MANAGEMENT OF ENDOCRINE DISEASE

Acromegaly and cancer: an old debate revisited

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Abstract

Based on experimental and animal models, epidemiological data from non-acromegaly populations, and longitudinal and cross-sectional cohorts of patients with acromegaly, a potential association between acromegaly and cancer has long been hypothesized, in particular colorectal cancer, and, to a lesser extent, breast, thyroid and prostate cancers. The exact mechanisms underlying this potential association have not been fully elucidated. Results from studies examining cancer incidence and mortality in acromegaly have been inconsistent, with some demonstrating increased risk, whereas others show no increase. This article reviews the existing data relating to cancer risk and mortality in acromegaly, exploring the limitations of study designs and the impact of changes in disease control and patient outcomes over time.

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Introduction

Acromegaly represents the best human model to understand the consequences of a continuous and prolonged exposure to high growth hormone (GH) and insulin-like growth factor-1 (IGF1) concentrations. It is a rare disease, typically caused by a GH-secreting pituitary adenoma, whose natural history has been modified in the past two decades by a combined therapeutic approach involving surgery, radiotherapy and pharmacological treatment (1).

The overall mortality rate is higher in patients with active acromegaly, mainly due to vascular and respiratory diseases, whereas normalization of GH and IGF1 levels is accompanied by reduction of mortality rate to

that of the normal population (2, 3). Retrospective mortality studies have shown that, on average, 15–24% of deaths in acromegaly are attributable to cancer, with a particular focus on colorectal cancer (CRC) and, to a lesser extent, on breast, thyroid, prostate and other cancers (4). What is not so clear is whether cancer risk is enhanced in active acromegaly due to excessive GH and IGF1 secretion. Over the years, this potential association has been sustained by a number of experimental and animal models, epidemiological data from non-acromegaly populations, and longitudinal and cross-sectional cohorts of patients with acromegaly (4, 5, 6, 7, 8, 9). It has also been suggested that genetic and/or epigenetic alterations in

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acromegaly, aging and the presence of some comorbidities, independent of hormone status, might predispose to cancer risk (4, 6, 9, 10). By contrast, a substantial number of clinical studies have failed to demonstrate increased neoplastic risk in acromegaly, and this association has been questioned (11).

In this review, we have revisited this old debate, with a special focus on large-scale population-based series, limitations of study designs, impact of changes in disease control, morbidities and patient's outcomes over the time, and we have explored the different proposed guidelines for cancer screening in acromegaly.

Clinical epidemiology

Incidence/prevalence

A review of 17 series published between 1957 and 2015, where overall cancer incidence in acromegaly was investigated, revealed 7723 patients with 708 cases of cancer, resulting in a mean cancer incidence of 10.8%, with percentages varying from 4.8 to 21.3% (12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28). Standardized incidence ratio (SIR) was available from 11 series, and in three of them, cancer incidence was not increased (12, 18, 28). In five series, the estimated overall SIR for malignancies was increased by a magnitude of 1.5- to 3.4-fold (15, 16, 19, 21, 23), whereas in two studies, increased risk was only observed for women (13) and in one only for men (20) (Table 1).

There are many problems and limitations in quantifying the risk of cancer in patients harboring a rare disease (Fig. 1). Most studies include small numbers of individuals, with no statistical power to adjust the data for confounding factors, such as age and gender. The comparison between older and more recent series is challenging, as both cancer incidence in the general population and life expectancy in patients with acromegaly have dramatically changed over the past few decades, influencing the prevalence of disease-associated morbidities (2, 29). In addition, population-based cancer registries and epidemiology may vary from site to site (29). Finally, another source of biases is the heterogeneity of comparative control populations used in the studies, which have varied from data published in literature to hospitalized non-acromegaly patients, matched controls, or the general population.

There are five larger series from the United States (16), the United Kingdom (18), Sweden/Denmark (21), Finland (23) and Germany (28), which have assessed the overall cancer rate in acromegaly in comparison with that in the general population. Together, they report on 439 cases of several types of malignancies in 4690 patients, with estimated SIR higher in three studies (16, 21, 23) and lower or not different from the general population in two (18, 28). One possibility for these conflicting findings, which still persist considering only large-scale comparable studies, is that cancer risk in both acromegaly and non-acromegaly populations might actually vary among different settings, preventing a reliable generalization of the results (30). For instance, CRC incidence and mortality rates vary up to

Table 1 Overall cancer incidence in acromegaly.

