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의학 석사 학위 논문

간의 국소 결절 과형성의 수술의 적응증;

48예의 단일 기관 연구

Surgical indications for focal nodular hyperplasia of the liver;

Single-center experience of 48 adult cases

울 산 대 학 교 대 학 원

의 학 과

정 진 민

간의 국소 결절 과형성의 수술의 적응증;

48예의 단일 기관 연구

지도교수 황 신

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정진민

정진민의 석사 학위 논문을 인준함

심사위원 정 동 환 인

심사위원 황 신 인

심사위원 송 기 원 인

울 산 대 학 교 대 학 원

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English abstract

Background : Focal nodular hyperplasia (FNH) is one of the most common benign tumors of the liver. There is still lack of evidence on surgical indication of FNH. This study intended to analyze the surgical indications of FNH.

Methods : We analyzed the 48 cases of FNH diagnosed after hepatic resection

Results : The common reasons leading to surgical resection were diagnostic uncertainty (n = 31) and persistent symptoms (n = 8). Percutaneous biopsy was performed in 14 patients and diagnosed as FNH in 9, hepatic adenoma in 1, hepatocellular carcinoma in 1, plasmacytoma in 1, angiosarcoma in 1, and atypical hepatocellular proliferation in 1. Minor hepatectomy (n = 37) was performed more frequently than major hepatectomy (n = 11). Open hepatectomy (n = 29) was performed more frequently than laparoscopic hepatectomy (n = 19), but laparoscopic and minimally invasive surgery was frequently performed during the late phase of the study period. Postoperative surgical complications occurred in two patients (4.1%).

Conclusion : FNH can be diagnosed by imaging studies, but surgical treatment can be considered if there is diagnostic uncertainty or persistent symptoms.

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Table 1. Patient profiles

Variables	
Age, median (range)	43 (21~68)
Sex, n (%)	
Female	20 (41.7%)
Male	28 (58.3%)
Use of oral contraceptive, n (%)	
Yes	0 (0%)
No	48 (100%)
Reasons for initial imaging study, n (%)	
Symptom	18 (37.5%)
Abnormal liver function test	3 (6.3%)
Regular check-up	23 (47.9%)
Routine cancer surveillance	4 (8.3%)

Table 2. Reasons for receiving surgical treatment

Variables	n (%)
Persistent symptoms	8 (16.7%)
Diagnostic uncertainty	31 (64.6%)
Others	9 (18.7%)

Table 3. Operative profiles

Variables	n (%)
Extent of hepatic resection, n (%)	
Major hepatectomy	11 (22.9%)
Minor hepatectomy	37 (77.1%)
Type of operation, n (%)	
Open surgery	29 (60.4%)
Laparoscopic surgery	19 (39.6%)
Morbidity, n (%)	2 (4.1%)
Mortality, n (%)	0 (0%)

