in the form of sodium iodide (NaI).

In all the series the female gender is predominant.

Hyperthyroidism is a disease of women over 40. When it is male, it usually occurs earlier. The age of patients who benefited from radio iodine therapy is telling in our review. Rezgani C *et al.* in Tunisia [4] focused particularly on radio iodine therapy in a cohort of 33 hyperthyroid children. Post-radiation hypothyroidism was obtained in 100% of cases, the average response time was 3.27 months (1 to 6 months). A single case of recurrence of hyperthyroidism was noted at 1 year, requiring a second treatment with installation of post-radiation hypothyroidism after 2 months. Thus the radio iodine therapy seems particularly effective in young subjects with a better response time.

Two main etiologies were underlying the radio iodine therapy. These are autoimmune hyperthyroidism (Basedow's disease: 55.89%), autonomic hyperthyroidism (multinodular goiter: 22.70% and toxic adenoma: 21.40%). Internationally accepted indications for outpatient radio iodine therapy have been established based on randomized trials, meta-analyses, and systematic reviews. The recognized indications are as follows [19]:

- Autoimmune hyperthyroidism: intolerance to synthetic antithyroid drugs, the impossibility of weaning from synthetic antithyroid drugs after 24 months of treatment, associated pathologies, non-compliance with medical treatment, recurrence regardless of the first treatment;
- Autonomic hyperthyroidism: diffuse, uni or multinodular non-compressive goiter in moderate hyperthyroidism without suspicion of associated cancer.

In our different series, radio iodine therapy was most often (61.11%) prescribed as second-line [6] [7] [9] [11] [12] [14] following failure of synthetic antithyroid drugs (non-compliance, abandonment, persistence of the hyperthyroidism, relapse after surgery) or following a refusal of surgical treatment.

The principles underlying the selection of the dose of radio iodine therapy to treat hyperthyroidism are based on studies and observations in populations that have not generally included African subjects. [5] Hence the importance of studying the dosimetric parameters of radio iodine therapy in Africa. These dosime-

tric parameters are different depending on the series. Two main protocols are described:

- A fixed dose is to be administered [5] [7] [8] [11] [14] [15] depending on the etiological diagnosis: 15 mCi for Graves' disease and 30 mCi for autonomic hyperthyroidism and diffuse goiter.
- A dose to be administered that can be adjusted, is called empirical [6] [12] [13] depending on age, ultrasound size of the gland, and treatment history.
- The French Society of Nuclear Medicine (SFMN) [19] recommends two main principles for calculating the dose to be administered based on the etiology. So:
- In hyperthyroidism on diffuse, autoimmune or autonomic goiter, the occurrence of post-therapeutic hypothyroidism is frequent. Therefore the recommended absorbed dose level reducing hyperthyroidism is 60 - 90 Gy. The recommended absorbed dose level for ablative purposes is 100 to 300 Gy.
- In nodular autonomic hyperthyroidism, the risk of hypothyroidism is moderate but increases with the extent of the autonomic lesions; incomplete extinction of healthy parenchyma; and a high target absorbed dose level. The recommended absorbed dose level is 130 to 200 Gy in unimodular goiters, and 80 to 130 Gy in multinodular goiters.

In Morocco [9] an innovative and practical strategy integrates the socio-economic level of the patient in the dosimetric approach. When the patient has a low income and comes from a remote location, the ablative dose is recommended with early management of post-radiation hypothyroidism.

It therefore seems judicious to establish standard protocols according to the context of the type of hyperthyroidism and the objectives set. The ablative objective being the most sought after, dose optimization implies a sufficient dose, *i.e.* between 100 and 300 Gy in Graves' disease. Studies carried out in the Maghreb [8] [9] [10] have shown more convincing results at optimal doses.

Post-radiation hypothyroidism or euthyroidism are radio iodine therapy efficacy criteria. This efficiency, all series combined, has been 86.08% over the past 5 years in Africa.

No cost data is available. But on an outpatient basis, a cure consists of the ingestion of a capsule or a solution of radioactive iodine. In France, a capsule of radioactive iodine costs less than 10 euros. Even with the costs (specific to each context) inherent in importing these products into Africa, it can be estimated that radio iodine therapy remains less expensive than taking synthetic antithyroid drugs daily for at least 18 months.

Importantly, no side effects of radio iodine therapy have been reported in the short to medium term. This is a fundamental point as the term "radioactivity" tends to serve this therapeutic modality. Also, no study in the international literature reports a side effect of a malignant pathology type after radio iodine therapy. Comparatively, taking synthetic antithyroid drugs is not devoid of side effects that are certainly rare (less than 1%) but not zero. Thus acute agranulocytosis (0.2% to 0.5%), bone marrow hypoplasia, cytolytic and retentional hepa-

titis, immuno-allergic vasculitis can occur after taking synthetic antithyroid drugs. [20]

5. Conclusion

This review shows that outpatient ira therapy is possible and effective in hyperthyroidism in Africa. Its implementation is simple and at the risk of repetition, no complications are reported in the short and medium term. Finally, ira therapy is less expensive than the 18-month treatment with ATS or surgical treatment. Furthermore, the existence of elderly hyperthyroid patients and/or carriers of multiple defects contraindicating surgery; the many cases of failure of drug treatment require local development of the management of hyperthyroidism in Burkina Faso. We hope that this clarification gives a place for outpatient radio iodine therapy in the management of hyperthyroidism in Burkina Faso.

Conflicts of Interest

The authors declare no conflict of interest.

References

[1] Ogbera, A.O. and Kuku, S.F. (2011) Epidemiology of Thyroid Diseases in Africa. *Indian Journal of Endocrinology and Metabolism*, **15**, 82-88. https://doi.org/10.4103/2230-8210.83331

[2] Hertz, B.E. and Schuller, K.E. (2010) A Pioneer in the Use of Radioactive Iodine. *Endocrine Practice*, **16**, 713-715. https://doi.org/10.4158/EP10065.CO

[3] Burch, H.B. and Cooper, D.S. (2015) Management of Graves' Disease: A Review. *JAMA*, **314**, 2544-2554. https://doi.org/10.1001/jama.2015.16535

[4] Rezgani Chelbi, I., Meddeb, I., Yeddeas, I., Limam, K., *et al.* (2016) La maladie de Basedow chez l'enfant: Placede l'irathérapie. *Annales d'Endocrinologie*, **77**, 390. https://doi.org/10.1016/j.ando.2016.07.455

[5] Yetunde, A., Ankrah, A. and Adedapo, K.S. (2016) Outcome of Radioiodine Therapy in a West African Population. *World Journal of Nuclear Medicine*, **15**, 24-29. https://doi.org/10.4103/1450-1147.167585

[6] Ben Souda, M., Marhari, H., Fokoue, F., Salhi, H., El Ouahabi, H. and Alaoui, N. (2018) Place de l'irathérapie dans le traitement de la maladie de Basedow: A propos de 50 cas. *Annals of Endocrinology*, **79**, 359. https://doi.org/10.1016/j.ando.2018.06.512

[7] Aschawa, H., Touil, S., Shimi, Y., Bendaoud, H., Meftah, S. and Aaouini, R. (2017) Hyperthyroidism: Short-Term Efficacy of Radioactive Iodine Treatment. *Moroccan Journal of Public Health*, **4**, 7-12.

[8] El Feleh, E., Mahjoubi, S., Bachir, N., Jaidane, A., Sellemb, A. and Ouertani, H. (2017) Place of Radio Iodine Therapy in the Treatment of Graves' Disease. *Annals of Endocrinology*, **78**, 326. https://doi.org/10.1016/j.ando.2017.07.352

[9] Rezgani, I., Meddeb, I., Yeddeas, I., Slim, I., Mhiri, A. and Ben Slimène, M.F. (2017) Comparative Study of the Efficacy of IRA Therapy in Graves' Disease and Toxic Thyroid Nodules. *Annals of Endocrinology*, **78**, 337. https://doi.org/10.1016/j.ando.2017.07.390

[10] Choukry, S., Benouhoud, J., Choukry, K., Aschawa, H. and Guensi, A. (2018)

Évolution des maladies de Basedow après irathérapie (à propos de 78 cas). *Médecine Nucléaire*, **42**, 164. https://doi.org/10.1016/j.mednuc.2018.03.083

[11] Nwatsock, J.F., Mbeng, A.V. and Dong-à-Zok, F. (2019) Indications et efficacité à 6 Mois de l'Irathérapie à activité ablative fixe dans l'hyperthyroïdie à Yaoundé. *Health Sciences and Disease*, **20**, 31-36. https://www.hsd-fmsb.org/index.php/hsd/article/view/1644

[12] Bounab, T., Ghennam, B., Zitouni, I.M., *et al.* (2019) Traitement de la maladie de Basedow chez l'enfant par l'iode 131: À propos de deux cas. *Médecine Nucléaire*, **43**, 198. https://doi.org/10.1016/j.mednuc.2019.01.073

[13] Fokoue, F., El Mselmi, S. and Ismaili, A.N. (2019) Epidemiological Profile and Therapeutic Efficacy of Iodine 131 in the Management of Hyperthyroidism: About 208 Patients. *Nuclear Medicine*, **43**, 199. https://doi.org/10.1016/j.mednuc.2019.01.076

[14] Bathily, E.H.A.L., *et al.* (2020) Traitement des hyperthyroïdies par l'iode 131: Bilan d'activité préliminaire du service de médecine nucléaire de l'hôpital général de Grand Yoff de Dakar. *Médecine Nucléaire*, **44**, 130-131. https://www.sciencedirect.com/science/article/pii/S0928125820300917 https://doi.org/10.1016/j.mednuc.2020.01.075

[15] Grassa, A., Jemel, M., Salhi, S., Kandara, H., Khemiri, M. and Kammoun, I. (2020) Graves' Disease Treated with Radiation Therapy: Indication and Therapeutic Response. *Annals of Endocrinology*, **81**, 345. https://doi.org/10.1016/j.ando.2020.07.575

[16] Sellem, A., Elajmi, W., Ben Mhamed, R., Oueslati, N., Ouertani, H. and Hammami, H. (2020) Role and Effectiveness of Radioactive-Iodine Therapy for the Treatment of Grave's Disease. *The Pan African Medical Journal*, **36**, Article 341. https://doi.org/10.11604/pamj.2020.36.341.21623

[17] Colombet, I. (2015) Revue systématique et méta-analyse en médecine palliative, Médecine Palliative. *Médecine* Palliative: Soins de Support-*Accompagnement*-É*thique*, **14**, 240-253. https://doi.org/10.1016/j.medpal.2015.04.001 https://www.sciencedirect.com/science/article/pii/S1636652215000380

[18] Onimode, Y.A., Magbagbeola, D. and Ellmann, A. (2018) Pattern of Presentation of Graves' Disease and Response to Radioiodine Therapy in South African Men. *Pan African Medical Journal*, **29**, Article 48. https://doi.org/10.11604/pamj.2018.29.48.13655

[19] SFMN: French Society of Nuclear Medicine (2021) Guide for Writing Treatment Protocols for Hyperthyroidism with Iodine 131. https://www.cnp-mn.fr/wp-content/uploads/2022/09/Traitement-hyperthyroidie-V1.0.pdf

[20] Borson-Chazot, F., Caron, P., Glinoer, D. and Wémeau, J.L. (2014) Synthetic Antithyroid Drugs: What to Choose? *La Presse Médicale*, **43**, 105-108. https://doi.org/10.1016/j.lpm.2014.01.003