Reference	Country	Patients (N)	Cancers (N)	Prevalence (%)	SIR (95% CI)	Conclusion
(12)	USA	223	13	5.8	1.33	Not increased
(13)	UK	256	26	10.2	Women: 1.87	Increased in women
(14)	UK	125	15	12	NA	
(15)	USA	87	7	8	2.4 (0.98–5.0)	Increased
(16)	USA	1041	89	8.5	1.6 (1.3–1.9)	Increased
(17)	Australia	50	7	14	Men: 1.2 (0.31–5.0) Women: 4.3 (1.7–10.5)	Increased in women
(18)	UK	1239	79	6.4	0.76 (0.6–0.95)	Not increased
(19)	Serbia	220	23	10.5	3.4 (2.12–5.12)	Increased
(20)	Japan	44	5	11.4	Men: 3.53	Increased in men
(21)	Sweden/Denmark	1634	177	10.8	1.5 (1.3–1.8)	Increased
(22)	Spain	1219	90	7.4	NA	
(23)	Finland	331	48	14.5	1.5 (1.1–1.9)	Increased
(24)	Turkey	105	16	15.2	NA	
(25)	Poland	101	12	11.9	NA	
(26)	Turkey	160	34	21.3	NA	
(27)	Mexico	442	21	4.8	NA	
(28)	Germany	446	46	10.3	0.75 (0.55–1.0)	Not increased
Total		7723	708	10.8		

SIR, standardized incidence ratio; NA, not available.

Figure 1

Balance between the hypothesized pros and cons contributors to cancer risk in acromegaly. Acromegaly is characterized by persistently elevated serum concentrations of GH, IGF1 and IGFBP3, which results in a dysregulated, unpredictable balance on cell cycle regulation. Clinical studies have produced inconsistent and conflicting results. Genetic/epigenetic susceptibility, increased life expectancy in acromegaly due to better therapeutic outcomes, and disease-associated morbidities have been suggested as potential players favoring cancer development, but their role has not been fully elucidated and deserves further studies. There are several problems and limitations in the study designs that make the balance go to one side or the other, depending on the patients, controls and methods used to estimate cancer risk in the protocols.

ten-fold worldwide, with distinct gradients across human development levels (31). As a general rule, however, most investigators agree that, regardless of the reason, if acromegaly increases the risk of cancer, the magnitude of this association is modest (3, 9, 10).

Mortality

The overall mortality rates in patients with acromegaly are comparable to population-based controls, if circulating GH and IGF1 levels are normalized by treatment. In this context, cancer-related mortality in acromegaly is not increased (2, 3). However, in two studies (18, 32), patients with active disease and persistently elevated GH and IGF1 values had significantly higher mortality from cancer, particularly CRC, than those with normal IGF1 or GH levels, although overall, the cancer-related mortality was not greater than the observed mortality in the general

population, and it is not affected by the duration of disease or patient's age at diagnosis (4, 10, 11).

In a recent cohort of 442 patients with acromegaly from a single-center in Mexico City, the standardized mortality ratio (SMR) was similar to that seen in the general population, but among 22 patients who died during the follow-up, cancer was the most common cause of death, and it was a significant predictor of mortality (27). Malignancies were also an independent predictor of mortality in a recent Italian multicenter study with 1512 patients, in which reduction of SMR was linked to the disease control (33). These are novel, unexpected findings, contrasting with all previous observations that cancer does not predict mortality in acromegaly, and that vascular and respiratory diseases are the leading causes of death. It remains to be further elucidated if a change in factors influencing mortality in acromegaly will occur in this new era where a higher proportion of patients live longer and have their disease controlled by the multimodal therapeutic approach and careful management of comorbidities.

Specific types of cancer

Over the years, a wide diversity of cancers has been described in association with acromegaly, including neoplasms of the gastrointestinal tract, thyroid, breast, lung, prostate, skin, soft tissues, brain, bone and lymphohematopoietic system (4, 10, 11). In the pioneering study by Mustacchi and Shimkin (12), the main tumors found were lung carcinomas in men and breast and endometrial adenocarcinomas in women. Interestingly, no colon cancer was recorded. Since then, CRC has become the spotlight with a still unsolved debate on the exact extent of its risk in acromegaly. Similarly, a high prevalence of thyroid cancer has been suggested by several investigators in the past years (24, 26), and these two malignancies are discussed in more detail below. Despite biological evidence and epidemiologic data from the non-acromegalic population suggesting an elevated risk of breast cancer in subjects in the higher IGF1 quartiles, in acromegalic women such an association has not convincingly been demonstrated in any large epidemiological series. The same observation applies to prostate cancer in acromegalic men and lung cancer in both sexes (4, 5, 6, 7, 8, 9).

