
Panel 1.
**HCC Treatment; The Art of
Multidisciplinary Approach**

**1. Early HCC; What is the best treatment
option for BCLC stage A?
1) Evidence**

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Early HCC (BCLC stage A) is defined in patients presenting single tumors >2 cm or 3 nodules <3 cm of diameter, ECOG-0 and Child-Pugh class A or B1. According to the tumor status and liver reserved function, curative aimed treatments including surgical resection, liver transplantation (LT) or local ablation are recommended as a first treatment option in patients with early HCC. These curative treatments showed 50-70% survival rate at 5 years after treatments in selected patients [2]. In circumstances where these treatments are available, recommendations for different treatment strategies are based on evidence-based data. I would like to review previous published studies and guidelines, and to find out the best indication of each treatment.

Liver resection

Surgery is the mainstay of HCC treatment [3]. Liver resection should be considered in patients with single HCC and well-preserved liver function. The ideal candidates for surgical resection are determined by the liver function reserve and tumor extension.

The golden standard method to determine the liver function reserve is Child-Pugh class. The Child-Pugh class A is considered to be surgical candidate, but the Child-Pugh A shows wide spectrum of postoperative liver dysfunction. Therefore,

additional more precise measurement such as indocyanine green retention at 15 min [4] and hepatic venous pressure gradient > 10mmHg as a direct measurement of significant portal hypertension [5]. Because measurement of hepatic venous pressure gradient is invasive, the presence of significant portal hypertension can be assessed by the detection of esophago-gastric varices on endoscopy, and platelet count below 100,000/mm³ associated with splenomegaly, which is defined as spleen size ≥ 12cm. In clinical practice, platelet count is the most simple and easily accessible parameter of significant portal hypertension.

The final parameter for selecting surgical candidates is the residual liver volume. Although the safe limit of residual liver volume to prevent postoperative liver failure has not been intensively investigated, it is usually recommended that the residual liver volume should be left more than 40% of total liver volume in patients with chronic liver disease and cirrhosis [6]. To increase the residual liver volume in patients who need major hepatectomy, preoperative portal vein embolization is applied by some groups [6,7]. Their studies suggested that preoperative portal vein embolization is the effective tool that enables the marginally resectable tumors to be safely resected. This approach is associated with a complication rate of 10-20% [8] and the effectiveness of preoperative portal hypertension has not been properly demonstrated in large controlled studies.

If the surgical candidates are properly selected in terms of the liver reserved function, the prognosis after resection was determined by the tumor extension such as tumor size, number and vascular invasion [3]. Although the tumor size and vascular invasion are well correlated, about one-third HCCs have no microscopic vascular invasion even if the tumor size increases more than 10cm [9]. Because these huge HCC without vascular invasion showed favorable surgical outcomes, the tumor size itself is not considered to be crucial factors for determining the respectability of HCC.

Multiple tumors with three or more nodules

show lower 5-year survival rates of 26% after resection, compared to that of 57% after resection. Recently, some centers reported improved 5-year survival rates above 50% after resection in patients with multiple tumors fulfilling Milan criteria, which is not suitable for transplantation [10,11]. The surgical outcomes in patients with two or three nodules should be further compared with loco-regional therapies in controlled randomized studies before being adopting by these guidelines.

Liver transplantation

Liver transplantation (LT) is the first treatment choice for patients with HCC within Milan criteria (single tumor $\leq 5\text{cm}$ or ≤ 3 nodules $\leq 3\text{cm}$) and advanced liver dysfunction [3]. The patients within Milan criteria showed 70% 5-year survival with a recurrence rate below 15% [12-14]. Overall 5-year survival of patients within the Milan criteria (65-78%) was similar compared with non-HCC indications according to European (ELTR) and American registries (OPTN) (65-87%) [15,16]. Now, the Milan criteria have been integrated in the BCLC staging system [1].

