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Editorial

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Trends in the treatment of pancreatic cancer in Japan

Ryota Matsuki, Takaaki Arai, Masaharu Kogure, Yutaka Suzuki, Yoshihiro Sakamoto*

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SUMMARY Pancreatic cancer is known to have the poorest prognosis among digestive cancers. With the development of new chemotherapeutic agents and introduction of multidisciplinary therapy, however, the treatment outcomes for pancreatic cancer have dramatically improved over the past two decades. The keys to successful treatment will be accurate assessment of resectability [resectable (R), borderline resectable (BR) or unresectable (UR)] at the time of diagnosis and prompt adoption of an appropriate multidisciplinary treatment strategy. Prep-02/JSAP-05 trial which is an RCT of upfront surgery versus neoadjuvant chemotherapy using GEM and S-1 (GS) and subsequent surgery for R-PDAC in Japan indicated neoadjuvant chemotherapy had a longer overall survival (OS) than those undergoing upfront surgery (36.7M *vs*. 26.6M, $p = 0.015$). In a retrospective multicenter study in Japan reported that in BR-PDAC, median survival time (MST) in the pretreatment group was significantly better than that in the upfront surgery group (25.7 months *vs*. 19.0 months, $p = 0.015$) according to a propensity score matching analysis. Another retrospective multicenter study with UR-LA PDAC in Japan reported that conversion surgery was more beneficial for patients with more than 8 months of preoperative therapy than those with less than 8 months of that therapy. Various clinical trials on pancreatic cancer are ongoing, and the results of trials on chemotherapeutic regimens and multidisciplinary treatments will be of further interest.

Keywords pancreatic cancer, resectability, multidisciplinary treatment

1. Introduction

Pancreatic cancer is known to have the poorest prognosis among digestive cancers; only 15-20% of cases are resectable while 30-40% of cases involve locally advanced cancer and 50-60% of cases involve distant metastatic cancer, which is unresectable (*1*). With the development of new chemotherapeutic agents and introduction of multidisciplinary therapy, however, the treatment outcomes for pancreatic cancer have dramatically improved over the past two decades. The treatment strategy for pancreatic cancer depends on the resectability of each cancer. The resectability of pancreatic cancer was first classified in the NCCN guidelines in 2004, and further objective classification based on anatomy and tumor extension on CT images was proposed by the M. D. Anderson Cancer Center (MDACC) in 2006 (*2*). In Japan, in 2016, the 7th Edition of the Classification of Pancreatic Cancer clearly stated that the resectability of pancreatic cancer should be classified as resectable (R), borderline resectable (BR), or unresectable (UR) based on local extension and the presence or absence of distant metastasis (*3*). The keys to successful treatment will be accurate assessment of resectability at the time of diagnosis and prompt adoption of an appropriate multidisciplinary treatment strategy

2. Multidisciplinary treatment for pancreatic ductal adenocarcinoma (PDAC)

2.1. Adjuvant treatment for PDAC

Since the beginning of the 21st century, gemcitabine (GEM) has frequently been used to treat UR pancreatic cancer. In response to that trend, the CONKO-001 trial in Germany (*4*) and the JSAP-02 trial in Japan (*5*) were conducted as randomized controlled trials (RCTs) on adjuvant therapy after surgery for R-PDAC. The results of these trials indicated that patients who received GEM for 3-6 months after surgery for R-PDAC had a longer recurrence-free survival (RFS) than the observation group. Subsequently, the JASPC 01 study in Japan (*6*) indicated that the administration of adjuvant S-1 significantly improved not only RFS but also overall survival (OS) in comparison to administration of GEM, and this finding was announced at the American Gastrointestinal Cancer Symposium (ASCO-GI) in 2013. Since then, administration of S-1 as adjuvant

Table 1. Results of perioperative adjuvant chemotherapy for resectable pancreatic cancer

Study	Country	Year	Journal	Therapy	*n*	MST (M)
CONKO-001	Germany	2007	JMA	GEM 6M	179	13.4 PFS
				observation	175	6.9 PFS
JSAP-02	Japan	2009	Br J Cancer	GEM 3M	58	11.4 PFS
				observation	60	5.0 PFS
JASPAC01	Japan	2016	Lancet	S-1 6M	187	46.5
				GEM 6M	190	25.5
ESPAC-4	European study group	2017	Lancet	GEM+Cape 6M	364	28.0
				GEM 6M	366	25.5
PRODIGE24-ACCORD24/CCTG PA6	Canada	2018	N Engl J Med	mFOLFIRINOX 6M	247	54.4
				GEM 6M	246	35.0
Prep-02/JSAP-05	Japan	2019	J Clin Oncol	Neo GEM+S-1 2M	182	36.7 OS
				Upfront surgery	180	26.6 OS

GEM: gemcitabine; Neo: neoadjuvant therapy; MST: median survival time; PFS: progression free survival.

chemotherapy has become the standard treatment for R-PDAC in Japan (Table 1). In addition, since 2016, two clinical trials of adjuvant chemotherapy [ESPAC-4: GEM *vs*. GEM plus capecitabine](*7*) and [PRODIGE24-ACCORD24/CCTG PA6 trial: GEM *vs*. mFOLFIRINOX](*8*) yielded positive results. Based on the results of these phase III trials, the2019 Clinical Practice Guidelines for Pancreatic Cancer (*9*) proposed adding the use of GEM plus capecitabine and modified FOLFIRINOX as recommended adjuvant chemotherapies. However, there are no data on the use of either of these adjuvant agents in Japan, and they are not recommended by Japanese guidelines.

2.2. Neoadjuvant therapy for PDAC

2.2.1. Neoadjuvant therapy for resectable PDAC

Prep-02/JSAP-05 trial (*10*) was conducted to clarify the significance of neoadjuvant chemotherapy for R-PDAC. This trial was an RCT of upfront surgery versus neoadjuvant chemotherapy using GEM and S-1 (GS) and subsequent surgery for R-PDAC. Both groups received adjuvant chemotherapy with S-1. The results of this study, announced at the ASCO-GI in 2019, were that patients receiving neoadjuvant chemotherapy had a longer OS than those undergoing upfront surgery. Based on these results, neoadjuvant GS and adjuvant S-1 therapy became the standard treatment for R-PDAC in Japan after 2019.

2.2.2. Neoadjuvant therapy for BR-PDAC

In Japan, the 2019 Clinical Practice Guidelines for Pancreatic Cancer proposed surgical resection for BR-PDAC after neoadjuvant therapy followed by re-evaluation of treatment efficacy and resectability. Upfront surgery for BR-PDAC is not recommended. Although several RCTs on neoadjuvant therapy for BR-PDAC are being conducted in Europe, the United States, and Japan, RCTs have yet to provide evidence of the efficacy of neoadjuvant therapy.

In a retrospective multicenter study in Japan, Nagakawa *et al*. reported that among 884 patients with BR-PDAC (530 patients in the pretreatment group and 354 in the upfront surgery group), median survival time (MST) in the pretreatment group (n = 297) was significantly better than that in the upfront surgery group (n = 297) (25.7 months *vs*. 19.0 months, p = 0.015) according to a propensity score matching analysis (*11*).

2.3. Chemotherapy for UR-PDAC

The use of GEM as the standard treatment for UR-PDAC lasted for more than a decade starting in 2000. However, since FOLFIRINOX therapy was approved in 2013 and the combination of GEM and nab-paclitaxel was approved in 2014, these two combination therapies have been widely used in Japan. The 2019 Clinical Practice Guidelines for Pancreatic Cancer also recommend the use of GEM monotherapy, S-1 monotherapy, and the combination of GEM and erlotinib in addition to the two aforementioned therapies. New anti-cancer therapies using molecularly targeted drugs and immune checkpoint inhibitors are expected in the near future.

2.4. Conversion surgery

UR-PDAC can be classified into UR-locally advanced (UR-LA) and UR-metastatic cancer. The 2019 Clinical Practice Guidelines for Pancreatic Cancer suggest that conversion surgery after multidisciplinary treatment could be a treatment option for UR-LA PDAC because favorable OS and/or RFS can be expected. In a retrospective multicenter study involving 97 patients with UR-LA PDAC in Japan, conversion surgery was more beneficial for patients with more than 8 months of preoperative therapy than those with less than 8 months of that therapy (*12*). Conversion surgery should be performed after tumor markers such as CA19-9 have decreased sufficiently. Although conversion surgery is expected to prolong survival for patients if it is

performed safely, it should be performed carefully by a specialized facility because it requires highly technical skills, such as combined resection and reconstruction of the hepatic artery and portal vein.

3. Conclusion

The keys to successful treatment of pancreatic cancer will be accurate assessment of resectability and adoption of an appropriate multidisciplinary treatment strategy. Ongoing clinical trials on pancreatic cancer will lead the way to new chemotherapeutic regimens and multidisciplinary treatments.

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Editorial

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Surgical treatment of hepatocellular carcinoma

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SUMMARY Hepatocellular carcinoma (HCC) is one of the most common cancers in the world, and cirrhosis is a risk factor for HCC. Resection is indicated for those unilobar tumors without vascular invasion and metastases in the liver and preserved liver function. Small HCC (< 2 cm) without microvascular invasion is associated with a 5-year recurrence rate as high as 50% to 60%, whereas liver transplantation is indicated for those within the Milan criteria (solitary tumor ≤ 5 cm or two or three nodules ≤ 3 cm) who have decompensated cirrhosis. The 1-, 3-, and 5-year survival rates of living donor liver transplantation for HCC are 85%, 75%, and 70%, respectively. This review summarizes the scientific evidence supporting the clinical practice recommendations for patients with HCC, and it discusses surgical treatment of HCC.

