Incidence and Etiology of New Liver Lesions in Pediatric Patients Previously Treated for Malignancy

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OBJECTIVE. The purpose of this study was to retrospectively evaluate the time course, cause, and imaging characteristics of all new liver lesions in pediatric patients with a previously treated malignancy.

MATERIALS AND METHODS. Our hospital cancer registry was used to identify patients between 1980 and 2005 who met the following criteria: solid tumor, survival > 2 years after diagnosis, no liver lesions at a posttreatment baseline, and cross-sectional imaging follow-up of > 2 years. Final dictated reports of all cross-sectional imaging examinations including the abdomen were reviewed for any mention of new liver lesions. Positive reports were followed by consensus review of the images and clinical data. Patients were divided into three groups: those with suspected or proven focal nodular hyperplasia (FNH), those with suspected or proven metastases, and those with other lesions. An exact Wilcoxon test was used to evaluate the differences between the groups.

RESULTS. Of 967 patients who met the initial inclusion criteria, 273 had adequate follow-up to be included in the study. Forty-six patients (16.8%) developed new liver lesions during the study period, and 14 of those 46 were classified into the FNH group (30.4%) and seven were classified into the metastasis group (15.2%). A significant difference was found in the median time to the development of FNH versus metastasis and other lesions (FNH, 92.9 months; metastasis, 43.2 months; other lesions, 18.5 months; p < 0.0001). A significant difference was also seen in the median length of follow-up between the groups (FNH, 115.6 months; metastasis, 57 months; other lesions, 50.8 months; p = 0.002). The imaging features of the groups also differed.

CONCLUSION. The most common liver lesion encountered in pediatric patients previously treated for malignancy was FNH, which occurred farther from the time of diagnosis and had different imaging characteristics from both metastases and other liver lesions.
Materials and Methods
A retrospective study was performed after approval by our medical center’s institutional review board. The registry of pediatric oncology patients treated at our institution was accessed to identify all patients diagnosed with malignancy between 1980 and 2005. Patients who met the following criteria were included in the initial study database: history of solid tumor, survival greater than 2 years from diagnosis of the initial malignancy, and no liver lesions either at diagnosis or on a posttreatment baseline imaging examination. Only patients with solid tumors were selected because this population has been the focus of several prior reports of liver lesions in pediatric oncology patients. The imaging records of the patients who met these initial criteria were further reviewed to identify those patients who received adequate imaging follow-up, which would allow them to be included in the final study database. Adequate imaging follow-up was defined as having at least one postbaseline cross-sectional imaging examination (CT and MRI) that included the entire liver. Patients with only a single imaging examination at the time of diagnosis were excluded from the study. Because this was a retrospective study that spanned 25 years, the examinations that met the inclusion criteria were performed on a variety of CT and MRI scanners using multiple different protocols. Demographic data and the number and timing of the imaging examinations were recorded for each patient. The final dictated reports of all CT or MRI examinations of the abdomen for each patient who met the inclusion criteria were then reviewed by one of two board-certified pediatric radiologists with 1 and 4 years of experience in pediatric radiology. The reports were evaluated for the mention of any new liver abnormality. Once a new liver abnormality was identified, the corresponding images and any relevant clinical documentation were reviewed by the two radiologists. All imaging was evaluated before review of any of the clinical data. Liver lesions were then classified by consensus into one of three categories: proven or suspected FNH, suspected metastases, or other lesions. Lesions were classified as a suspected or proven FNH if they had the following imaging characteristics: focal rounded or oval-shaped lesion, slightly hypointense to isointense signal on T1-weighted images, isointense to slightly hyperintense on T2-weighted images, and hyperenhancement on arterial or early portal venous contrast-enhanced images [8–10]. The presence or absence of a central scar and multiplicity were not used as imaging criteria for classification of lesions because previous studies have shown that these findings are not reliable for the characterization of FNH in pediatric oncology patients [5, 11]. In addition to the imaging characteristics, lesions classified as FNH were required to be either stable in size and appearance on follow-up imaging or have pathologic confirmation. Additionally, patients with lesions classified as FNH were confirmed to be clinically stable without evidence of other metastatic disease. Lesions were classified as metastases if they had any of the following characteristics: mass lesion that was rapidly increasing in size, clinical deterioration with evidence of other metastatic disease, or biopsy results diagnostic of metastases. Lesions that did not meet the imaging or pathologic criteria for the proven or suspected FNH or metastasis groups were classified into a third group designated “other lesions.”

Results
The oncology registry identified 967 patients who met the initial criteria for inclusion in the study. After querying the hospital electronic medical record system, 273 patients had adequate imaging follow-up and met the study inclusion criteria. All available abdominal CT and MRI reports for these patients were obtained and reviewed. For the final study population, 1816 reports were reviewed. The mean number of reports per patient was 6.7 (range, 1–43). After a review of the original imaging reports, 46 patients were identified who had developed a new liver lesion or lesions (16 girls and 30 boys; median age at initial cancer diagnosis, 37.8 months; range, 12.1–69.9 months). The incidence of new liver lesions in our patient population during the study period was 16.8% (46/273) (Table 1). On the basis of consensus review of the imaging, clinical data, and histopathologic results (when available), 14 patients were classified as having proven (4/14) or suspected FNH (10/14). All proven or suspected FNHs were hyperenhancing on early contrast-enhanced imaging (Fig. 1). The majority of patients with proven or suspected FNH had multiple lesions (12/14, 86%). In patients who underwent MRI, FNH lesions were slightly hyperintense compared with adjacent liver on T2-weighted sequences and showed arterial phase hyperenhancement (Fig. 1). Most lesions were isointense or remained slightly hyperenhancing compared with adjacent liver on the more delayed phases of contrast enhancement.

Seven patients were classified as having suspected or proven hepatic metastases.
Fig. 1—14-year-old boy treated 9 years previously for CNS malignancy who presented with new liver lesion pathologically proven to be focal nodular hyperplasia.

A, Axial contrast-enhanced CT image obtained because of clinical concern for appendicitis shows hyperenhancing lesion in left hepatic lobe (arrow).

B, Axial T1-weighted image shows lesion (arrow) is slightly hypointense compared with adjacent parenchyma.

C, Axial T2-weighted fast spin-echo image shows slightly hyperintense lesion (arrow) compared with background parenchyma.

D, Arterial phase image from axial liver acquisition with T1-weighted volume acceleration sequence shows brisk homogeneous contrast enhancement (arrow).

E, Axial T1-weighted contrast-enhanced image shows lesion (arrow) becomes isointense to background hepatic parenchyma in late portal venous phase.
proximately half of the patients classified in this group had multiple liver lesions (47/73, 57%). All metastatic lesions were hypodense on contrast-enhanced CT (Fig. 2). None of the patients with liver lesions classified as metastatic disease underwent MRI.

The remaining 25 patients were classified into the other lesions group. These patients had a variety of nonneoplastic lesions, including cysts, perfusion abnormalities, postsurgical or posttreatment effects, and stable but nonspecific subcentimeter lesions (Fig. 3). The specific types of lesions classified as other lesions are described in Table 2.

There was a significant difference (p < 0.0001) between the number of follow-up studies in the 46 patients with liver lesions (median number of examinations, 10; range, 2–27) and the 227 patients without new liver lesions (median number of examinations, 4; range, 1–43).

The median time to development of lesions was significantly longer in the FNH group (median, 92.9 months; range, 44.0–237.9 months) compared with both the metastasis group (median, 43.2 months; range, 17.5–59.5 months) and the other lesions group (median, 18.5 months; range, 0–291.6 months) (p < 0.0001 for both). There was no difference between the metastasis group and the other lesions group (p = 0.166). There was a significant difference in the length of follow-up between the groups. The median length of follow-up for the FNH group was 115.6 months (range, 57.2–337.5 months), which was significantly longer compared with both the metastasis group (median, 57 months; range, 23.2–129.6 months; p = 0.014) and the other lesions group (median, 50.8 months; range, 14.4–332.4 months; p = 0.002). There was no difference between the length of follow-up in the metastasis group and the other lesions group (p = 0.959). Of the 46 patients with lesions, there was not a significant difference between the three groups in terms of sex (p = 0.4862), age at diagnosis (p = 0.076), and number of follow-up imaging examinations (p = 0.495).