The good prognosis after LT in HCC within Milan criteria has led to the expansion and competition as the first option in early HCC with well-preserved liver function. Resection and transplantation achieve the best outcomes in well-selected candidates (5-year survival of 60-80%) [3]. Although LT can ideally cure the tumor and the underlying cirrhosis at the same time, the several drawbacks of LT such as the scarcity of donors, high surgical complications and side effects of long-term immunosuppression justify that hepatic resection is the first treatment of choice for HCC in non-cirrhotic patients and single HCC in well-preserved cirrhotic patients. LT can be reserved for the second-line curative treatment, named as "salvage LT", in patients with recurrent HCC or deteriorating liver function after liver resection.

Living donor LT has introduced as an alternative to deceased LT [17]. Because of risk of donor

death and life threatening complication, it has not gained popularity in west transplant community and comprises less than 5% of adult LT. However, living donor LT is the main procedure of LT in Asian country due to the scarcity of deceased donors. Because of operative complexity, living donor LT should be performed in the tertiary center equipped with both expert hepatic and transplant surgeon. Organ donation in living donor LT is based on its voluntarism within private relationship. Therefore, living donor LT has been performed in HCC beyond the Milan criteria. The guideline of living donor LT in patients with HCC should be further discussed.

Local ablation

Local ablation is considered the first line treatment option for patients at early stages not suitable for liver resection or LT. Percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) have been commonly performed in patients with early HCC. Five randomized controlled trials have compared RFA versus PEI for the treatment of early-stage HCC. These investigations consistently showed that RFA has a better local control of the disease (2 year local recurrence rate: 2-18% versus 11-45%) [18-22]. Two additional RCT from the same group reported survival advantages in the subgroup analysis of tumors larger than 2cm favouring RF compared with PEI [18,20]. Two independent meta-analyses also showed the same results that RFA provides a survival benefit as compared with PEI in tumors larger than 2cm [23,24]. Therefore, the first line treatment option for patients with BCLC stage A is RFA. The main drawback of RF is its higher rates of major complications compared to PET (4% vs. 2.7%).

RFA has been conducted for patients with small, single HCC, competing with surgical resection as a first-line treatment. Two RCT have been reported with opposite results [25,26]. While the first one showed similar outcomes between RFA and surgical resection, the second trial demonstrated higher

survival rate after treatment, compared to RFA. Therefore, there are no data to support RFA as the first-line treatment for patients with BCLC stage A.

In conclusion

In patient with BCLC stage A, liver resection is the mainstay of treatment. The ideal surgical candidates are selected by assessing the liver reserved function and tumor extension. LT is the first treatment choice for patients with HCC within Milan criteria and advanced liver dysfunction. In patients with early HCC which is suitable for resection or LT, surgical resection is the first option and LT is reserved for the second-line curative treatment (salvage LT). In patients with multiple tumors fulfilling Milan criteria, which is not suitable for transplantation, surgical resection showed improved 5-year survival rate of 50% in some center. But these results should be further compared with loco-regional therapies in controlled randomized studies. Local ablation is considered the first line treatment option for patients at early stages not suitable for liver resection or LT. Until now, there are no data to support RFA as the first-line treatment for patients with BCLC stage A.

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1. Early HCC; What is the best treatment option for BCLC stage A?

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서 론

원발 간암은 우리나라에서 등록 순위 4위인 암으로 꾸준히 증가 추세에 있으며, 전 세계적으로도 발생이 증가하고 있다 [1]. 간세포암종 병기 분류는 해부학적 분류인 TMN (tumor node metastasis) 병기

와 간기능, 수행능력 등을 고려한 Okuda, CLIP, BCLC (AASLD), JIS 등의 종합적 병기 분류법이 여러 나라에서 실정에 맞춰 제시되고 있으나 현재 전세계적으로 통일된 병기법은 없는 실정이다 [2-4]. 우리나라도 2003년 간암연구학회에서 간세포암종 진료 가이드라인을 발표하여 간세포암종의 진단 및 치료를 제시한 후 2009년 이를 개정하여 현재 우리나라 실정에 맞는 간세포암종 진료의 참고가 되고 있다 [5]. 그러나 현재 통용되는 진료 가이드라인은 간세포암의 병기에 따른 치료법을 미리 결정해 놓아 병기 감소(downstaging) 후 근치적 치료법, 구제 치료(Salvage treatment)와 여러 치료법의 혼합 치료에 관한 기술이 부족하다. 본 연제에서 세계에서 가장 많이 통용되는 간세포암종 병기 분류 상 초기 간세포암종(Early stage)의 치료 및 다학제 접근의 적용에 대하여 다루고자 한다.