Keywords liver transplantation, living donor, hepatocellular carcinoma

1. Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancers, the sixth most common neoplasm, and the third most common cause of cancer death (*1*). Risk factors for HCC include the hepatitis B and C viruses, alcohol use, and nonalcoholic fatty liver diseases (*2*). Approximately half of HCC cases are diagnosed early (*3*). For early-stage HCC, curative treatment with partial liver resection or liver transplantation remains the mainstay of therapy, and it is discussed in this review.

2. Resection

Partial liver resection is a potentially curative therapeutic option for HCC. Indications for partial resection include unilobar tumors without vascular invasion and metastases in the liver without cirrhosis. The 5 -year survival rate after resection for HCC is 50 % to 68% in experienced centers (*4-7*). Impaired hepatic function and/or significant portal hypertension are related to poor tolerability of resection. Regional lymph node metastases are associated with decreased survival (*8*).

Selection of appropriate candidates for resection is based on the Child-Pugh classification as determined by bilirubin and albumin levels, prothrombin time, the presence of ascites, and encephalopathy (*9*). Child-Pugh class A is a good indication for partial liver resection, whereas Child-Pugh class C is not indicated due to the risk of liver failure after resection. Varices, ascites, and portal hypertensive gastropathy can be surrogate indices of portal hypertension. In East Asia (including Japan), the retention rate of indocyanine green has been used to determine the extent of the liver resection (*10*). Improved surgical techniques and careful patient selection have decreased the mortality rate to nearly 0% and the major complication rate to approximately 3% (*11*).

The future liver remnant – the liver volume estimated to remain after resection– is an important factor for patients undergoing liver resection. The minimum safe amount of remaining liver parenchyma ranges from 20% to 40% of the total (*12*). In preparation for hepatic resection, portal vein embolization (PVE) can be safely and effectively utilized to induce hypertrophy of the remnant liver without causing liver dysfunction (*13*). Combining liver partition and portal vein ligation for staged hepatectomy results in more marked and faster regenerative ability than PVE (*14*) but is associated with high morbidity and mortality.

From an oncological point of view, anatomic resection is recommended when the tumor invades the segmental portal branches or it has satellite lesions. Ultrasound is useful for detection of tumor vessel (*15*) and the lesions missed in preoperative imaging or intraoperatively (*16*). Anatomic resection is associated with better recurrence-free survival than non-anatomic resection (*17*).

Unfortunately, a cure is not always obtained and the 5-year recurrence rate is around 50% to 70% (*18*). Risk factors for recurrence include macro and/or micro vascular invasion, multifocal tumors, and high alpha fetoprotein levels preoperatively (*19,20*). Small HCC

(< 2 cm) without microvascular invasion is associated with a 5-year recurrence rate as high as 50% to 60% (21). Approximately 80% of recurrent lesions are in the liver. Only 15% of recurrent tumors can be resected (*22*). The peak of recurrence is bimodal: the first peak occurs around 1 year after resection and the second, 4 to 5 years after resection (*18*). Late recurrence is reported to represent de novo HCC.

Currently, adjuvant chemotherapy offers no established benefit in preventing recurrence. A randomized clinical trial (*23*) comparing sorafenib versus a placebo after partial hepatectomy or ablation for HCC revealed no statistical inter-group difference in survival. Systemic chemoembolization is also ineffective, whereas retinoids, vitamin K2, transarterial ^{131}I-lipiodol, and interferon have shown promising results, but a real benefit has yet to be established (*24*). A randomized, open-label, phase 3 trial (*25*) noted that adjuvant immunotherapy with autologous cytokine-induced killer cells ($CD3^+/CD56^+$ and $CD3^+/CD56^-$ T cells and $CD3^-/CD56^+$ natural killer cells) increased recurrence-free and overall survival after curative treatment.

3. Liver transplantation

Liver transplantation is indicated when HCC is deemed to be unresectable due to impaired liver function, severe portal hypertension, or tumor location. The tumors should meet the Milan criteria, which include a single tumor ≤ 5 cm or two to three tumors ≤ 3 cm without major vessel invasion or extrahepatic tumor spread based on imaging studies (*26*). The 4-year patient survival rate of patients fulfilling the Milan criteria who undergo liver transplantation is 75%, with a recurrence-free survival rate of 83%.

The Milan criteria have been adopted by the United Network for Organ Sharing (UNOS) as the inclusion criteria for deceased donor liver transplantation. They have also been adopted by the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver guidelines, and an international HCC consensus conference (*27-29*). UNOS data indicate a 5-year survival rate of 61% for patients receiving a liver transplantation under the Milan criteria (*30*). UNOS has a "sickest first" approach, which prioritizes candidates whose liver function has been evaluated using the Model for End Stage Liver Disease (MELD) score. UNOS adopted the HCC exception score.

In Japan and other Asian countries, most transplants are living - donor liver transplantations (LDLT). As LDLT is a private issue among patients and their families, indices of tumor status are considered on a case-by-case basis. Accordingly, the expanded Milan criteria (*26*) have been adopted by many transplantation centers performing LDLT, without a significantly higher rate of HCC recurrence.

In Japan, the Japanese Organ Transplantation Act was approved in 1997 and revised in 2006. The number of livers from deceased donors, however, is inadequate for the number of potential recipients. As of the end of 2016, 378 deceased donor liver transplantations were performed. During the same period, 8,825 LDLTs were performed; of these, 1,598 involved patients with HCC. The 1-, 3-, 5-, 10-, 15-, and 20-year survival rates of LDLT for HCC are 85%, 75%, 70%, 62%, 55%, and 54%, respectively.

One study enrolled 965 patients who underwent LDLT for HCC between 1990 and 2005 (*31*). Of those patients, 301 had tumors outside the Milan criteria. New criteria consisting of the tumor number, serum alpha-fetoprotein levels, and a maximal tumor diameter of 5 cm that allowed for enrollment of the maximal number of subjects resulted in a 5-year recurrence rate of less than 10%. Based on the study's results, new criteria for LDLT, *i.e.*, candidates with a tumor ≤ 5 cm in size, tumor number ≤ 5, and alfa-fetoprotein level ≤ 500 ng/mL (the so-called "5-5-500" rule), were established.

Following that study, patients who satisfy the 5-5-500 rule for LDLT or on the list for deceased donor liver transplantation are now covered by Japan's National Heath Insurance. Tumors are diagnosed as HCC based on computed tomography or magnetic resonance images obtained within 1 month of transplantation. Tumors are diagnosed based on dynamic computed tomography, hypodensity on plain computed tomography, and hyperintensity during the arterial phase and hypointensity during the portal phase of contrast-enhanced computed tomography. Local treatment of HCC must be administered at least 3 months before transplantation.

One topic of debate is the indications for liver transplantation when HCC outside the criteria is downstaged to a level within the criteria. The therapeutic modalities for downstaging include locoregional therapies such as transarterial chemoembolization or radioembolization and radiofrequency ablation.

One review reported a > 40% success rate of downstaging (*32*) with a 1-year overall survival rate ranging from 87% to 100, a 4- to 5-year survival rate varying from 90% to 70%, and a recurrence rate of 16%. The utility of downstaging might depend on the selection of patients expected to have a more favorable outcome. Current UNOS policy includes a downstaging protocol to allow patients to obtain HCC MELD exception points if specific criteria are met (*33*).

4. Conclusions

Surgical resection and transplantation remain curative therapeutic options for patients with early-stage HCC, and both result in comparable survival rates for properly selected patients. A successful outcome for transplantation due to HCC is a 5-year survival rate comparable to that for transplantation due to reasons other than HCC.

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Changes in and challenges regarding the surgical treatment of hepatocellular carcinoma in China

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SUMMARY Hepatocellular carcinoma (HCC) is a common malignant tumor with a high morbidity and mortality in China and elsewhere in the world. Due to its tumor heterogeneity and distant metastasis, patients with HCC often have a poor prognosis. A surgical treatment such as a radical hepatectomy is still the treatment of choice for patients with HCC in current clinical practice. However, the high rate of recurrence and rate of metastasis after surgery diminishes the survival of and prognosis for these patients. In an era of targeted therapy and immunotherapy, the surgical treatment of HCC must change. This review focuses on the definition, feasibility, and criteria with which to evaluate neoadjuvant therapy for HCC in order to provide a new perspective on surgical treatment of HCC.

Keywords hepatocellular carcinoma, surgical treatment, neoadjuvant therapy

1. Introduction

China has the most patients with hepatocellular carcinoma (HCC), and it accounts for nearly half of the world's patients with HCC (*1*). HCC is the second most prevalent malignancy in China, and 300,000 to 400,000 Chinese die from it every year (*2*). A survey of the current status of HCC treatment in China indicated that most patients with HCC have cancer in an intermediate or advanced stage when diagnosed, precluding the chance for surgery (*3*). Although the 2019 version of the "Guidelines for the Diagnosis and Treatment of Primary Liver Cancer" has expanded the indications for surgical resection from stage Ia to stage IIIa according to Chinese Liver Cancer staging (CNLC) (*4*), the postoperative rate of recurrence has increased, and the effectiveness of treatment still needs to be improved.

Over the past few years, targeted therapies and immunotherapies for HCC have continued to emerge, offering hope for the non-surgical treatment of HCC. This review describes the history of the development of HCC surgery, the use of neoadjuvant therapy, and surgical treatment of advanced HCC in order to provide some insight to devise strategies for surgical treatment of HCC and to update guidelines.