Discussion

Long-term survival rates in pediatric cancer, defined as survival greater than 5 years after diagnosis, have improved significantly over the past several decades [1]. With the increased survivorship, there has been a concomitant increase in follow-up imaging in these patients. The increased survival also brings with it an increase in the late effects of treatment with both chemotherapy and radiation therapy. In our experience, new liver lesions found on surveillance imaging in pediatric cancer patients often present a diagnostic dilemma because the liver is a relatively common site for metastatic disease as well as benign lesions such as FNH. Because of the concern for metastatic disease, patients with new liver lesions on imaging are often subjected to an invasive biopsy for histopathologic classification [11].

FNH is a benign lesion pathologically characterized by hepatocyte hyperplasia, often surrounding a central fibrous scar [12]. It is rare in the general pediatric population, with prior studies reporting an incidence of 2.25 per million [2]. The precise cause of FNH is unclear. One theory states that FNH may be related to a congenital or acquired hepatic vascular abnormality, which leads to secondary hyperplasia of hepatic parenchyma [12]. A second theory states that FNH may arise from vascular injury with resultant thrombosis and recanalization of vessels leading to hepatocyte proliferation [12, 13]. There is evidence that the increased incidence of FNH in patients who have been treated with chemotherapy is best explained by the latter theory because development of venoocclusive disease is a risk factor for the development of FNH [2, 4].

Imaging features of FNH on both CT and MRI have been previously described, mostly in adult populations. The diagnosis of FNH on CT can sometimes be challenging because FNH may enhance similar to adjacent liver parenchyma during the most commonly imaged portal venous phase of enhancement. During the arterial phase, however, FNH is typically hypoenhancing compared with adjacent hepatic parenchyma. On MRI, FNH is usually isointense to slightly hypointense on T1-weighted images and slightly hyperin-
tense on T2-weighted images. After administration of contrast material, FNH enhances avidly during the arterial phase of imaging and becomes iso- to slightly hyperintense on later contrast-enhanced images. Although a T2-weighted hyperintense central scar that shows delayed contrast enhancement is typically associated with sporadic FNH, this may be a less common appearance in FNH seen in long-term cancer survivors [5, 14].

The incidence of proven or suspected FNH in our population of long-term survivors of pediatric cancer was 5.1% (14/273), which was similar to prior studies of FNH and more than 100 times higher than the reported incidence of 0.045% in the general pediatric population [2]. Although other studies have shown an increased incidence of FNH in pediatric cancer survivors, those studies did not compare the incidence of FNH with other hepatic lesions in these patients [2–5, 10]. Because FNH is a benign lesion that does not require resection, it is important to determine the incidence of FNH compared with all liver lesions in long-term cancer survivors and to determine whether radiologists can distinguish between FNH and metastasis. To our knowledge, the study is the first to examine a large group of pediatric oncology patients and to describe the incidence and etiology of all liver lesions in that group, with a focus on reporting the incidence and imaging appearance of FNH compared with that of other liver lesions, including metastases.

In patients with a history of malignancy, the most pressing clinical dilemma is to differentiate benign and malignant (metastatic or recurrent) processes. The increased incidence of FNH in these patients contributes to this dilemma. In our study, 30% of all patients with new hepatic abnormalities (14/46) were classified as FNH, whereas only 15% (7/46) were classified as metastases. In every case, it was possible to distinguish FNH from metastases and other hepatic abnormalities on the basis of the imaging appearance of the different lesions. All of the FNH lesions in our study were hyperenhancing in the arterial or early portal venous phase of imaging after the administration of IV contrast material, whereas all metastatic deposits were hypoenhancing compared with adjacent liver parenchyma. In those patients who underwent MRI, the FNH lesions were isointense to the liver on T1-weighted sequences, slightly hyperintense on T2-weighted sequences, and hyperenhancing in the arterial phase of imaging after administration of contrast material. Overall, the imaging findings of FNH in our study were consistent with those previously reported in pediatric patients [5, 6, 8]. Although 86% (12/14) of patients with proven or suspected FNH had multiple lesions, this was not a distinguishing characteristic because hepatic metastatic disease also commonly presented with multiple lesions (4/7, 57%).