Colorectal cancer

The strongest and most controversial debate on the link between acromegaly and cancer is, undoubtedly, related

Review	C L Boguszewski and J Ayuk	Acromegaly and cancer	175:4	R150
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to CRC. In most developed countries, CRC is the third most commonly diagnosed malignancy and, worldwide, is the fourth leading cause of cancer-related deaths, which was slightly more predominant in men than in women (31). CRC incidence, mortality and trends have shown significant variations both regionally and across countries, with numbers rising in many low- and middle-income countries or decreasing or maintaining stable in the most developed countries, where the rates remain among the highest in the world (31). Although the risk of CRC increases with age, the incidence of both hereditary and sporadic forms is increasing gradually per year in individuals younger than 50 years (34). Genetic, ethnic, environmental, and especially dietary factors are important determinants of colorectal carcinogenesis (35, 36). CRC most often begins as precancerous polyps, and it is assumed that a malignant transformation takes approximately 10–15 years to occur (7). The impact of all these factors known to influence the development of CRC in the general population should be taken into account when epidemiologic studies are carried out in specific populations.

From the 1970s to the beginning of 2000s, a multitude of case reports, small retrospective series, and a dozen of prospective studies have suggested an increased incidence of colonic precancerous polyps and adenocarcinomas in patients with acromegaly. Considering four case–control cohorts where at least 100 patients were examined, the prevalence rate of adenomatous polyps varied from 12 to 26%, which was considered higher than expected in three studies (37, 38, 39) and not different from the controls in one (40). Increased risk for CRC was observed in two series (38, 39), with prevalence rates around 4–5% and odds ratios (ORs) and 95% confidence intervals (CIs) of 4.9 (1.1–22.4) and 13.5 (3.1–75). Two of three large population-based retrospective studies published in that period found higher SIRs (3.1 (95% CI: 1.7–5.1) and 2.6 (95% CI: 1.6–3.8)] for CRC in acromegaly patients (16, 21), but in one study, an estimated SIR of 1.68 (95% CI: 0.87–2.93) was found, which was not associated with an increased risk (18). Altogether, these three large population-based studies showed a two-fold increase in CRC risk. As expected, the interpretation and implications of these results clearly differed among leaders in the field. One side claimed that the evidence was strong and acromegaly patients should be considered as a high-risk group for the development of this neoplasia (7, 16, 21). The other side pointed out to several biases in the studies, particularly the lack of appropriate age-, sex- and environmentally matched controls, which could have overestimated the risks (11, 40).

From this point of view, acromegaly patients have risks just above those for average-risk individuals and should not be aggressively screened (9).

A meta-analysis including nine controlled studies, with no significant heterogeneity or publication bias among them, was published in 2008 (41). In total, data from 701 acromegaly patients and 1573 controls were retrieved, and the results showed a significantly increased risk of colon adenomas and colon cancer in the acromegaly group compared with controls, with ORs of 2.5 and 4.3 respectively. By contrast, two of the more recently published population-based studies did not find any excess risk of CRC in acromegaly (23, 28); however, in the Finnish cohort, the authors observed three cases of CRC vs 0.7 expected after 5 years of follow-up (SIR4.44, 95% CI: 0.91–13.0) among patients with poor treatment results (23).

Besides all caveats in investigating overall cancer incidence in acromegaly population, there are specific problems to assess the risk of CRC in these patients. About 35–68% of the adenomatous polyps in acromegaly are right-sided lesions, situated in the ascending or transverse colon, which means that a full colonoscopy is required to precisely estimate its prevalence (4, 7, 10, 42). This requirement is commonly not fulfilled in acromegaly patients due to inadequate bowel preparation, increased colonic length, and high frequencies of complex looping in different colonic segments. However, these technical obstacles may increase the risk of serious procedure-related complications such as pain, perforation and bleeding, affecting the balance between benefits and risks of screening colonoscopy policies (9). Certainly, colonoscopy in acromegaly is a procedure for well-experienced endoscopy staff.

Age-related risk for polyps and CRC is another controversial issue, with some studies (39), but not all (40), showing a significantly higher number of acromegaly patients presenting lesions at younger ages in comparison with controls. The acromegaly-associated colonic lesions exhibit other peculiarities. Adenomatous polyps seem to be larger, multiple and more dysplastic than in non-acromegaly patients, all characteristics associated with higher risk for a malignant progression (42). They are also more common in men, in patients with a disease duration longer than 5 years, in those with three or more skin tags, and in cases with a family history of colonic polyps (4, 11). When a polyp is found, there is around 25–41% chance of recurrence within 3 years, and the risk of new adenomas is related to the presence of polyps at the initial colonoscopy and persistently elevated GH and IGF1 levels (43). By contrast, normal initial colonoscopy

combined with controlled acromegaly highly predicts a negative follow-up exam. With so many variables at play, it is not surprising that the recommendations for screening and follow-up of colonic lesions in acromegaly differ from one place to another.

Thyroid cancer

In a review of 11 series published before 2004, thyroid cancers represented 3.1% of malignant events in acromegaly, a percentage considered similar to or slightly higher than the normal (4, 10). Three large-scale studies published in that period found estimated SIRs (95% CIs) of 4.3 (0.2–21.4), 2.5 (0.07–14.1) and 3.7 (1.8–10.9), with only one to three acromegaly patients in each cohort harboring thyroid cancer (16, 18, 21). A meta-analysis of these three large studies resulted in a SIR of 3.6 (95% CI: 1.6–8.1). However, after 2004, a group of 11 small studies, including 125 acromegaly patients at most who were under investigation for thyroid disease, revealed 73 thyroid cancers (68 papillary and 5 follicular) in a total of 1041 patients, giving a prevalence of 7%, more than double compared with the older period (24, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53). The number of affected patients in these series varied from 3 to 15. In this period, two large studies were published. In one of them (23), six thyroid cancers were seen in 331 patients, with an estimated SIR significantly higher both in men (28.6, 95% CI: 5.9–83.5; three cases) and in women (8.8, 95% CI: 1.8–25.9; three cases). In the second study (28), three cases of thyroid cancer in 446 patients were found, resulting in a nonsignificant estimated SIR of 2.0, with a large 95% CI spanning from 0.4 to 5.8, due to the low number of observed and expected cases. Additionally, a meta-analysis involving five case–control studies found an OR of 7.5 (95% CI: 2.8–21.9) and concluded that thyroid cancer risk is significantly increased in acromegaly (54).

At first glance, it seems that thyroid cancer risk in acromegaly has increased considerably in the last decade, but this is unlikely (55, 56, 57). A cross-sectional analysis comparing a cohort of acromegaly patients with a matched control group usually results in overstated estimates, reflecting the underlying low incidence of the malignancy in the general population (9, 28). In this context, minimal changes in incidence may lead to a dramatic change in relative risk. Nodular goiter is a highly prevalent disorder, and many individuals in the general population have asymptomatic thyroid malignancy (58). In several studies, all acromegaly patients were subjected to a thyroid ultrasound at diagnosis, without the inclusion of

a comparative group or with the inclusion of unmatched controls. Moreover, criteria for indication of fine-needle aspiration biopsy varied among the studies, and in some instances have not followed the guidelines recommended for investigation of thyroid nodules (58). Consequently, there are many examples of micropapillary carcinomas and incidentally diagnosed tumors in these series whose natural history and impact on acromegaly survival is unknown. This observation is in line with studies in the general population, suggesting that the apparent increase in thyroid cancer incidence can be attributed to a screening effect linked to the use of modern diagnostic tools, which has produced a high number of ‘incidentally’ discovered less aggressive thyroid tumors (55, 56, 57).

Thyroid cancer behavior in acromegaly does not differ from that in non-acromegaly patients, exhibiting good prognosis and low mortality rate, with only a few reported cases of aggressive, multifocal or anaplastic tumors (4, 7, 9, 10, 11). The frequency of *BRAF* mutations is not increased, and it might be even decreased, in papillary thyroid cancer associated with acromegaly (51, 59).

Disease activity

The role of the GH and IGF1 in tumorigenesis has been extensively investigated in states of GH excess and GH deficiency. There is substantial evidence from *in vitro* and *in vivo* studies that GH and IGF1 stimulate cell proliferation, differentiation and motility, and inhibit apoptosis, both in normal and in tumoral tissues. By contrast, the GH-dependent IGF-binding protein 3 (IGFBP3) promotes apoptosis, regulates IGF1, and exerts antiproliferative effects (5). In the general population, circulating IGF1 levels are positively associated with the risk for CRC, breast, thyroid and prostate cancers, whereas IGFBP3 levels are negatively associated with prostate and postmenopausal breast cancers (6, 60). Humans with congenital GH and IGF1 deficiencies caused by GHRH receptor or GH receptor mutations are protected against cancer (61, 62). Although all these data are very convincing on the role of GH-IGF axis in tumorigenesis, it is a mistake to simply extrapolate these findings to acromegaly.