2. Overview of the development of HCC surgery in China

Before the 1950s, hepatectomies were seldom reported in China. Since the 1950s, Chinese surgeons have gradually performed regular extensive liver resection after bile duct exploration (*5*). However, the patients who underwent surgery at that time all had advanced HCC, the surgical procedure was complicated and time-consuming, and the postoperative mortality rate was as high as 30% (*6*). As surgical techniques continued to improve after the early 1960s, procedures such as a hepatectomy, a hemihepatectomy, and a regular hepatectomy began to be widely performed. In the 1970s, local resection of small HCC was proposed as a treatment model, and alpha-fetoprotein was measured. At the same time, the concept of "subclinical HCC" appeared, gradually leading to clinical orthotopic liver transplantation. After the 1980s, a regular hepatectomy was mainly performed, and surgical restrictions on the liver were lifted (*6*). In the 1990s, resection of giant HCC and laparoscopic liver resection were developed, and PVTT and bile duct tumor thrombus removal have been successful (*7*). The first living donor liver transplantation in China was completed (*8*). As modern liver surgery has rapidly developed since the beginning of the 21st century, many difficult liver surgeries can be completed laparoscopically or with robot assistance. New assistive technologies for liver surgery also continue to emerge, such as preoperative assessment of liver reserve function, preoperative three-dimensional imaging, intraoperative ultrasound, indocyanine green fluorescence imaging, laparoscopy and robotics, combined liver segmentation, and staged liver resection with portal vein ligation; these

technologies have improved the efficiency and accuracy of surgery (*9*). As surgical procedures and preoperative assistive technologies have continued to improve, the mortality rate for liver resection has dropped to less than 1% (*6*). However, the high rate of recurrence of HCC still limits the prospects of surgical treatment of HCC.

3. The concepts of down-staging therapy, conversion therapy, and neoadjuvant therapy

Down-staging therapy refers to converting a tumor in a later stage that was originally inoperable into one that is operable and in an earlier stage through systemic or local treatment. Conversion therapy refers to converting a tumor that was originally inoperable into one that can be resected using systemic or local treatment. However, conversion therapy is not the same as down-staging therapy. As an example, a tumor thrombus in the portal vein or superior mesenteric vein falls under BCLC stage C, which is not suitable for surgical resection. Conversion therapy is used to limit the tumor thrombus to the portal vein so that surgery can be performed. The tumor thrombus still falls under BCLC stage C and has not been down-staged, but it has been converted for resection. Therefore, conversion therapy can be regarded as a form of down-staging therapy. Neoadjuvant therapy refers to a tumor that can be surgically resected but it may have a high risk of recurring postoperatively. Therefore, local or systemic treatment is used for a period of time before surgery.

4. The focus of the use of neoadjuvant therapy in HCC

At present, research on neoadjuvant therapy for HCC has just started. Data from a clinical trial database indicate that as of October 2020, there are only 24 promising projects related to neoadjuvant therapy for HCC around the world. Only 15 of those projects are related to targeted immunotherapy, and neoadjuvant therapy for HCC in conjunction with surgery has not received sufficient attention (Table 1).

Table 1. Global studies related to neoadjuvant therapy for HCC (35 projects)

Status of research	Number
Hepatocellular carcinoma & neoadjuvants	35
Discontinued project	2
Non-neo-adjuvant treatment	9
Promising neoadjuvant therapies for HCC	24
Chemotherapy	1
Sorafenib	2
Radiotherapy	2
HAIC/TAI/TACE-TAI	6
Immunity therapy	6
Combined therapy based on immunotherapy	7
Phase III study or more than 150 subjects	9
Research from China	15

Data as of: November 18, 2020, source: *https://www.clinicaltrials.gov/*

4.1. The necessity and feasibility of neoadjuvant therapy for patients with HCC

According to the 2019 version of "Guidelines for the Diagnosis and Treatment Standards" (*4*), the indications for resection of HCC in China range from stage Ia to IIIa, which correspond to stage A, B, and part of C according to BCLC staging. HCC itself has a high rate of postoperative recurrence and expanded surgical indications involve more risk factors for recurrence including multiple tumors and vascular invasion, so the risk of recurrence increases further. Research on other types of cancer, such as colorectal cancer, has indicated that tumor micrometastasis occurs much earlier than expected. Metastatic seeding usually occurs several years before diagnosis or surgery. At the current point in time, tumor metastasis cannot be detected clinically (*10*).

In the event of early metastasis, an advantage of neoadjuvant therapy is that patients can receive multidisciplinary and systemic treatment earlier, micrometastasis can be controlled, the tumor burden can be reduced before surgery, the rate of R0 resection can be increased, recurrence can be delayed, and survival time can be prolonged (*11-13*). Patients with disease progression within 2 to 3 months are considered to benefit little from surgery. At the current point in time, neoadjuvant therapy can be used as a form of screening to avoid unnecessary surgical trauma to those patients (*14*). Neoadjuvant therapy has yielded favorable results in the treatment of various forms of cancer such as breast cancer (*15*), bladder cancer (*16*), colorectal cancer (*17*), and melanoma (*18*). Immunotherapy drugs have unique advantages in neoadjuvant therapy. Tumor-specific CD8+ T cells that are revitalized by immunotherapy will be activated, kill tumor cells, and circulate in the blood again. After the primary tumor is removed, the tumor-specific CD8+ T cells in the circulatory system and the T cells present at a metastatic focus can serve as a stable tumor-specific CD8+ T cell bank (*11*).

4.2. Indications for neoadjuvant therapy in patients with HCC

Wei *et al*. (*19*). compared the survival of patients with PVTT III HCC who received neoadjuvant radiotherapy and surgical resection with those who only received surgical resection. The neoadjuvant radiotherapy group had a longer long-term overall survival and disease-free survival than did the group receiving surgery alone. Neoadjuvant radiotherapy can reduce the risk of HCC recurring and death due to PVTT, and patients with large HCC can also benefit from preoperative TACE. Li *et al*. (*20*). retrospectively analyzed patients who underwent radical resection of massive HCC without large vessel

invasion in a multi-center database from 2004 to 2014, and they found that patients who received TACE before surgery had a lower mortality rate (67.9% *vs*. 81.0%) and rate of recurrence (76.2% *vs*. 85.7%) than did patients who did not receive TACE (P = 0.052 and 0.116). Patients receiving TACE before surgery had a median overall survival time of 32.8 months and a disease-free survival time of 12.9 months, which were better than the median overall survival time of 18.1 months and the disease-free survival time of 4.1 months for patients not receiving TACE (P = 0.023 and 0.009). TACE before surgery was an independent predictor of overall survival. Therefore, neoadjuvant therapy is crucial for patients with HCC with PVTT, giant liver tumors, and multiple liver tumors, and especially for patients who undergo resection in line with the expanded surgical indications according to BCLC staging in the 2019 version of the "Guidelines for the Diagnosis and Treatment of Primary Liver Cancer." Those patients all have a high risk of postoperative recurrence. Thus, rationally determining when to use neoadjuvant therapy is crucial. Establishing objective indicators with which to evaluate the efficacy of these therapies is vital.

4.3. Objective indicators with which to screen and evaluate neoadjuvant therapy

The objective response rate (ORR) refers to the ratio of patients with complete or partial remission of tumors as a result of treatment. This is an important indicator that is used to evaluate the efficacy of neoadjuvant therapy. Only therapies with a higher ORR are ideal neoadjuvant therapies. The current ORR benefit of single-drug therapy is limited, and combination therapy may have a higher ORR. Results of a phase Ib clinical study of lenvatinib combined with nivolumab in the treatment of patients with unresectable HCC were announced at the 2020 American Society of Clinical Oncology (ASCO) Gastrointestinal Tumor Symposium, and the study noted an ORR of 54.2%. Data from a phase Ib study of drug K combined with lenvatinib in the treatment of advanced HCC at the European Society for Medical Oncology (ESMO) conference in 2019 indicated that the ORR after the combination was 40.3%. Qin *et al*. (*21*) found that carrelizumab combined with apatinib resulted in an ORR of 44.4%. In 2019, the Fifth European Society of Medical Oncology Asian Annual Meeting reported that atezolizumab combined with bevacizumab to treat patients with unresectable HCC who had not received systemic treatment before resulted in an ORR of 27.0%. Xu *et al*. (*22*) found that carrelizumab combined with the FOLFOX4 regimen resulted in an ORR of 26.5% (Figure 1).