BCLC 병기에서는 3개이하, 3cm 이하의 간세포암종을 초기 간암(Early stage HCC, stage A)로 분류하고 치료 방법으로 간이식과 고주파 열소작술 또는 에탄올 주입술과 같은 국소치료법을 권하고 있다. 그러나 실제 임상에서는 Milan 병기 내의 간세포암 환자에서 결절이 간 내 제한된 영역 내 위치하며, 기저간기능이 허용되면 수술적 절제가 가장 널리 시행된다. 실제 간절제술은 간이식과는 달리 대기 시간이 없으며, 국소치료법과는 달리 술 후 조직학적으로 종양의 완전 제거를 확인할 수 있는 장점이 있다. 그러나, 간문맥항진증의 증거가 있는 경우 이식 후 간부전의 위험이 높아 간절제술을 시행 받을 수 있는 환자는 제한적이다 [6]. 이를 극복하기 위해 간절제술 전 종양이 위치하는 간엽의 문맥을 막아 종양이 침범한 간엽(lobe)를 위축(atrophy)시키고 잔존간을 비후(hypertrophy)시키는 간문맥 색전술이 시도되고 있으나 시술의 결과에 대해서 향후 추가 연구가 필요하다 [7]. 수술전 보조요법으로 간동맥화학색전술을 시행하지 않은 환자군에 비해 예후가 나쁘거나, 큰 차이를 보이지 않아 더 이상 권하지 않는다 [8,9].

간세포암 뿐만 아니라 기저 간경변을 치료할 수 있는 간이식은 간세포암 병기가 밀란 기준(Milan criteria) 이하인 경우 좋은 치료 방법이 된다. Mazzaferro 등은 밀란 기준 이내 환자들을 대상으로 간이식후 85%의 무병생존율을 보고하였다 [10]. 그러나 서양에 비해 공여간이 부족한 국내에서는 간세포암의 치료로서 간이식은 주로 생체간이식이 시행되고 있으며, 진행된 간세포암 병기, 간이식 비용과

이식 후 장기간 면역억제제 투여 등으로 인하여 소수의 환자에서 간이식이 시행되고 있다. 환자의 나이(보통 70세 이하), 동반질환(기저 심폐질환, 흡연, 당뇨, 또는 신장 질환), 환자의 영양 상태(영양 실조 또는 심한 비만), 사회적 요인(적절한 지지, 환자 순응도, 금주여부, 적절한 재활 프로그램) 역시 간이식 대상 환자의 선택에 있어 고려해야 한다 [11]. 현재 밀란 기준이 전세계적으로 가장 널리 통용되는 간이식의 적응증이며, 밀란 기준에 해당되지 않는 간세포암의 간이식을 위해 병기하향(downstaging)이 시도되고 있다 [12]. 또한 간세포암 환자를 이식 대기에 유지시키기 위한 교량 치료(bridge therapy)역시 널리 시행되고 있다 [13].

국소치료법 중 고주파 열소작술은 기저간기능 저하 및 사회경제적인 이유로 수술적 치료가 불가능한 경우 시행될 수 있다. 국소치료법 중 고주파 열소작술이 에탄올 주입술보다 더 높은 치료 성공률, 낮은 재발, 그리고 높은 생존율을 보여 국소치료법 중 가장 선호되고 있다 [14]. 그러나 간내 종괴의 위치에 따라 에탄올 주입술이 선호되기도 한다 [15]. 그러나 3cm 이상의 간세포암의 경우 고주파 열소작술의 치료 성적이 아직 부족한 실정이며, 고주파 열소작술 전 간동맥 화학색전술등을 시행하여 치료 성적을 높이기 위한 시도들이 시행되나 이에 대한 치료 성적은 아직 부족하다.