Acromegaly is characterized by a prolonged and excessive secretion of GH, which, in turn, induces both IGF1 and IGFBP3 production, resulting in a dysregulated, unpredictable balance of cell cycle regulation, characterized by signals for cell growth competing with signals for cell death (4, 8, 11). The ultimate consequences of these antagonistic mechanisms are the basis for concerns and

Review	C L Boguszewski and J Ayuk	Acromegaly and cancer	175:4	R152
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disputes on the cancer risks in patients with active acromegaly. As previously discussed, the association between GH and IGF1 levels, the duration of the acromegaly, and the presence of malignancies, especially CRC and thyroid cancer, is still an unsolved issue. There is some evidence that persistence of posttreatment high-serum GH and IGF1 levels is associated with the appearance of new colonic adenomas, and possibly CRC, particularly in patients with a previously abnormal colonoscopy (43). It is unclear if a relationship between thyroid volume, duration of the disease and hormone levels exists (56). Recently, the German Acromegaly Registry, which included retrospective and prospective data collected at 57 specialized endocrine centers throughout Germany, could not find significant associations between any type of cancer, disease duration or disease activity (28). Taken together, these findings suggest that the excess GH and IGF1 seen in acromegaly play a modest role in tumorigenesis, and if any link exists between acromegaly and cancer, the interplay of other risk factors needs to be considered (Fig. 1).

Genetic and epigenetic events

Most GH-secreting pituitary adenomas are sporadic tumors, but genetic predisposition can account for a minority of cases. Familial syndromes associated with acromegaly include multiple endocrine neoplasia type 1 (MEN 1), MEN 4, McCune–Albright, and Carney complex. Moreover, germline mutations in the aryl hydrocarbon receptor-interacting protein (AIP) gene and X-chromosomal microduplication have been linked to pituitary adenomas (1). There are also reports on acromegaly patients harboring several different tumors where a genetic defect was suspected but not identified (63).

It has been hypothesized that genetic–epigenetic factors predisposing to the development a GH-secreting pituitary adenoma may also predispose to the development of different benign and malignant tumors (10). The rationale for this idea originates mainly from studies using the Swedish Family-Cancer Database, which found a significant association between pituitary adenomas with nervous system hemangiopericytomas, leukemia, CRC and breast cancer, in addition to some other tumor types, using parents and sibling of probands (64). It is unknown from these results the proportion of cases occurring in the setting of familial syndromes, but most of the described tumors have not been associated with MEN, McCune–Albright, or Carney complex. Experimental models have

also been used to support this hypothesis, providing a link between environmental factors and common epigenetic events taking part in the development of pituitary adenomas and many other tumors, such as breast, prostate, colon, liver and lung (10, 65).

In some large-population series, a significant number of patients were excluded from the analysis because the diagnosis of cancer preceded that of acromegaly, which certainly affected cancer risk estimates in the studies (16, 18). The exclusion was justified as the idea behind was to investigate whether excessive hormone secretion in acromegaly was the cause of tumor development. However, the possibility that acromegaly and cancer share common genetic–epigenetic links has raised some questions about the methodology of the studies. The German Acromegaly Registry has shed some light on the problem (28). The registry includes 445 acromegaly patients, with 42 diagnosed with cancer. The authors estimated SIRs at three different observation times: i) cancer incidence from birth onward, ii) from the diagnosis of acromegaly, and iii) from the time beginning 8 years before diagnosis. Only four patients were diagnosed with cancer more than 8 years before being diagnosed with acromegaly, and SIRs were similar at different observation times. These results imply that genetic–epigenetic factors do not play an important role on cancer risk in acromegaly.

Aging and morbidities

Patients with acromegaly now live longer, and cancer risk is age dependent. This means that age-related cancer incidence and mortality, previously not clinically apparent in acromegaly, might be unmasked from now on. In agreement with that, two recent studies have shown that mortality in acromegaly can be successfully reduced with current therapies, and in both of them, cancer was the most common cause of death, and it emerged as an independent predictor of mortality (27, 33).