The disease control rate (DCR) refers to the proportion of patients whose cancer has completely remitted, partially remitted, or which remains the same (stable) for a certain period because neoadjuvant therapy can be used to treat a surgically resectable tumor. If the DCR is low, many patients will have disease progression during treatment and tumors that could be surgically resected will become inoperable. This will have a great negative effect not only on the patient but also on the doctor. Studies have indicated that a combination of medications results in a higher DCR than does a single medication (*23*). The REFLECT study compared the effects of lenvatinib and sorafenib as first-line treatments for unresectable advanced HCC, and it found that the DCR was 73.8% in patients receiving both drugs and 50% in those receiving sorafenib alone. A study announced at the 2019 ASCO annual meeting indicated that treatment of HCC with pabolizumab alone had a DCR of 62.2%. The Phase 1 and Phase 2 CheckMate-040 clinical study, which was announced at the same conference announced, found that nivolumab combined with ipilimumab for the treatment of HCC had a DCR of 54%. At the ESMO conference held in Barcelona, Spain in 2019, Lee at al. announced that the PD-L1 inhibitor atezolizumab combined with bevacizumab in the treatment of advanced HCC had a DCR of 72%. At the 2019 Annual Meeting of the American Association for Cancer Research, a study of the safety and efficacy of pembrolizumab combined with lenvatinib in the treatment of unresectable HCC indicated that the combination of drugs had a DCR of 93.3%. A study of lenvatinib combined with nivolumab in the first-line treatment of unresectable stage Ib HCC was announced at the ASCO Gastrointestinal Tumor Symposium held in 2020, and it found that the combination of drugs had a DCR as high as 96.7%. As is evident, a combination of medications has a significant advantage in terms of the

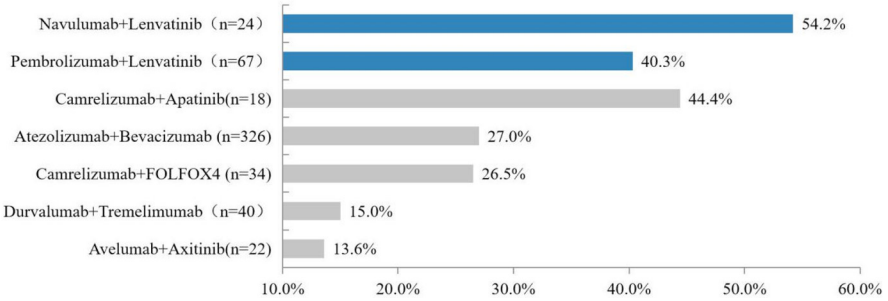

Figure 1. The ORR for several first-line combined immunotherapies for advanced HCC.

DCR compared to a single medication.

Progression-free survival (PFS) refers to the time from the beginning of treatment to tumor progression. This indicator can determine the course of neoadjuvant therapy to a certain extent. At present, the shortest PFS for single-agent therapy to treat advanced HCC is 2.8 months (sorafenib) (*24*) and the longest is 7.4 months (lenvatinib) (*25*). The shortest PFS for combination therapy is 5.6 months (atezolizumab combined with bevacizumab) (*26*) and the longest is 9.3 months (pembrolizumab combined with lenvatinib) (*27*). If the current duration of neoadjuvant therapy for advanced HCC is kept to 4 to 6 cycles (2 to 3 months), then it is within the PFS for most forms of treatment.

Liver-related adverse reactions that are grade III or worse should serve as an important indicator with which to evaluate the safety of neoadjuvant therapy. The ideal neoadjuvant therapy should try to ensure minimal impact on liver function and avoid postoperative liver failure in order to ensure that patients can successfully and safely undergo liver resection after neoadjuvant therapy. At present, the rate of all liver-related adverse reactions to neoadjuvant therapy that are grade III or worse is ≤ 10% for targeted monotherapies or immunotherapies. The rate of adverse reactions to pembrolizumab combined with lenvatinib is about 10.4%, and that for nivolumab combined with lenvatinib is about 10%. Therefore, whether targeted therapy or immunotherapy should be used as a preoperative neoadjuvant therapy should ideally be based on how safe it is to the liver.

4.4. Neoadjuvant treatment plan

At present, most guidelines for neoadjuvant therapy do not have recommended regimens or protocols. Only the 2020 edition of CSCO's "Guidelines for the Diagnosis and Treatment of Primary Liver Cancer" recommend neoadjuvant radiotherapy for patients with a tumor thrombus in the portal vein trunk or branch (*28*). TACE has yet to be accepted as a neoadjuvant therapy because of its low effectiveness and related liver toxicity. As targeted therapies and immunotherapies are developed, they will need to be screened to determine if they qualify as an ideal neoadjuvant therapy in terms of ORR, DCR, PFS, or the incidence of liver-related adverse reactions. Neoadjuvant therapies offer great promise for the future.

5. Clinical significance of surgical treatment for patients with CNLC stage IIIb HCC

The 2019 version of the "Guidelines for the Diagnosis and Treatment of Primary Liver Cancer" specified that patients with stage IIIb cancer mainly receive systemic treatment (sorafenib, lenvatinib, FOLFOX4, and regorafenib), TACE, or radiotherapy. Surgical treatment was not an option. As systemic therapy is further used to treat patients with advanced HCC, in the current authors' clinical experience several patients with stage IIIb HCC who have undergone combined treatment have become eligible to undergo surgical resection. Postoperative pathological examinations have indicated that the main body of the tumor was partially or completely necrotic, suggesting that some stage IIIb tumors can be surgically removed after systemic treatment, but there is still a lack of indicators with which to objectively evaluate whether patients with stage IIIb HCC can undergo surgical treatment.

No evidence of disease (NED) refers to the fact that no evidence of residual tumor is found after a tumor is treated using existing methods of testing. This means that a tumor is no longer present in a patient. NED is a static concept. It only indicates that tumor cells cannot be detected at the time of testing. False negative results due to insufficient sensitivity of the method of testing cannot be ruled out. If, however, NED continues for a sufficient amount of time, then a radical cure is deemed to have been achieved. In 2016, ESMO's guidelines for metastatic colorectal cancer listed NED as a treatment target. However, current Chinese and Western guidelines and expert consensus opinions on treatment of primary HCC have not mentioned the concept of NED, and no studies have reported on both primary HCC and NED.

As systemic treatments develop, the goal of surgical treatment of primary HCC is no longer limited to radical resection. Patients with stage IIIb HCC can become eligible for surgical resection after systemic treatment and NED is achieved. Therefore, the concept of NED could be applied to treatment of HCC to objectively evaluate whether patients with stage IIIb HCC can undergo surgery. As the effectiveness of systemic treatment continues to improve, the proportion of patients with HCC in whom NED is achieved will also increase substantially, and NED will be an important goal for the surgical treatment of HCC in the future. Therefore, guidelines are not static. With an effective evaluation system in place, some patients with stage IIIb HCC could receive surgical treatment, and the indications for surgical treatment of HCC in the Chinese guidelines should be further expanded.

6. Problems and challenges

Surgical treatment is still the main treatment for patients with resectable HCC. That said, researchers are increasingly exploring multimodal therapies to reduce the rate of recurrence and increase the proportion of patients who are eligible for surgery. However, the role of neoadjuvant therapy in treating HCC still needs to be studied further due to the lack of high-level evidence in the literature. Therefore, future research on neoadjuvant therapy should obtain more data by paying more attention to the standardization of endpoints and trial design and by identifying biomarkers

of therapeutic response and mechanisms of resistance. As neoadjuvant therapy continues to develop thanks to advances in immunotherapy and targeted therapy, randomized controlled trials of large samples will need to be conducted to determine the best combination and sequence of multimodal therapies.

7. Conclusion

The probability of postoperative recurrence has increased as surgical indications for HCC have expanded, and postoperative adjuvant therapy has become a topic of interest. The use of neoadjuvant therapy to treat HCC has just started. It is theoretically feasible and requires more practical experience. At the same time, the current era of targeted therapy and immunotherapy has made that therapy more feasible. Neoadjuvant therapy will definitely become a new area of interest in the treatment of resectable HCC with a high risk of recurrence. With effective systemic treatment, extrahepatic metastasis will no longer be a contraindication for surgery. Therefore, surgical treatment needs to be gradually expanded to include advanced HCC, and medical treatment using neoadjuvant therapy needs to be provided in the early stages of HCC. In addition, knowledge about treating HCC needs to be standardized so that new treatment strategies and protocols can be developed.

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Review

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The multidisciplinary management of hepatocellular carcinoma with portal vein tumor thrombus

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SUMMARY Portal vein tumor thrombus (PVTT) is one of the most common complications of hepatocellular carcinoma (HCC), which refers to the advanced stage of HCC and indicates an extremely poor prognosis. Monotherapy cannot effectively prolong the survival benefit of patients with HCC-PVTT characterized by a high recurrence rate. With great progress in the area of immune and molecular targeted therapy, there comes a promising era of multidisciplinary management of HCC. Survival benefits can be achieved based on accurate diagnosis, staging, and multidisciplinary management. Additionally, in terms of the presence of controversy about the standard treatment algorithm and the absence of universal treatment guidelines, a multidisciplinary management program may afford the best hope for HCC-PVTT patients *via* appropriate implement of various treatment protocols.

Keywords hepatocellular carcinoma, portal vein tumor thrombus, management

1. Introduction

As the sixth most common cancer and the fourth leading cause of cancer-related deaths, liver cancer, which is intractable to treat and has a high rate of recurrence, seriously threatens the health of people around the world (*1*), simultaneously poses a great challenge to the liver disease specialists. Hepatocellular carcinoma accounts for about 75-85% of liver cancer with aggressive biological characteristics invading the portal vein, causing one of the most common complications of HCC- portal vein tumor thrombus (PVTT). It is commonly accepted that PVTT indicates a poor prognosis with median overall survival (MST) of 2.7-4.0 months without any intervention implemented (*2*). According to the Barcelona liver cancer staging system (BCLC staging), HCC with PVTT refers to the BCLC C stage and the only modality of treatment patients can benefit from is oral sorafenib with MST of 6.5 months (*3,4*). However, the BCLC staging system has not defined the extent of PVTT, which is significantly related to prognosis after treatment. There are only two classifications about PVTT, the Japanese Vp classification and the Chinese Cheng's classification worldwide (*5*). Referring to the classification based on the extent of PVTT, patients that may obtain better survival benefits from surgical resection can be selected. Numerous studies have demonstrated the significant survival benefit of surgical resection, and the postoperative 5-year survival ranges from 10% to 59% (*6-10*), Unfortunately, nearly half (44-62%) of patients with HCC will develop PVTT, and only a few of them can obtain a curative operation after being carefully selected. Therefore, it is necessary to identify such patients that can achieve better survival through surgical treatment and meanwhile provide more active treatment suggestions for other unresectable HCC patients with PVTT to prolong survival time and quality of life.