타 병기에 비해 초기의 간세포암 환자의 경우 고주파 열소작술 또는 수술적 절제로 완전 관해에 도달하기 쉬우나, 재발 역시 적지 않아 재발 암의 치료가 환자의 예후에 매우 중요하다. 그러나 현재 BCLC 지침은 근치 치료 후 재발된 간암에 대한 접근 방향을 제시하는데 부족하며, 이에 대한 향후 치료 계획의 개발이 요구된다.

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1. Early HCC; What is the best treatment option for BCLC stage A?

2) Practice

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Since the first clinical study in 1995, clinical implications of percutaneous radiofrequency ablation (RFA) in the treatment of early-stage hepatocellular carcinoma (HCC) have expanded. Currently, RFA is recognized as a curative modality for early-stage HCC whose outcomes are comparable to those of surgery, as evidenced by many studies. Recently, long-term (i.e., more than 10 years) follow-up results are reported, because of its relatively short history of clinical applications although there has been plenty of reports regarding 5-year outcomes.

Although favorable outcomes of RFA for HCC in many reports in small HCC (less than 3cm), the results of RFA in medium size HCC (3 to 5cm) are similar or inferior to those of surgery according to the previous reports. Thus, surgery has been still considered as the treatment of choice for curative treatment of medium size HCC.

Meanwhile, RFA technique and equipment have been developed for an effective and safe RFA, for example, the use of artificial ascites techniques, multiple overlapping ablations, the use of ultrasound contrast, fusion image guidance, the use of multiple electrodes and the combined treatment with transarterial chemoembolization (TACE). In addition, a few results of RFA combined with TACE for medium size HCC recently began to be reported. In those reports, the outcomes of RFA are comparable to those of surgery. Thus, combined treatment of TACE and RFA also could be performed for medium size HCC as first-line treatment. However, it is required to evaluate exactly the outcome of RFA compared with those of surgery through further studies.

2. Advanced HCC; How to approach HCC with portal vein invasion, with preserved liver function?

1) Evidence

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Hepatocellular carcinoma with portal vein invasion is one of the most challenging clinical scenarios to the professionals in this field. If the patient maintains preserved liver function at the time of diagnosis, it becomes more challenging to make decision on the best treatment option.

Natural disease course of patients in this group is usually very poor [1] and treatment outcomes have been disappointing regardless of treatment of modality [2-4]. Since most of the guidelines are generated as evidence-based, in this session, several significant guidelines and their suggested evidences are reviewed focusing on patients with HCC with portal vein invasion.

American association for the study of liver disease

(AASLD) [5] and European Association for the Study of the Liver (EASL) [6] guidelines are on the same stance. They specifically mention that resection, transplantation, and TACE are contraindicated. Sorafenib is the only recommendation based on 3 months survival benefit in median survival based on level I evidence [3].

National Cancer Center Network (NCCN) of U.S. guideline [7] states that hepatic resection is controversial but can be considered and arterially directed therapies are relatively contraindicated in this setting. It emphasizes that there is growing evidence for the usefulness of stereotactic body radiation therapy.

Asian Pacific Association for the Study of the Liver (APASL) guideline states that this group may be associated with worse prognosis but surgical resection is still considered the best treatment in terms of long-term survival [8]. At the same time, sorafenib is recommended for whom are not suitable for locoregional therapy in this group.

Evidence-based clinical practice guideline of Japan [9] states that liver resection may be selected. Consensus-based clinical practice guideline states [10] that sorafenib and hepatic arterial infusion chemotherapy are recommended for HCC patients with Vp3/Vp4 and resection and TACE is frequently performed when portal invasion is minimum such as Vp1/Vp2. But, in both guidelines, no specific reference was listed.

Finally, Korean Liver Cancer Study Group guideline permits resection, chemoembolization, radioembolization, and external beam radiation therapy based on various References [11], but it did not provide priority in terms of treatment modality. Interestingly, it recommended sorafenib only for patients with extrahepatic disease or locoregional treatment failure.

References

1. Llovet, J.M., et al., Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic