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ORIGINAL ARTICLE – COLORECTAL CANCER

Adrenal Incidentalomas During Diagnostic Work-up of Colorectal Cancer Patients: What is the Risk of Metastases?

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ABSTRACT

Background. Adrenal incidentalomas (AIs) are regularly discovered on staging computed tomography (CT) of patients with colorectal cancer (CRC). Although CRC is considered unlikely to metastasize to the adrenal gland, it is not known how often an AI appears to be a CRC metastasis. This causes a diagnostic dilemma for many patients with newly diagnosed CRC. This study aimed primarily to describe the incidence of AIs and adrenal metastases in CRC patients.

Methods. A single-center cohort of 475 consecutive patients with newly diagnosed CRC was defined. Retrospectively, all radiology reports and multidisciplinary team meeting reports were assessed for the presence of adrenal abnormalities. All AIs shown on staging CT were reevaluated for the purpose of this study, and the sizes of these adrenal glands were determined. Based on the CT reevaluation, follow-up imaging, and clinical follow-up assessment, conclusions on the presence or absence of adrenal metastases were drawn.

Results. The incidence of AIs in this CRC patient cohort was 10.5% (50/475). In 96% (48/50) of the patients with AIs, adrenal metastases could be ruled out. No solitary adrenal metastases were encountered. In two patients who had widespread systemic disease without curative treatment options, the AIs were considered to be adrenal metastases (cohort incidence, 0.4%).

Conclusion. This is the first study to report on adrenal incidentalomas in CRC patients. In newly diagnosed CRC patients without disseminated disease, AIs can be considered benign, and no additional imaging is indicated to rule out adrenal metastases in this group.

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During diagnostic workup for patients with newly diagnosed colorectal cancer (CRC), adrenal incidentalomas (AIs) are frequently discovered on staging computed tomography (CT) of the abdomen. An AI is defined as an adrenal mass without clinical symptoms detected serendipitously during radiologic examination for indications not related to suspicion of adrenal disease.[1]

The prevalence of AIs in radiologic studies of the general population ranges from 0.2 to 7%, and the detection rate increases with age.[2] Autopsy studies describe a prevalence of 1–8% for adrenal masses not apparent clinically.[3,4]

The differential diagnosis of AI includes many entities, although the vast majority of true AIs in unselected patient groups are lipid-ridge non-hyperfunctioning adrenocortical adenomas.[5] Less common causes for adrenal abnormalities are subclinical hypercortisolism (Cushing's syndrome), pheochromocytomas, adrenal cysts, metastases, aldosteronomas, myelolipomas, ganglioneuromas, and adrenocortical carcinomas, with incidences varying between 0.2 and 6%.[4,5] Most likely, the number of clinically relevant entities found after further investigation of AIs is decreasing because improved CT technology increases the ability to detect smaller, more likely benign lesions.

In patients with newly diagnosed CRC, AIs are regularly encountered as well. It is not known how often these AIs appear to be CRC metastases. In general, CRC primarily disseminates to the liver, lungs, or peritoneum, and is not likely to metastasize to the adrenal glands. Autopsy reports of patients with metastasized CRC do describe adrenal metastases, but isolated CRC metastases to the adrenal gland are exceptional.[6]

The absence of evidence indicating AIs in CRC patients causes a diagnostic dilemma for many patients with newly diagnosed CRC and regularly leads to discussions in multidisciplinary team (MDT) meetings. Is it clinically and prognostically relevant to obtain further diagnostic imaging to exclude adrenal metastases? Or should the AI be ignored, with the conception that CRC primarily does not metastasize to the adrenal glands?

To address these questions, this study first aimed to investigate the incidence of AIs and adrenal metastases in patients with newly diagnosed CRC. Second, the study aimed to determine the standard sizes of normal adrenal glands and AIs to improve adrenal gland interpretation and clinical decision making during MDT meetings.

METHODS

In Northwest Clinics, a regional high-volume CRC center in the Netherlands, 475 consecutive patients with newly diagnosed CRC in the period between October 2013 and April 2015 were included in this study. The study had no exclusion criteria. For all the patients, an abdominal and pelvic CT scan was obtained for tumor staging as part of the diagnostic workup, and all the patients were discussed in the MDT meeting. The radiology reports and MDT meeting reports were retrospectively reviewed for the presence of adrenal gland abnormalities. The tumor-node-metastasis (TNM) staging system was considered as the reference standard, and as part of the local protocol, the aspect of the adrenal glands was documented in all staging CT reports.

All the patients were scanned on a multidetector CT with either 64 or 2 × 128 detectors. All the patients received iodinated contrast (Ultravist 300; Bayer Pharmaceuticals, Mijdrecht, Netherlands). A contrast dose program (p3T; Medrad, Maastricht, Netherlands) was used with every patient to calculate the contrast dose and the administration rate. All the patients were scanned with a delay of 70 s.

For the purpose of this study, the staging CT images of all the patients with an identified AI were reviewed a second time by an experienced radiologist with 14 years of experience reading abdominal CTs. This reader was blinded to the former CT results and to follow-up outcomes. To characterize the AIs, the radiologist scored whether the adrenal gland was diffusely thickened, suggesting adrenal hyperplasia, or whether it included a well-defined nodular lesion, most likely suiting a non-hyperfunctioning adrenocortical adenoma. Furthermore, to assess the size of normal and hyperplasic glands in this cohort, the body together with the medial and lateral adrenal limb were measured according to Vincent et al.[7] who in 1994 published the only available study on standard adrenal gland size measurements (Fig. 1).

All the patients had clinical follow-up assessment, and in almost all cases, abdominal imaging was performed during the follow-up assessment as well. The AIs were considered not to be colorectal metastases if (1) the adrenal gland magnetic resonance image (MRI) in the opposed phase showed no characteristics of metastases, (2) if the positron emission tomography (PET)-CT showed no adrenal 18-fluorodeoxyglucose uptake, (3) if a repeated abdominal CT after at least 3 months showed no growth of the AI, or (4) if the patient at the end of the follow-up period did not show colorectal metastases. In case of doubt or absence of follow up imaging, the patient's radiologic and MDT reports were assessed by a jury panel consisting of two surgeons and one radiologist.

The institutional ethics committee waived the need to obtain informed consent for this retrospective study. Data were analyzed with the statistical package SPSS version 20 (SPSS Inc., Chicago, IL) for Windows.

RESULTS

After a review of all the staging CT scan reports and the MDT meeting report, adrenal abnormalities were documented for 56 of the 475 CRC patients. Six patients were excluded from the analysis. In four of these patients, the AIs were already present on earlier radiologic imaging and did not show any changes or growth. In the two remaining patients, the adrenal glands did not appear abnormal when reviewed on adequate multi-planar reconstructions (MPRs) for the purpose of this study.

After exclusion of the six patients, the incidence of AIs in this cohort of CRC patients appeared to be 10.5% (50/475). The selected group of patients with AIs consisted of

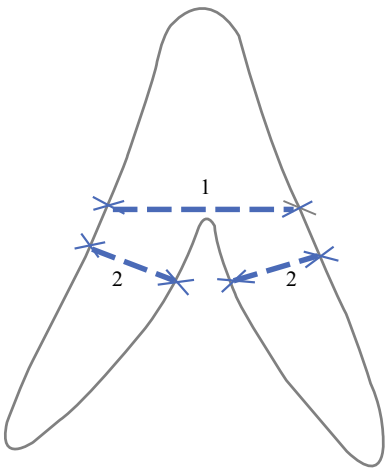

FIG. 1 Adrenal gland configuration on computed tomography

30 male and 20 female patients, and the mean age was 69 ± 10.2 years (range 47–91 years). Of the 50 selected patients, 17 (34%) had bilateral AIs, and 39 (78%) received an operation with curative intent. The remaining 11 patients (22%) received either palliative chemotherapy or best supportive care. Further cohort characteristics are shown in Table 1. The mean clinical follow-up period for this patient cohort was 19.1 ± 9.9 months (range 1–36 months).

For 48 of the 50 patients with AIs (96%), adrenal metastases could be ruled out (Fig. 2). Two patients showed high suspicion for adrenal metastases. The first patient had a high-risk rectal carcinoma (cT3N2, invaded mesorectal fascia) with extensive mediastinal lymphatic and pulmonary metastases. The CT scan also showed a 34-mm right-sided adrenal lesion suspicious for metastasis. No adrenal biopsy for histolopathologic evaluation was performed due to the absence of clinical consequences. A new CT scan 2 months after the start of palliative chemotherapy showed progression in the amount of pulmonary metastases, growth of the right adrenal metastasis to 50 mm, and a new lesion in the left adrenal gland (size 45 mm) suspicious for metastasis.

In the second patient, the left adrenal gland was moderately suspicious of metastasis. The diagnostic workup for this patient showed both a large right-sided coloncarcinoma and a rectal tumor, irresectable liver metastases, and a 25-mm irregular lesion in the left adrenal gland, which was suspicious for adrenal metastasis. Biopsy was not performed. A repeat CT scan 2 months after the start of palliative chemotherapy showed growth of the liver metastases. The adrenal lesion had not changed. The consensus of the jury panel stated that the adrenal lesion should be interpreted as a colorectal metastasis, mainly because of the suspicious configuration on the CT scan.

TABLE 1 Oncologic characteristics of the CRC patients with adrenal incidentalomas (n = 50)

Cohort characteristics	No. (%)
Primary tumour	
Right hemicolon	12 (24)
Left hemicolon	18 (36)
Rectum	19 (38)
Right hemicolon + rectum	1 (2)
Tumour stage	
Stage I	9 (18)
Stage II	15 (30)
Stage III	14 (28)
Stage IV	12 (24)
Treatment	
Curative intent	39 (78)
Palliative chemotherapy/best supportive care	11 (22)

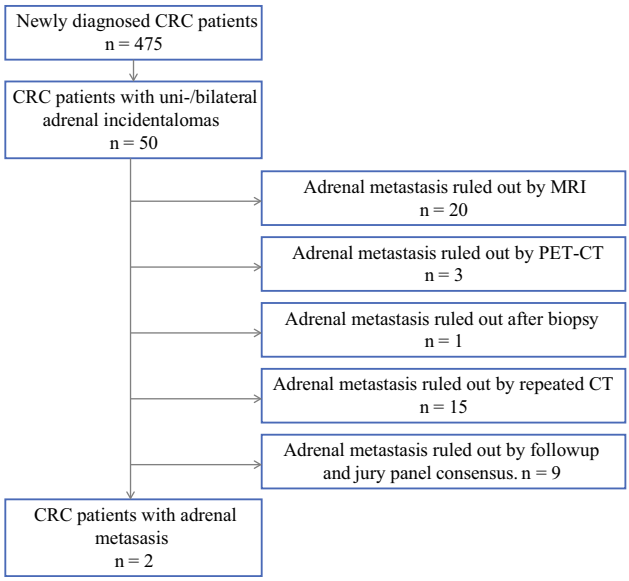

FIG. 2 Flow chart of adrenal incidentalomas in CRC patients

The remaining 48 patients did not have adrenal metastases, as shown in Fig. 2. After it was discussed in the MDT meeting, an MRI of the adrenal gland was obtained for 20 patients, which ruled out adrenal metastases in all cases. The presence of adrenal metastases was ruled out by PET-CT for three patients and by negative biopsy for one patient. For 15 patients, repeated CT scans ruled out adrenal metastasis. In approximately half of these cases, the repeated CT was performed primarily for a reason other than the AI, but showed no growth or other characteristics suspicious for metastases. The mean time until this repeated CT was 160 days. For nine patients, no further imaging of the adrenal glands was available. However the panel unanimously decided that an adrenal metastasis was highly unlikely due to the radiologic configuration of these AIs, the tumor stages, and the follow-up outcomes.

Overall, the incidence of adrenal metastases in this cohort of CRC patients was 0.4% (2/475). Primary synchronous dissemination to the adrenal gland without any other metastases did not occur. During the follow-up period, none of the patients without AIs and none of the 48 patients with benign incidentalomas experienced the development of metachronous adrenal metastases.

Radiologic reevaluation of the staging CT scans of the patients with AIs showed well-defined adrenal nodular lesions suiting lipid-ridge adrenocortical adenomas, adrenal hyperplasia, unilaterally normal adrenal glands, and suspected CRC metastases. The distribution of these entities in this cohort is shown in Table 2. Although

TABLE 2 Distribution of adrenal incidentalomas and their underlying entities

	Number of patients	Number of adrenal glands
Adrenal incidentalomas	50	67
Unilateral adrenal incidentaloma	33	33
Unilateral adenoma	22	22
Unilateral hyperplasia	11	11
Unilateral metastasis CRC	1	1
Bilateral adrenal incidentaloma	17	34
Bilateral adenoma	9	18
Bilateral hyperplasia	4	8
Bilateral metastases CRC	1	2
Adenoma and hyperplasia	2	4
Adenoma and metastasis CRC	1	2
Adenoma	34	43
Hyperplasia	17	21
Metastasis CRC	2	3
Hyperfunctional lesions	0	0

biochemical analysis was not a part of the standard AI management in this cohort, assessment of the patient charts showed no hyperfunctional adrenal diseases. Neither were adrenocortical carcinomas or any other clinically relevant entities encountered during the follow-up period.

Finally, the adrenal gland sizes in this CRC patient cohort were measured during radiologic reevaluation. In 33 patients, a normal adrenal gland was seen unilaterally, with a mean adrenal gland body size of 6.4 mm, a medial limb size of 3.7 mm, and a lateral limb size of 3.6 mm (Table 3). The 21 hyperplastic adrenal glands were almost twice the size of the normal adrenal glands. The mean size of the 43 adenomas within the adrenal glands was 18.3 mm (range 7–34 mm), and 39.5% of the adenomas were located in the body of the adrenal gland, 39.5% in the medial limb, and 21% in the lateral limb.

DISCUSSION

To our knowledge, this is the first study to report on AIs in a specific cohort of CRC patients. The incidence of AIs appeared to be 10.5% on abdominal staging CT, which is higher than in other AI studies.[3,4] A possible explanation is the relatively high mean age in this cohort because the incidence of AI is known to increase with age.[2] Furthermore, in contrast to some older AI studies, improved CT quality might have resulted in a higher detection rate of smaller adrenal abnormalities. Also, the radiologists had to mention the aspect of every adrenal gland by protocol, and the focus on adrenal gland enlargement may have been more specific in this group of oncologic patients than in the general population.

In the group of patients with AIs, 96% of the underlying entities were benign adrenocortical adenomas or adrenal hyperplasias. None of these patients had symptoms of hormone excess. Only 4% of the AIs appeared to be a CRC metastasis, resulting in a cohort incidence of 0.4%. These

TABLE 3 Size measurements of the adrenal glands

	Number of adrenal glands	Mean size (mm) of body/med limb/lat limb	Standard deviation	Range
Normal adrenal gland	33	6.4/3.7/3.36	1.3/0.7/0.8	4–9[b]
Adrenal incidentaloma	67			
Adenoma[a]	43	18.3	7.4	7–34
Hyperplasia	21	10.6/8.3/7.5	3.6/2.9/3.0	3–20[b]
Metastasis CRC[a]	3	34.6	8.2	25–45

[a]The sizes of the adenomas and metastases within the adrenal glands were measured; the total size of the adenoma containing adrenal glands was not determined

[b]Range of the adrenal gland body sizes

patients already had stage 4 CRC with multiple liver, lung, and/or distant lymph node metastases, excluding curative treatment possibilities. The detection of the adrenal metastases therefore had no clinical consequences. Primary dissemination to the adrenal gland without other organ metastases did not occur. This agrees with the available literature showing only a few case reports and small case series on solitary adrenal CRC metastases.[6,8–13] These reports describe adrenalectomies for metachronous metastases, in which most patients had received adjuvant chemotherapy or other organ metastasectomies before detection of the adrenal metastases. Generally, the disease-free survival rate was low. Only one study reported on adrenalectomies for synchronous metastases. However, the three patients reported in that study underwent metastasectomies for other metastatic sites in the same procedure as well.[14]

To our knowledge, no studies have reported on synchronous adrenal oligometastases and they were neither detected in this study. This supports the plausible hypothesis that CRC does not cause synchronous adrenal metastases without other organ dissemination.

The second aim of this study was to determine the standard sizes of normal and abnormal adrenal glands. The CT showed a mean adrenal body diameter of 6.4 mm and limb diameters of 3–4 mm. The sizes of the normal adrenal glands were comparable with the results in the only other published study describing normal adrenal gland sizes on CT by Vincent et al.[7] in 1994. This study thus validated Vincent's standard adrenal gland measurements and provides a reference baseline for adrenal gland interpretation on CT in both clinical and research settings.

When the results of this study are considered, it should be kept in mind that this study had some limitations. First, a semantic remark can be made for readers of this article. Some previous studies have stated that AIs on imaging for staging of oncologic patients are not true AIs.[4] This can rightly be argued in the case of patients with malignancies originating from organs known to metastasize to the adrenal gland such as lung, kidney, and breast cancer. However, due to the low incidence of adrenal metastases in CRC patients, in our opinion, adrenal abnormalities found on staging CT can truly be seen as incidentalomas.

Second, attenuation of 10 or fewer Houndsfield units at CT, shown to be consistent with a benign adrenal mass,[15] could unfortunately not be used in this study as a parameter to exclude malignancy. For staging purposes, all patients received contrast with a delay of 70 s, whereas noncontrast images needed for attenuation measurements were not available.

Third, the presence of histopathologic analysis as a gold standard for showing the etiology of an AI might have strengthened the conclusions drawn from this study. Yet, in this cohort of AIs, adrenal metastases could be ruled out with sufficient reliability due to the follow-up assessment by radiologic imaging combined with an adequate clinical patient follow-up time. Therefore, the current acceptance of imaging as highly accurate makes histopathology unnecessary in the case of radiologic benign adrenal lesions.[16] Evaluation of hormone excess in patients with AIs fell beyond the scope of this study. Additional testing for diagnosis of unusual hyperfunctional adrenal entities such as hypercortisolism, pheochromocytomas, and aldosteronomas were obtained only occasionally in this patient cohort.

Apart from the management of AIs in CRC patients, the optimal diagnostic management of AIs in general remains controversial.[2] Clear guidelines are lacking. Unenhanced CT contrast washout analysis, FDG-PET uptake, and the chemical-shift artifact on MRI are widely used to distinguish between benign and other entities. However, the diagnostic value of individual imaging tests is based on limited evidence, and it remains unclear whether and when imaging should be repeated.[15–17]

For the application of additional tests to evaluate the presence of hormone excess, the guidelines of the European Society of Endocrinology in collaboration with the European Network for the Study of Adrenal Tumors can be used.[15] However, with the increasing rate for detection of small and more likely benign non-hyperfunctioning adrenal lesions, broad use of the suggested laboratory and imaging tests will lead to increased health care costs. Behbahani et al.[18] justly stated that in this era of cost containment and appropriate use of resources, it is undesirable to perform follow-up imaging for every low suspicious AI. Furthermore, from an ethical point of view, extensive investigations may lead to clinician and patient uncertainty, and repeated CT to possible unnecessary radiation exposure.[5] Further research for a tailored and cost-effective AI management strategy is needed.

In conclusion, this is the first study to report on adrenal incidentalomas in CRC patients. The incidence of AIs is high, but adrenal metastases are rare, and they occur only in patients with other organ metastases. In patients with newly diagnosed CRC but no disseminated disease, AIs can be considered benign and, no additional imaging is indicated to rule out adrenal metastases in this patient group.

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