2. Multidisciplinary management program of hepatocellular carcinoma

In China, approximately 80% of patients with HCC have a background of hepatitis B virus (HBV) infection and various degrees of liver function damage. In recent years, with great progress in surgical technique, locoregional therapy, radiation therapy, molecular targeted, and immune therapy, through the combination of these treatment modalities, the outcome of HCC patients complicated by PVTT has significantly improved. In terms of heterogeneity and multiple treatment protocols of patients with HCC-PVTT under the absence of established guidelines, it is important

to achieve better cooperation and collaboration from different disciplines through a multidisciplinary management paradigm, subsequently making individual suggestions for patients with HCC-PVTT (*11,12*). The HCC multidisciplinary team (MDT) consists of hepatologist, medical oncologists, surgical oncologists, diagnostic radiologists, pathologists, interventional radiologists, and radiation oncologists, which formulate treatment strategies by referring to the Chinese expert consensus on multidisciplinary diagnosis and treatment of HCC with PVTT (*13*)

2.1. Resectable or downstage to resectable HCC-PVTT

Different from Western countries, HCC-PVTT tends to be addressed using potentially curative treatment, such as surgical resection in combination with various local therapy or systemic treatment, in Asia-pacific countries under careful evaluation. For those deemed as unresectable HCC with PVTT, MDT members tend to utilize multiple local or systemic therapies to downstage HCC to fall into resectable criteria, where salvage surgery can promote the prognosis (*14,15*). The MST and mortality rate ranged from 8 to 22 months, 0% to 10%, respectively, for HCC-PVTT patients who underwent surgical resection (*16*). The 3-year survival rate is approximately 11.7% in conjunction with transcatheter arterial chemoembolization (TACE) following surgery (*6*). The MST reported by different institutions varies significantly, partly due to the evaluation criteria of resectability. In this setting, the selection of patients who may potentially benefit from surgery using certain criteria is critical in clinical practice. Generally, PVTT confined to the first branch of the main portal vein trunk (MPV) or above referring to type I, or II of Cheng's classification can get better survival than type III/IV PVTT after surgical resection. Zhang *et al.* established a scoring system (EHBH-PVTT) that can identify candidates that may obtain better MST postoperatively based on four clinical variables (total bilirubin (TB), α-fetoprotein (AFP), tumor diameter, and satellite lesions) (*7*). Considering the extremely high recurrence rate and poor prognosis of PVTT, not only carefully selecting surgical candidates but combining different local or systemic therapies for neoadjuvant or adjuvant treatment is necessary to augment the pathologic response rate and survival benefit. For neoadjuvant therapy, a randomized, open-label, multicenter controlled study demonstrated that neoadjuvant three-dimensional conformal radiation therapy (3DCRT) combined surgery can obtain better overall and disease-free survival compared with surgery alone (*17*). Harris Liou *et al.* reported that using yttrium-90 (Y-90) transarterial radioembolization (TARE) combined with nivolumab for neoadjuvant therapy following liver transplantation or surgical resection, two cases of HCC with PVTT had a complete pathologic response (*18*). However, it is also argued that the tumor may progress during the interval to surgical resection especially for patients who respond poorly to neoadjuvant therapy. Additionally, pre-operative TARE, 3DCRT, and other modalities of neoadjuvant therapy may increase the difficulty of operations because of tissue adhesion arising from the side effects of radiation or chemical drugs. Therefore, it is of clinical significance to build prediction models that can identify the potential candidates responding well to neoadjuvant therapy. For adjuvant therapy, postoperative adjuvant TACE (PA-TACE) is a commonly used method to improve the postoperative long-term outcome (*19,20*). A retrospective study by propensity score matching, which included 464 patients with HCC and PVTT indicated that PA-TACE has better MST compared with surgery alone, especially for type II/III PVTT according to Cheng's classification (*21*). A subgroup analysis of systemic review and meta-analysis revealed that adjuvant TACE following surgery is associated with improved disease-free survival (DFS) and overall survival (OS) compared with surgery alone (*22*). However, subgroup analysis of the meta-analysis included only one RCT and one NRCT, allowing the adjuvant role of TACE to be controversial. The small number of RCT with PVTT is partially due to the risk of liver failure caused by TACE. However, more prospective randomized control trials are greatly needed to further illuminate the role of neoadjuvant and adjuvant therapy following surgical resection for PVTT.

2.2. Unresectable PVTT

For patients with unresectable PVTT, local therapy and systemic treatment by combination or monotherapy are the backbone to prolong survival time and improve quality of life. TACE, hepatic arterial infusion chemotherapy (HAIC), radiation therapy (RT), molecular target, and immune therapy are commonly used treatments for unresectable HCC with PVTT. In terms of this refractory complication of HCC, monotherapy is not enough. Additionally, Mechanized diagnosis and treatment based solely on established guidelines are likely to omit patients who may benefit from active treatment. With the breakthroughs of molecular targeted therapy and immune therapy, plenty of clinical trials combining various treatment methods emerged, leading to improvement of the prognosis of HCC-PVTT (*23*).

2.2.1. Locoregional therapy

TACE is the most common palliative local modality used for unresectable HCC. Theoretically, TACE is considered a relatively contraindication in patients with PVTT, especially for type III/IV PVTT, since

portal vein occlusion caused by PVTT will lead to liver failure after TACE (*24-26*). However, recent studies have demonstrated the role of TACE in well-selected patients with good liver function and adequate collateral circulation around the obstructed portal vein, which can also obtain MST of 5.6-8.7 months in all types of PVTT as reported (*27*). A retrospective study by propensity score matching suggested that TACE is associated with better 1,2 and 3-years OS rates compared with best supportive care (45.3%, 27.7%, and 19.3 *vs.* 41.1%,15.7%, and 11.6%; p = 0.002) (*28*). However, tumor necrosis caused by TACE will lead to the release of angiogenic growth factors simultaneously, which may confer a negative effect on tumor control. Combined with sorafenib and other tyrosine kinase inhibitors (TKIs), which can block angiogenic growth factors may reduce the side-effects attributed to TACE, thereby improving the outcome of TACE, theoretically. A nationwide population-based cohort study comparing TACE monotherapy with TACE plus sorafenib suggested that the TACE-sorafenib combination strategy has a better median OS (6.7 months *vs.* 12.5 months, respectively) (*29*). However, a phase III STAH trial had the opposite outcome. The median OS was 12.8 in the TACE plus sorafenib group and 10.8 months in the TACE monotherapy group (p = 0.290), which suggested that no difference was found between the two groups. As for the time to progression, progression-free survival, and tumor response rate, results were found to be better in the TACE-sorafenib group. Therefore, the effect of TACE combined with TKIs on oncological outcome in advanced HCC still needs to be further delineated by more prospective control trials. Apart from TACE combined with sorafenib, another combination protocol showing potential benefits is HAIC plus sorafenib. A randomized phase 3 trial demonstrated that sorafenib combined with HAIC using oxaliplatin, fluorouracil, and leucovorin (FOLFOX) achieved better median OS, higher response rate, and longer median progression-free survival compared to sorafenib monotherapy in patients with portal vein invasion (*30*). Except for HAIC, TARE with Yttrium-90 (Y-90) microspheres has also presented promising results on tumor control, which is characterized by minimizing damage to liver parenchyma surrounding the tumor and alteration of hepatic arterial flow (*31*). Two III-phase randomized control trials comparing TARE and sorafenib in locally advanced HCC failed to demonstrate better OS by TARE. However, better tolerance of treatment and quality of life in patients with HCC was observed in the TARE group (*32,33*). As to the combination of sorafenib with TARE, a retrospective study suggested that no significant differences in survival outcomes were identified between sorafenib plus TARE and TARE monotherapy (median overall survival 10 *vs.* 10 months; p = 0.711) (*34*). Albeit the uncertainty of TARE in treating HCC-PVTT, TARE may be used as an alternative modality to increase the surgery eligibility as well as enhance OS.

2.2.2. Systemic therapy

Sorafenib, one TKI whose effect was proved by two large RCT trials, is generally accepted to apply to patients with advanced HCC (*3,4*). Lenvatinib another TKI also deems as the first-line therapy which is no-inferior to sorafenib for advanced HCC (*35*). Nevertheless, the response rate to TKIs is low and the benefit of patients with advanced HCC from sorafenib is modest with overall survival time being extended by approximately three months (*3*). Therefore, the combination of systemic therapy with local-regional therapy is still the mainstay of the treatment protocol for advanced HCC, especially those complicated by PVTT. Recently, immune checkpoint inhibitors (ICIs) also revealed promising outcomes for advanced HCC and multiple RCTs testing the outcome of combinations with other ICIs or TKIs are ongoing. The reported response rates to ICIs monotherapy ranged from 15% to 23% and increased to approximately 30% after combination with other systemic agents (*36*). However, considering the relatively low response rate and hyper-progression caused by ICIs in a small group of patients, a further study focusing on the biomarkers for the selection of candidates is urgently needed.

3. Conclusion

Currently, HCC complicated by macro portal vein invasion is a hard to treat bottleneck, which worsens the prognosis of HCC patients. Surgical resection is still the best potential curative method for patients with HCC and PVTT under careful estimation and selection. Combination strategies are necessary to effectively control tumor burden and reduce the risk of recurrence postoperatively. In the era of multidisciplinary management, communication and cooperation between different disciplines make patients with HCC have a better survival *via* accurate diagnosis and individual treatment. In the future, more RCTs focusing on the combination of different treatments and innovative treatments need to be performed to offer more effective choices for clinical practice.

4. The MDT of West China Hospital

Based on the BRIDGE study, a large retrospective cohort study reviewing the diagnosis and treatment data of 18,031 HCC patients from 2005 to 2012, it was indicated that patients with HCC in China have significant characteristics, including younger age of onset, more HBV infections, and relatively advanced staging. The patients with BCLC stage C and portal

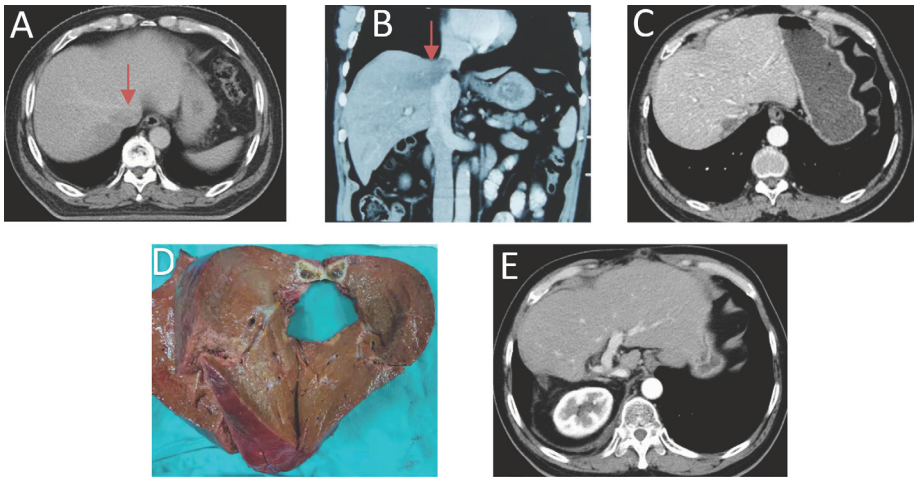

Figure 1. (A), The imaging of contrast-enhanced CT demonstrating a tumor 4.3 × 6.3 cm in diameter in the upper right posterior lobe of the liver with inferior vena cava tumor thrombus (red arrow). **(B)**, Contrast-enhanced CT demonstrating tumor invading into inferior vena cava (red arrow). **(C)**, Contrast-enhanced CT 2 months after SBRT combined with targeted therapy showed significantly decreased main tumor and thrombus. **(D)**, the specimen of resected liver. **(E)**, Contrast-enhanced CT 1 year after surgery demonstrating no obvious tumor recurrence.

vein invasion accounted for 55% and 23% of patients with HCC in the China cohort, respectively (*37*). Similarly, in our institute, the West China Hospital, there are 15,000 patients with HCC visiting the outpatient clinic annually, of whom 1,700 cases were surgically treated, and 493 cases were complicated by macro PVTT, of which 90 cases had undergone surgical resection. About 90% of HCC patients required comprehensive treatment other than surgery. Therefore, the West China Hospital launched a multidisciplinary management program for HCC, especially for HCC patients with PVTT, on March 7, 2019. In 2019, a total of 262 patients with HCC visited our MDT outpatient clinic, of which approximately 49% had a PVTT complication, 2% of patients with inferior vena cava tumor thrombus, and 2% with two kinds of tumor thrombus. Approximately 40% of patients underwent combined treatment and 6 patients underwent surgical resection after successful downstaging. While the MDT outpatient clinic can make more accurate diagnoses, comprehensive and individual treatment suggestions to patients, it saves time by avoiding the referral between different disciplines, which usually happens in traditional clinics. Even though the number of patients with vascular tumor thrombus getting curative surgery after downstage treatment is small, MDT still offers the best hope for them to prolong survival time.

5. Case presentation

Case 1

The patient was a 52-year-old Chinese man with a history of treatment for hepatitis B and child-pugh A cirrhosis presented to our center with abdominal CT examination revealing that HCC 4.3 × 6.3 cm in diameter in the upper right posterior lobe of the liver and inferior vena cava tumor thrombus. His AFP and Protein Induced by Vitamin K Absence II (PIVKA-II) were 614.1 ng/mL and 119 mAU/mL, respectively. Neoadjuvant stereotactic body radiation therapy (SBRT) combined with sorafenib (400 mg po. bid.) was planned after MDT was reviewed, in an attempt to eliminate the inferior vena cava tumor thrombus while controlling tumor growth to allow for a biologic test-of-time. The planning target volume was 40 Gy, with a fractional size of 8 Gy at five fractions per week. Imaging evaluation performed 2 months after treatment demonstrated that the size of the tumor and thrombus were significantly smaller than pre-neoadjuvant therapy with no evidence of intrahepatic tumor progression or metastatic disease (Figure 1). Laboratory results revealed that AFP decreased from 374 to 57 ng/mL and PIVKA decreased from 119 to 37 mAU/mL with well-preserved liver function. The patient subsequently underwent open right posterior lobe resection with inferior vena cava incision and tumor thrombus removal. The patient experienced no major postoperative complications and was discharged 9 days after surgery. Pathology of the resected liver tissue demonstrated negative margins and no viable malignancy. Surveillance imaging 19 months after resection demonstrated no evidence of recurrence.

Case 2

A 51-year-old male with a history of treated hepatitis B and Child-Pugh A cirrhosis presented to our institution with a left and right liver lobe giant HCC and intrahepatic metastasis. The diameter of the largest tumor in the left lobe increased from 9.1 × 6.1 cm to 10.3 × 7.1 cm and serum PIVKA-II rose from 9,108 mAU/mL to 15,153 mAU/mL with a normal AFP after sorafenib treatment of two weeks and the first TACE. MDT members decided to perform a second TACE, and then use PD-1 inhibitor (camrelizumab) combined with Lenvatinib, because of the insensitivity of sorafenib

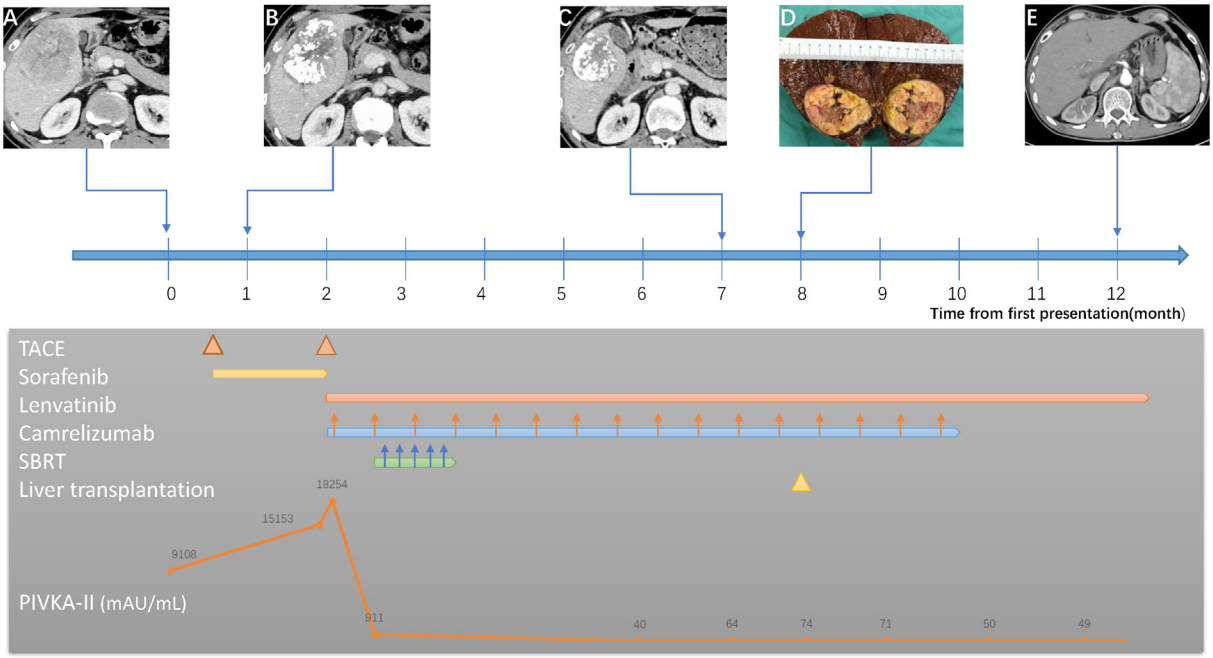

Figure 2. The figure demonstrates the variation of treatment procedures and tumor marker level with the passage of time. Blue line in the middle of the figure represents the timeline. The images of CT and postoperative specimen are presented above the timeline. (A), Contrast-enhanced CT of liver revealing the left and right liver lobe giant HCC (9.1 × 6.1 cm) combined with intrahepatic metastasis. **(B)**, Contrast-enhanced CT demonstrating the diameter of the lesion increased from 9.1 × 6.1 cm to 10.3 × 7.1 cm after 3 weeks treatment of TACE combined with sorafenib. **(C)**, Contrast-enhanced CT demonstrating a significant decrease of main tumor after 5 months treatment of targeted and immune therapy. **(D)**, Contrast-enhanced CT 4 months after liver transplantation demonstrating no obvious tumor recurrence. **(E)**, The resected specimen of diseased liver. CT: computed tomography; TACE: transcatheter arterial chemoembolization; SBRT: stereotactic body radiation therapy. PIVKA-II: protein induced by vitamin K absence II

after 6 weeks of treatment. The patient was started on the second TACE, camrelizumab (200mg *iv.* every two weeks) combined with Lenvatinib (8 mg po. qd.), and underwent SBRT with a planning target volume of 5,000 cGy and a fraction size of 1,000 cGy. Imaging demonstrated a complete response, with PIVKA-II decreased from 18,254 mAU/mL to 40 mAU/mL within 4 months and well-preserved liver function. Subsequently, the patient underwent liver transplantation 2 months later (Figure 2). Liver explant pathology revealed complete necrosis. The patient was discharged postoperatively after 3 weeks with normal liver graft function. Imaging evaluation demonstrated no evidence of tumor recurrence within 6 months of follow-up.

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Conversion therapy and maintenance therapy for primary hepatocellular carcinoma

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SUMMARY The preferred treatment for hepatocellular carcinoma (HCC) is surgery, which is the only way to achieve long-term survival and even a cure. However, the vast majority of patients with liver cancer in China are already in the middle to advanced stage of the disease and no longer have the opportunity to undergo surgery. The goal of conversion therapy is to transform unresectable advanced liver cancer or potentially resectable liver cancer into resectable cancer, so it has become a topic of interest in the treatment of advanced liver cancer. Common modalities of conversion therapy are: local treatment (TACE, TARE, or HAIC), systemic treatment (targeted therapy alone or combined with immunotherapy), and a therapeutic alliance (TACE combined with radiation therapy, TACE combined with targeted therapy, HAIC combined with targeted therapy, or HAIC combined with targeted therapy and immunotherapy). The plan for maintenance treatment after conversion therapy is determined based on the outcome of conversion therapy to obtain the best survival benefit for patients.

Keywords hepatocellular carcinoma, conversion therapy, maintenance therapy, China

1. Introduction

Hepatocellular carcinoma (HCC) is the second most common malignant tumor in China; about half of the new patients with HCC worldwide are Chinese, and approximately 300,000-400,000 people die from HCC each year (*1,2*). A survey of the current status of treatment for HCC in China indicates that most patients with HCC are already in the middle to late stages of the disease when diagnosed and no longer have the chance to undergo surgery (*3*). In the past, systemic treatment had limited effectiveness, and the emergence of targeted and immunotherapy drugs over the last two years has brought hope for the non-surgical treatment of HCC. In this context, several old terms from other fields have become topics of interest in the field of liver cancer treatment: downstaging therapy, conversion therapy, and neoadjuvant therapy. The aim of the current review is to provide some ideas for conversion treatment strategies and updates for HCC guidelines in China in this new era by systematically discussing the definitions of these terms, the related treatment modalities, and the subsequent treatment strategies.

2. Downstaging therapy and conversion therapy

Downstaging therapy is a method of turning an inoperable tumor in an advanced stage into an operable tumor in an earlier stage via systemic or local treatment. The term was first used in liver transplantation for HCC. As an example, patients who fell outside the Milan criteria and were not eligible for priority liver transplantation (United Network for Organ Sharing (UNOS) stage T3) were treated locally (transhepatic artery chemoembolization (TACE), ablation, *etc*.) to shrink or reduce the number of tumors to meet the Milan criteria (UNOS stage T2), and then transplantation was performed (*4*). The prognosis of successful liver transplantation was similar to that of a standard stage I liver transplantation. Conversion therapy is the conversion of an otherwise unresectable cancer into a surgically resectable one by means of systemic or local treatment. However, conversion therapy is again not equivalent to downstaging therapy. For example, HCC involving the main trunk of the portal vein or the main trunk of the superior mesenteric vein is BCLC stage C, meaning it is inoperable or unsuitable for surgical resection, but through conversion therapy, the tumor thrombus is reduced to the branch of portal vein and then operated on. If the tumor thrombus disappears completely after conversion therapy, it changes from BCLC stage C to BCLC stage B or A, and then conversion therapy lowers the tumor stage, so conversion therapy can be regarded as a part of

downstaging therapy. In the treatment of HCC in particular, liver resection is the goal of treatment rather than liver transplantation, so conversion therapy has greater practical value in clinical terms. Although the use of conversion therapy (including the combination of targeted therapy, immunotherapy, and interventional therapy) in the treatment of advanced HCC is still in its infancy, it has become a topic of interest in the treatment of advanced HCC because it can reduce the tumor size and focal necrosis, which can convert unresectable or potentially resectable HCC into radically resectable HCC.

3. Common modalities of conversion therapy

In 1993, Sitzmann & Abrams (*5*) were the first to report on unresectable cancer in 14 patients that was converted to resectable cancer after radiotherapy combined with chemotherapy. This opened the door to down-staging conversion of HCC. Various approaches subsequently emerged, including local and systemic treatments and more often a combination of the two.

3.1. Local treatment

Most commonly used local treatments include TACE, transhepatic artery radioembolization (TARE), and hepatic artery infusion chemotherapy (HAIC). TACE has been widely used in the treatment of mid- to late-stage HCC. Cancer in about 8-18% of patients is converted into an operable form after TACE treatment, and the 5-year survival rate of patients treated with surgery after downstaging TACE may be as high as 24.9-57%, and an even longer survival has been achieved in some patients (*6*). TACE has yielded long-term clinical results and offered a chance to those patients with HCC who were ineligible for radical surgery when initially diagnosed. TARE, which has 2 actions to kill a tumor, usually uses yttrium-90 as an embolic agent. Of 35 patients with UNOS stage T3 cancer, Kulik *et al*. (*7*) reported that TARE treatment successfully downstaged the cancer to T2 in 19 of 34 patients (56%) and that cancer in 23 (66%) of the 35 patients was downstaged to the extent that the patients were eligible for RFA or resection, creating a bridge to surgical procedures and yielding better results. In a recent study (*8*), however, only 9% of patients with HCC who were treated with TARE underwent liver transplantation (LT) or liver resection (LR). However, a promising result of that study is that the OS was 47 months while survival rates at 1-, 3-, and 5-years reached 97, 86, and 86%, respectively. Although the conversion rates differ considerably among studies, the long-term outcomes are consistent (*7-9*), suggesting that as long as conversion is achieved, the prognosis should be as good as that for patients undergoing radical resection following initial diagnosis. A point worth noting is that the extent of tumor necrosis still increases 3-6 months after TARE due to the lagging effect of radiotherapy on tumor cell killing, so repeated use of TARE is not required within 6 months.

HAIC has not been validated in large-scale randomized clinical trials, and thus guidelines on liver cancer from the American Association for the Study of Liver Diseases (AASLD), the National Comprehensive Cancer Network (NCCN), the European Society of Liver Diseases (EASL) and the Asia-Pacific Association for the Study of the Liver (APASL) (*10-13*) do not consider HAIC to be a recommended treatment for advanced HCC. However, HAIC has been used in Asia, and especially in Japan and South Korea, as an approach that can improve outcomes in advanced HCC and it is included in treatment guidelines (*14*). HAIC is greatly underestimated due to the small sample size in previous studies and the lack of large-scale randomized trials. In fact, HAIC is theoretically more effective than systemic chemotherapy for HCC because hepatic arterial infusion of anticancer drugs allows direct delivery of high doses of drugs to highly vascular HCC, including those micro metastases that cannot be detected with imaging and that may not have an obvious arterial blood supply. The intrahepatic first-pass effect results in lower systemic levels of HAIC drugs than systemic administration, reducing toxic effects and adverse events. In a randomized phase III study (9810) announced at ESMO 2020, HAIC (oxaliplatin, fluorouracil, and folinic acid) *vs*. hepatic artery chemoembolization for unresectable HCC with TACE resulted in a significant difference in the surgical conversion rate of 23.8% in the HAIC group *vs*. 11.5% in the TACE group ($p < 0.004$).

3.2. Systemic treatment

Sorafenib was effective as the first first-line standard systemic therapeutic agent for advanced HCC that was unresectable when diagnosed. Since then, many other promising drugs, including tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors, have been developed, making significant advances in systemic therapy for liver cancer. However, a single agent yields limited clinical results. The overall response rate (ORR) after sorafenib monotherapy was only 3.3% (*15*), that for cabozantinib was 4.0% (*16*), and that for regorafenib was 6.5%. Lenvatinib, which is an inhibitor of VEGF receptors 1-3, FGF receptors 1-4, PDGF receptor α, RET, and KIT, is reported to have an ORR as high as approximately 18.8%, which is much higher than that of sorafenib (*17*). However, lenvatinib and sorafenib groups have a similar OS, and patients with a tumor occupying ≥ 50% of the liver, obvious invasion of the bile duct, or portal vein invasion at the main portal vein were excluded from that study, which may explain the difference in ORR. At ESMO 2019,

nivolumab was reported to have an ORR of 15.0% alone, and the ORR for pembrolizumab alone was 18.3%. In a multicenter randomized phase II trial, Qin *et al*. found that carrilizumab alone had an ORR of only 14.7% (*18*). Although these results from worldwide centers are interesting and promising, the level of effectiveness is insufficient to meet clinical needs. Thus, combination therapy may yield a higher ORR compared to monotherapy and may signal the advent of a new era of conversion therapy for advanced HCC. As announced at ASCO-GI 2020, a phase 1b clinical study on lenvatinib in combination with nivolumab in patients with unresectable HCC noted an ORR of 54.2% after lenvatinib in combination with nivolumab (ASCO-GI 2020, Ib (117)). As announced at the 2019 ESMO Congress, the latest data from a phase 1b study on pembrolizumab combined with lenvatinib for advanced HCC indicated that the combination had an ORR of 46.3% (2019 ESMO (747P)). Qin *et al*. found that carrilizumab combined with apatinib had an ORR of 44.4% (*18*). Prognosis has sharply improved for patients with advanced HCC and the low rate of liver-related adverse reactions with combination therapy has made subsequent surgery safer. As a result, targeted therapy combined with immunotherapy is now the most commonly used approach for the conversion of HCC. At the 2020 ASCO Annual Meeting, Sun *et al*. (*19*) reported on 60 patients with unresectable cancer who received targeted therapy with a small-molecule TKI combined with immune checkpoint inhibitors. The cancer in 11 (18.3%) of those patients was converted to resectable HCC. As announced at ESMO Asia 2020, a study by Zhang *et al*. (*20*) found that HCC with portal vein tumor thrombosis (PVTT) was converted to a surgically resectable form in 42.4% of 33 patients received targeted therapy with a small molecule TKI combined with immune checkpoint inhibitors. These two recent studies provide further evidence for the feasibility and effectiveness of combination therapy.