In addition to the different imaging appearance, the median time to develop an FNH was significantly longer than the median time to develop metastases (FNH, 92.9 months; metastasis, 43.2 months; \( p < 0.0001 \)). Prior reports have described similar findings, with several years between the initial diagnosis of malignancy and the development of FNH [2, 3, 5]. In one series, the mean time between initial cancer diagnosis and pathologically proven FNH was 14.4 years [5].

There are a few limitations to this retrospective study. First, the imaging follow-up in our study group was inconsistent, with some patients having several regular follow-up imaging studies and others having only one or two posttreatment examinations. The period of follow-up was also quite varied. It is possible that this variance would lead to a smaller than expected number of FNHs because patients with benign lesions may not be imaged as frequently or not at all. This potential bias would be less likely to affect the number of patients with new metastases because these patients would likely undergo imaging on the basis of the development of clinical symptoms.

The second limitation is that the study design may have introduced a selection bias regarding which patients underwent follow-up imaging studies. It is possible that the patients who were followed more closely with imaging may have been those who were at higher risk of developing metastatic disease or other clinical complications. This effect was decreased as much as possible by reviewing all abdominal CT and MRI examinations performed in cancer survivors over an almost 30-year period.

Third, we only directly reviewed the imaging studies of those patients who were reported to have a new liver lesion on the original dictated imaging report. It is possible that liver lesions may have been missed or incorrectly documented on the original imaging interpretation. Although this limitation may have affected the number of benign lesions, it is unlikely to have affected the number of metastases because metastatic disease would most likely progress over time and would become evident on follow-up imaging studies.

A fourth limitation is that we only had histologic proof in four of the 14 lesions classified as suspected or proven FNH. We attempted to mitigate this limitation by using diagnostic criteria described by other researchers as well as by evaluating the clinical and imaging follow-up for these patients [8–10]. In those patients with clinical and imaging stability coupled with typical imaging features of FNH, the classification of FNH could be made with relative certainty.

Finally, because the study group included a variety of different primary malignancies, the patients were also likely treated by a variety of different methods. For example, some patients included in the study may have been treated with surgical resection alone and might not have received chemotherapy. If so, these patients would not necessarily be at an increased risk for development of FNH compared with the general population. Because the purpose of our study was to define the incidence and cause of liver lesions across all long-term survivors of pediatric malignancy, we believe that including all patients, regardless of treatment modality, is appropriate. In addition, because of the relatively small number of liver lesions in relation to the number of different primary tumors represented in our population, we did not have the statistical power to compare the incidence of proven or suspected FNH, metastases, and other lesions between the different primary oncologic diagnoses.

The strengths of our retrospective study are the large sample size (273 patients) and the potential bias would be less likely to affect the number of patients with new metastases because these patients would likely undergo imaging on the basis of the development of clinical symptoms.

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The strengths of our retrospective study are the large sample size (273 patients) and the
long-term follow-up for the patients. All patients included in the study had survived for at least 2 years from their diagnosis, and most had survived longer. We had several patients who had regular imaging follow-up over the course of several years, with the longest follow-up interval being 337 months. The sample size and the length of the follow-up in these patients allow a more representative sample of all long-term pediatric cancer survivors.

In the future, with continued advances in the care of pediatric oncology patients, more and more patients will be classified as long-term survivors. Awareness of the increased incidence of liver lesions in these patients will become increasingly important to radiologists. Advances in imaging techniques, such as the use of hepatocyte-specific contrast agents, may allow more confident differentiation between hepatocyte-containing lesions, such as FNH, and other liver lesions [14, 15]. Knowledge of the increased incidence of FNH and the differentiating features between FNH and metastatic or recurrent malignancy in these patients can aid the radiologist in helping to define the management and imaging surveillance of pediatric cancer survivors.

**Conclusion**

Proven or suspected FNH was the most common new hepatic lesion in pediatric patients who had survived at least 2 years from the diagnosis of a malignancy and was twice as common as hepatic metastases in our patient population. FNH was reliably distinguished from metastatic disease on the basis of its characteristic imaging appearance. In every case, FNH had intense arterial phase enhancement whereas metastatic disease enhanced less than the adjacent liver. In addition to its characteristic imaging appearance, FNH occurred significantly later after the diagnosis of malignancy than after a diagnosis of metastatic disease. It is increasingly important for radiologists to be able to identify the different hepatic lesions in pediatric patients as the number of long-term cancer survivors increases.

**References**