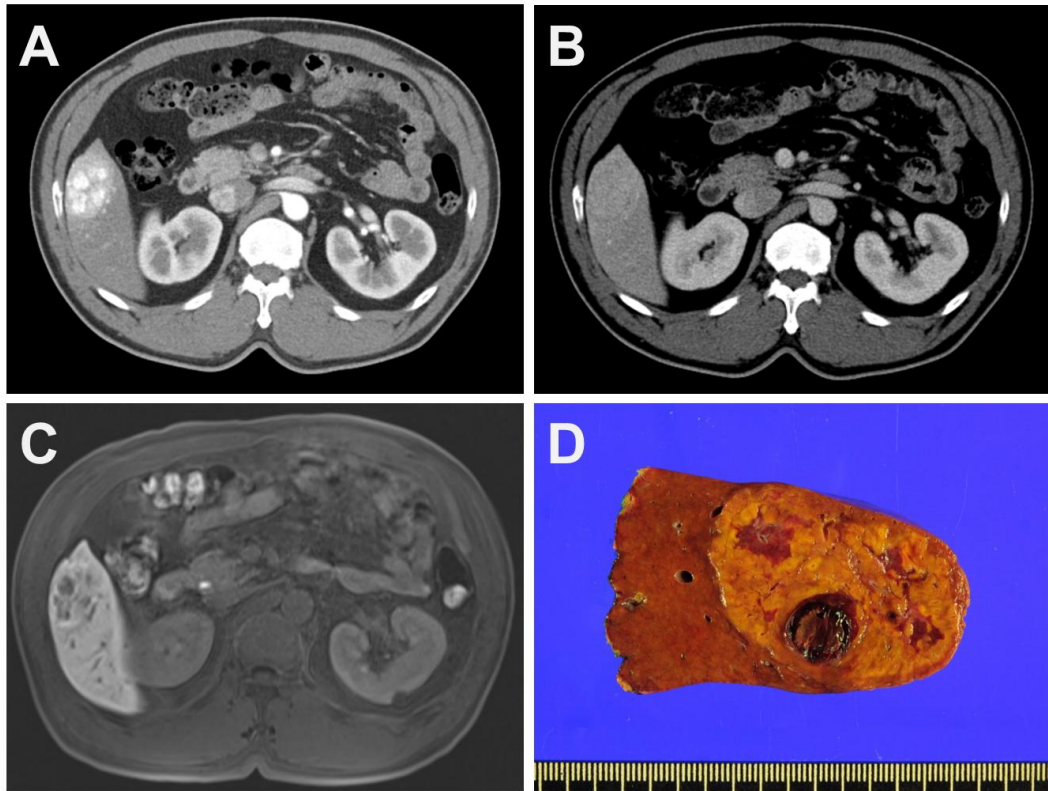


Figure 1. Preoperative imaging and operative findings of a 58 year-old male patient showing focal nodular hyperplasia (FNH) with angiosarcoma component. Computed tomography (A: arterial phase and B: portal phase) and magnetic resonance imaging (C) suggested FNH or adenoma. Percutaneous biopsy finding suggested angiosarcoma. The pathological examination of the resected specimen (D) revealed that the final diagnosis was FNH with multifocal well-differentiated adenomas.

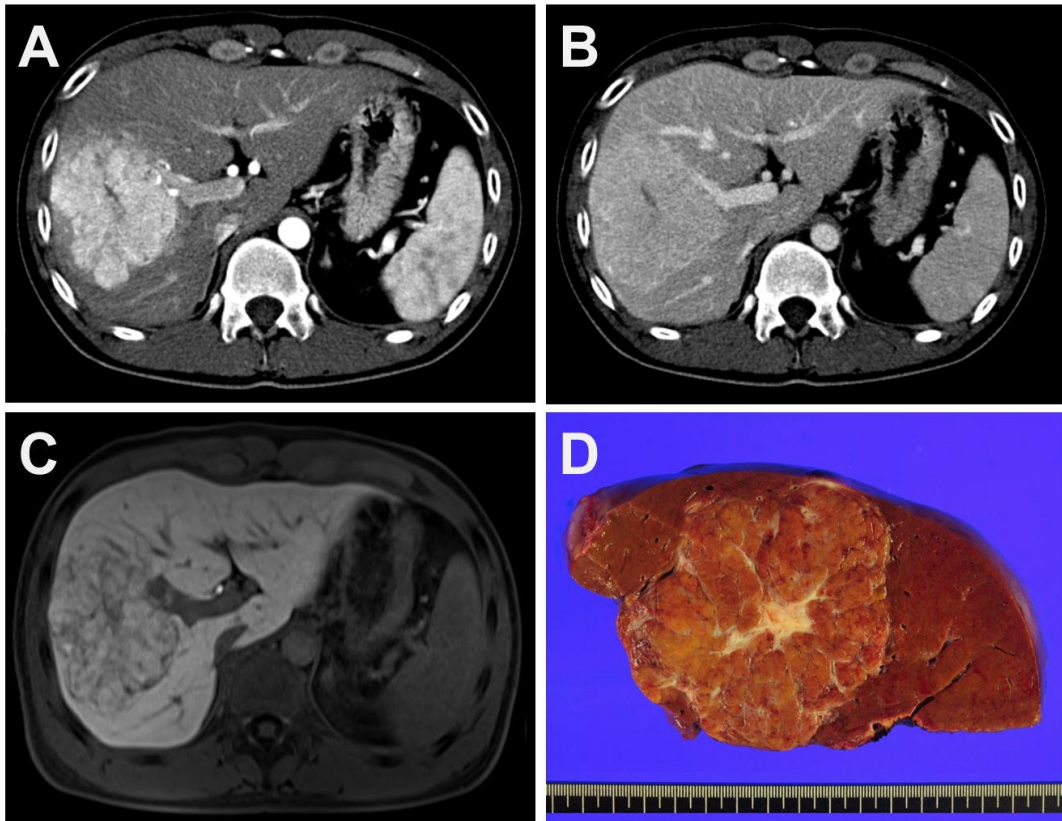


Figure 2. Preoperative imaging and operative findings of a 31 year-old male patient showing large focal nodular hyperplasia (FNH). Computed tomography (A: arterial phase and B: portal phase) and magnetic resonance imaging (C) suggested FNH. The pathological examination of the resected specimen (D) revealed that the final diagnosis was FNH.

Introduction

Focal nodular hyperplasia (FNH) is one of the most common benign tumors of the liver. Hyperplastic nodule and stellate central scar are characteristic. It is not known to progress to malignancy. It is known to be associated with antihormonal therapy and contraceptive use, but is still lacking in evidence. It may cause epigastric pain and discomfort, but it is often asymptomatic thus incidentally found on health screening. If symptoms are present, appropriate conservative treatment should be performed. Surgical resection can be taken into account if symptoms persist or imaging findings are difficult to distinguish from other diseases requiring surgical treatment. Because there is no report of transformation to malignancy so far, it is important to appropriately select indication of surgical resection [1-6].

The aim of this study is to analyze the surgical indications and postoperative outcomes of FNH.

Patients and Methods

The liver resection database of our institution was queried to identify patients who underwent primary surgical treatment for FNH at our institution during 11 years between January 2005 and December 2015 [7]. The Institutional Review Board of Asan Medical Center approved this study.

This study was performed as a retrospective observational study. Patients were followed until September 2018 by institutional medical records review and the assistance of the National Health Insurance Service. Data were collected on age, gender, contraceptive use, comorbid liver disease, initial hospital visit, preoperative examination/diagnosis, surgical indication, operative procedures, postoperative outcomes, pathologic findings.

Results

Patient profiles

The profiles of the 48 patients were summarized at **Table 1**. Interestingly, none of our patients had a past history of contraceptive use. The reasons to undergo first imaging study were regular check-up (n = 23), presence of symptom (n = 18), routine cancer surveillance (n = 4), and abnormality of liver function test (n = 3).

Preoperative imaging findings

Ultrasonography (USG), computed tomography (CT) and magnetic resonance imaging (MRI) were used for diagnosis of liver mass in our institution. In our patients, US, CT and MRI were performed in 51%, 100% and 90% of patients, respectively.

Percutaneous biopsy was performed in 14 patients: of them 9 were diagnosed of FNH and other 5 patients were diagnosed of hepatic adenoma (n = 1), hepatocellular carcinoma (HCC) (n = 1), plasmacytoma (n = 1), angiosarcoma (n = 1), and atypical hepatocellular proliferation (n = 1).

Reasons and decision to surgical resection

The reasons to decide surgical treatment were summarized at **Table 2**. Diagnostic uncertainty (n = 31) was the most common reason for surgical resection. First, FNH was suspected on imaging studies, but if other diseases requiring surgical treatment were cannot be excluded such as hepatic adenoma and HCC, such patients underwent surgical treatment. Second, surgical treatment was performed to the patients were initially suspected to have other diseases other than FNH, such as metastatic liver tumor and paraganglioma. Third, patients who had percutaneous biopsy finding of plasmacytoma, angiosarcoma (**Fig. 1**) and HCC underwent surgical treatment.

Eight patients underwent surgical treatment due to persistent abdominal pain or discomfort despite conservative treatment, in whom the size of tumor was greater than 4 cm.

Continuously growing tumor on follow-up was one of the common reasons for surgical treatment (n = 5, **Fig. 2**). Three patients wanted surgery rather than prolonged observation. Surgical treatment was preferred in young patients (≤ 35 year of age) with large-sized mass (≥ 7 cm in maximal diameter). A young woman planning to have pregnancy underwent surgery because of suspicion of hepatic adenoma as well as FNH in preoperative imaging studies (**Table 2**).

Operation and outcomes

Minor hepatectomy (n = 37) was performed more frequently than major hepatectomy (n = 11). Open hepatectomy (n = 29) was performed more frequently than laparoscopic hepatectomy (n = 19), but laparoscopic approach and minimally invasive surgery were preferred during the late phase of the study period comparing with the early phase.

Postoperative complication developed in 2 patients, in who one patient minor bile leak and the other one patient had fluid collection at the liver cut surface. There was no mortality case **(Table 3)**.

Tumor characteristics

The median size of the tumor was 3.9 cm (range: 0.7 – 15). Tumor number was single in 44 patients and two in 4 patients. Three patients had small mass < 1 cm in diameter and they underwent surgical treatment due to risk of malignant potential. The location of tumor was the right lobe in 16, left lobe in 26, caudate lobe in 4 and bilateral in 2.

Two patient showed concurrent pathology of hepatic adenoma (n = 1) and angiosarcoma (n = 1), which were the same as the preoperative percutaneous biopsy findings.

Discussion

FNH of the liver is a benign lesion occurring in 0.6-3% of the general population that probably reflects a local hyperplastic response of hepatocytes to a vascular abnormality. Most lesions are diagnosed incidentally and the natural history of the disease remains largely unknown. It has been shown that most FNH remain stable, or even regress, over a long follow-up period [1-5].

It is difficult to select the surgical indication in patients with benign disease such as FNH. FNH itself is benign disease, thus it does not require surgical resection unless the symptom persists. However, currently available diagnostic modalities do not reliably confirm the diagnosis of FNH with exclusion of other diseases requiring surgical treatment [8], thus surgery has been considered on occasion.

The most common reason leading to surgical treatment in our study was uncertainty of diagnosis through imaging studies. Even though percutaneous biopsy was diagnosed of FNH, if the imaging study findings were still suspicious of hepatic adenoma, HCC or other malignant disease, surgical treatment had to be performed.

In a single-center study with 100 case of FNH, the indications for liver resection included

tumor-associated symptoms with abdominal discomfort (40.7%), balance of risk for malignancy/history of cancer (47.8%/33.3%), tumor enlargement/jaundice of vascular and biliary structures (11.5 %) and incidental findings during elective operation (0.9 %). The authors suggested that hepatic resection remains a valuable therapeutic option in the treatment of either symptomatic FNH or if malignancy cannot finally be ruled out. If clinically indicated, liver resection for FNH represents a safe approach and may lead to significant improvements of quality of life especially in symptomatic patients [9].

Continuously growing tumor was also one of the common reason leading to surgery because such a finding can be associated with the possibility of malignant diseases. However, it was reported that FNH may grow significantly without causing symptoms and a significant increase in size does not have any implications on clinical management if confident diagnosis by imaging has been established [10]. It is reported that FNH has the potential for spontaneous regression thus giant FNH can be managed conservatively rather than by resection [11].

The typical imaging findings of FNH are as follows: Isoattenuating in pre-contrast CT, T1, T2 isointense with T2 hyperintense central scar on MRI, homogenous arterial enhancement on CT or MRI post-contrast, and delayed enhancement of central scar. Dynamic CT and dual contrast MRI are important tools for diagnosing FNH. However, it is very difficult to

diagnose FNH without central stellate scar findings. A Korean study suggested that contrast-enhanced ultrasonography (CEUS) using Sonazoid for FNH showed typical vascular patterns of central artery vascularity, stellate vascularity, and centrifugal enhancement. Most cases were either hyperenhanced or isoenhanced on serial dynamic- and Kupffer-phase imaging. Based on these results, CEUS can provide useful information for noninvasive focal nodular hyperplasia diagnoses [12]. A Japanese study reported the points useful in the imaging differentiation of HCC showing hyperintensity on the hepatobiliary phase of gadoxetic acid-enhanced MRI and FNH and FNH-like nodules. The apparent diffusion coefficient (ADC) was lower in hyperintense HCC than in FNH. The enhancement patterns of hyperintense HCC and FNH at dynamic CT were significantly different. Multivariate logistic regression analysis showed that ADC ratio ($p = 0.03$; odds ratio = 0.12) and enhancement pattern at dynamic CT ($p = 0.04$; odds ratio = 16.21) were the independent factors for differentiation between hyperintense HCC and FNH. The authors suggested that arterial phase enhancement and washout pattern at dynamic CT and decrease of ADC ratio would be important findings for diagnosis of hyperintense HCC differentiated from FNH and FNH-like nodule [13]

The development patterns of liver tumors can be very complex, thus FNH can be concurrently happen with other disease entities. In this study, two patients had concurrent

pathology of hepatic adenoma and angiosarcoma in preoperative percutaneous biopsy findings, which were confirmed at the post-resection pathology. In fact, these diseases of pre- and malignant lesions became the primary causes leading to surgical treatment. The possibility of concurrent other lesions cannot be excluded, especially in patients with multiple lesions [14].

There are limitations in this study. First, this is a retrospective study. The patients who were diagnosed of FNH after surgery were selected, thus the patients that had been suspected FNH before operation but diagnosed of other diseases after operation were not included. Second, it is a small-volume single-center study, thus it is difficult to draw out reliable conclusion. Third, administration of oral contraceptives is not common in Korean society, thus its association with development of FNH cannot be assessed.

In conclusion, FNH can be diagnosed by imaging studies, but surgical treatment can be considered if there is diagnostic uncertainty or persistent symptoms.

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Korean abstract

배경 : 국소 결절성 과형성은 간에 발생하는 흔한 양성 종양 중 하나이다. 수술 대상 선정에 대한 적립된 기준이 없다. 이 연구는 국소 결절성 과형성의 수술 적응증을 분석하고자 하였다.

방법 : 간 절제술 후 국소 결절성 과형성으로 진단된 48명의 환자를 분석하였다.

결과: 수술적 절제를 시행한 이유는 진단적 불확실성(n=31)과 지속적인 증상(n=8)이었다. 경피적 생검은 14예에서 시행되었고, 9예에서 국소 결절성 과형성, 1예에서 간선종, 1예에서 간세포성암, 1예에서 형질세포종, 1예에서 혈관 육종, 1예에서 비정형 간세포 증식으로 진단되었다. 소량 간절제술(n=37)은 대량 간절제술(n=11)보다 더 많이 시행되었다. 개복 수술(n=29)이 복강경 수술(n=19)보다 더 많이 시행되었지만, 복강경 및 최소 침습 수술이 후기 연구 단계에서 더 많이 시행되었다. 수술 후 합병증은 2예(4.1%)에서 발생하였다.

결론: 국소 결절성 과형성은 영상학적으로 진단될 수 있다. 하지만 진단의 불확실성이나 지속적인 증상이 있는 경우 수술적 절제를 고려할 수 있다.