The influence of acromegaly-associated morbidities in cancer risk is another point of interest. Obesity and diabetes are associated with an increased incidence and mortality from malignancies in the general population, including CRC, breast, prostate and thyroid cancers, among many others (66). There are several potential factors to explain the link between obesity, diabetes and cancer, including insulin resistance, hyperinsulinemia, high IGF1, hyperglycemia, dyslipidemia and abnormalities of gut microbiome (66). Noteworthy, all these factors are also present in acromegaly, and they might act in line

amplifying the risk for cancer. In the normal population, a meta-analysis of 15 studies has shown that diabetes is associated with an increased risk of CRC, and it is tempting to speculate that the same rule applies to CRC development in acromegaly (67). In this direction, an increase in fasting insulin levels has been associated with an 8.6- to 14.8-fold increased risk of colonic adenomas in acromegaly (68). In one recent study from three Canadian referral centers involving 408 cases, acromegaly patients with diabetes developed malignant tumors almost 3 times as frequently as those without diabetes (69).

Guidelines

Several guidelines for acromegaly management have been published over the years, spanning from the pioneering article reporting the conclusions of an international workshop held in 1999 in Cortina, Italy, to develop a consensus for cure in acromegaly (70), to the most recent clinical practice guideline published on behalf of the Endocrine Society (71). In the older publication, it was stated that 'the association between acromegaly and malignant diseases is not resolved fully', whereas in the last one, published in 2014, we can read that 'the impact of acromegaly and its control on neoplasia risk and mortality is controversial'. These two sentences, 15 years apart, show that there are still questions to be answered in this matter.

In relation to breast cancer in acromegaly women and prostate cancer in acromegaly men, there is, in fact, a remarkable agreement among all experts and reported guidelines, pointing that surveillance should follow the same recommendations as for the general population (70, 71, 72). As expected, such harmony in opinion is not seen for CRC screening. The report from Cortina's workshop concluded that aggressive diagnostic vigilance is justified for CRC in acromegaly, recommending pan-colonoscopy at diagnosis to all patients, which should be periodically repeated according to individual risk factors, such as the presence of polyps, skin tags and family history (70). Further reports from the Acromegaly Consensus Group advocated, as a 'strong recommendation (SR)', to perform colonoscopy at diagnosis in all patients (73). By contrast, a statement from a joint conference of the Growth Hormone Research Society and the Pituitary Society, published in 2004, stated that colonoscopy should be undertaken in patients with acromegaly only at the age of 50 years, according to conventional guidelines for CRC screening (72). Other groups have claimed that initial

surveillance should begin earlier in acromegaly, at the age of 40 years, for early detection of precancerous polyps (7, 42, 43). In the Endocrine Society guidelines, screening colonoscopy was suggested (rather than recommended) at diagnosis for all acromegaly patients, reflecting the fact that the recommendation was categorized as being weak with low quality of evidence (71). Perhaps, the answer to reconcile the different views and to attain an optimal risk/benefit approach is on 'the middle way'. There is little evidence to justify colonoscopy at diagnosis for acromegaly patients younger than 40 years, whereas there is no reason for not doing it in patients over 50 years, as adenoma excision at this age reduces CRC rates in average-risk individuals, and acromegaly risks are just above the threshold for those individuals (4, 9, 74). In the age group of 40–50 years, the decision should consider cancer epidemiology at each setting and the presence of risk factors. In places where the skill of endoscopic team is an issue, other safer screening procedures, as computed tomographic colonography, may be considered as an option (74, 75, 76).

For acromegaly patients with a normal initial colonoscopy and controlled disease, the follow-up is the same as for the general population. If a polyp is detected in the first examination, there is a good agreement that a second colonoscopy has to be done in an interval of 3–5 years, depending on the number, size and histology of the resected lesion. The interval for a second exam in patients with a normal initial colonoscopy and persistently elevated GH and IGF1 levels is controversial, but 5 years seem to be a reasonable approach (42, 43, 73).

Despite several studies in the last decade showing that thyroid cancer is one of the most commonly detected malignancies in acromegaly, the majority of guidelines do not say a word about it. The exception is the report from the Endocrine Society, which stated that thyroid ultrasound should be offered for patients with a palpable thyroid nodule (71). This is also our view, as there is no evidence that an aggressive and systematic approach to detect small, asymptomatic, low-risk, thyroid malignant nodules has any impact on the mortality rates of acromegaly patients and, indeed, might contribute to unnecessary morbidity and poorer quality of life.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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