3.3. Other combined treatment modalities

3.3.1. TACE-based combined therapy

The role of external radiation therapy in the treatment of liver cancer has gradually been highlighted, and the effectiveness of radiotherapy for HCC has significantly improved due to precise positioning technology. It has become an important tool for the conversion of HCC, and especially for the control of a tumor thrombus. External radiation therapy is mainly combined with interventional therapy for the conversion of advanced HCC with portal vein and inferior vena cava tumor thrombi.

In 2017, Li and Zhou (*21*) reported 21 cases of HCC treated with TACE combined with sorafenib that were unresectable on initial evaluation. In this Chinese study, the 1-, 2-, and 3-year OS rates were 85.7, 71.4, and 57.1%, respectively; these rates were much higher than that for regular treatment such as TACE or sorafenib alone. An important point is that sorafenib was used as maintenance therapy after surgery, which may enhance the survival rate accordingly. Although sorafenib was unable to improve the prognosis for patients who underwent radical resection following initial diagnosis, its value as maintenance therapy for down-staged advanced HCC warrants more attention and related clinical trials should be conducted like those with other TKIs and immuno-agents.

3.3.3. HAIC-based combined therapy

In a retrospective cohort study, Hamaoka *et al*. (*22*) evaluated the survival benefit and safety of hepatectomy after down-staging with 3-dimensional conformal radiation therapy (3D-CRT) for major PVTT and HAIC for unresectable HCC. Seven of the 52 patients became eligible for surgery, and there was a significant difference in overall survival (OS) between the surgical and non-surgical resection groups ($p = 0.009$). In 2019, He *et al*. (*21*) reported a conversion rate of 12.8% in patients with unresectable HCC treated with HAIC in combination with sorafenib, indicating that HAIC-based combined therapy could also yield results as good as those of TACE-based therapies. A recent study by Shi *et al*. (*23*) announced at ESMO Asia in 2020 (*24*) found that HAIC plus targeted therapy and immunotherapy for advanced HCC had an ORR of 67.6% according to the mRECIST criteria, which is the highest of all combination regimens available and offers a new option for HAIC-based conversion therapy in the future.

Conversion therapy is currently performed using a variety of approaches and regimens, and conversion therapy for advanced HCC is currently being studied, but there is no higher level evidence to confirm which treatment option is best. Thus, close collaboration of multidisciplinary teams is essential, requiring individualized treatment plans tailored to the patient's condition or the skills and experience of the treatment teams. That said, the overall trend is towards combination therapy. The conversion rate of combined therapy is higher than that of monotherapy, and the efficiency of combined local and systemic therapy is higher than that of local or targeted therapy combined with immunotherapy. A goal-oriented treatment strategy, the aim of conversion therapy is to achieve radical surgical resection and obtain a higher conversion rate. The most potent combination therapy regimen may be used in the future as long as the patient's physical condition and liver and kidney function permit. This could include HAIC combined with small-molecule TKIs and immune checkpoint inhibitors or TACE combined with radiotherapy, TKIs, and immune checkpoint inhibitors.

4. Maintenance therapy after conversion therapy is determined by the outcome of conversion therapy

4.1. Tumor progression is stable or the tumor is in partial remission but there is still no possibility of surgical resection

If the first-line conversion option is to use a potent and efficient local and systemic regimen, then the second-line treatment option should be a combination therapy causing fewer and less severe adverse reactions or a monotherapy, such as a second-line targeted drug or a targeted drug combined with an immune checkpoint inhibitor. After all, the main treatment goal for patients at this point is no longer conversion to surgery but to prolong survival as long as possible.

If the patient's physical status and liver, kidney, bone marrow function are sufficient and conversion is not prolonged, then the current treatment can be maintained until yielding results. The tumor may shrink further with additional rounds of treatment and be downgraded to a resectable status; if the patient has already received sufficient rounds of conversional therapy and his or her physical strength or liver, kidney, and bone marrow function are no longer sufficient to tolerate a potent treatment regimen, then options in the event of failure should be considered.

4.2. Successful tumor conversion following radical surgical resection

There is currently no recommendations for postoperative adjuvant therapy in any guidelines on HCC, and the 2020 CSCO (*25*) guidelines for the management of primary HCC (which usually has a high risk of recurrence) recommend postoperative administration of TACE. Although the STORM study of targeted therapy as postoperative adjuvant therapy (as exemplified by sorafenib) yielded negative results (*26*), numerous subsequent studies have concluded that targeted agents would still have a survival benefit in HCC with a high risk of recurrence (*27,28*). With the increased availability of numerous targeted agents and immune checkpoint inhibitors, more postoperative adjuvant therapy options will emerge in the future, with single agents such as lenvatinib, regorafenib, and apatinib, and with immune checkpoint inhibitors such as PD-1 or PD-L1 antibodies, and even targeted combination immunotherapy. Numerous clinical studies on postoperative adjuvant therapy for HCC with a high risk of recurrence have been initiated, and these therapies include nivolumab monotherapy (NCT03383458), carrilizumab combined with apatinib (NCT03722875), and lenvatinib combined with TACE (the LANCE study). Those findings will surely provide a stronger basis for postoperative adjuvant therapy to treat HCC in the near future.

Conversion therapy for HCC has just emerged. There are various conversion protocols but no standard protocol, so there is no definitive postoperative maintenance therapy for cancer that has been successfully converted and treated surgically. However, information can be gleaned from more established procedures for perioperative treatment of colorectal cancer liver metastases. Perioperative treatment of resectable colorectal cancer liver metastases with a high risk of recurrence usually lasts six months, and the postoperative regimen is basically a continuation of the preoperative chemotherapy regimen. Colorectal cancer metastases that are initially unresectable need to be treated with a more potent and efficient combination of two or three drugs than neoadjuvant therapy. The post-conversion regimen is weaker than the preoperative regimen, such as using targeting drugs only if there is a clear therapeutic response and then continuing to use them after surgery or using a shorter course of chemotherapy or even performing an observational follow-up. If, therefore, a more potent and efficient combination therapy is used on advanced HCC preoperatively (such as HAIC combined with targeted small-molecule TKI therapy and immune checkpoint inhibitors, or TACE and radiotherapy combined with targeted small-molecule TKI therapy and immune checkpoint inhibitors), then targeted therapy combined with 1-2 rounds of TACE or HAIC therapy can be used postoperatively. For patients with a significant treatment response, targeted therapy and immunotherapy, or even targeted therapy or immunotherapy alone can be used.

Antiviral therapy targets the etiology of HCC, but all other postoperative adjuvant therapies including targeted therapy and immunotherapy are focused on early recurrence after surgery, so what is traditionally considered to be radical surgery is actually a palliative resection. While the main tumor is removed, there are already tiny metastatic lesions outside the resection area. As described in the literature, colorectal cancer may already have the potential to metastasize to the liver or lungs even when the primary focus is only the size of a pinpoint, and metastatic seeding usually occurs much earlier, years before diagnosis and surgery, when tumor metastasis is not yet clinically detectable (*25*). Progression in patients with HCC is more due to progression of an underlying liver disease (like cirrhosis) and the malignant transformation of high- and low-grade dysplastic nodules, which in turn become early-stage carcinomas. Thus, the presence of potential microscopic carcinomas that are undetectable on imaging is more likely. These micro metastases may not have an obvious arterial blood supply. In principle, HAIC should be more effective than TACE, and multi-targeted targeted drugs that are both anti-proliferative and anti-angiogenic are better than targeted drugs that are solely anti-angiogenic. Therefore, an additive approach to preoperative conversion therapy for HCC is adopted as much as possible, combining effective

Table 1. A summary of conversion therapy

Modality	
(1) Local treatment	Ttransarterial chemoembolization (TACE) Transarterial radioembolization (TARE) Hepatic artery infusion chemotherapy (HAIC)
(2) Systemic treatment	Targeted therapy combined with Immunotherapy: Due to the low rate of liver-related adverse reactions, it has become the most common treatment of conversion therapy.
(3) Therapeutic alliance	TACE combined with radiation therapy TACE combined with targeted therapy HAIC combined with targeted therapy HAIC combined with targeted therapy and immunotherapy
Outcomes	Maintenance Treatment Plan
(1) Tumor progression and conversion therapy failure	The maintenance treatment should be combination therapy or monotherapy with few adverse reactions to prolong survival as long as possible.
(2) The tumor was partially alleviated or stable, but there was no possibility of surgical resection	If the patient has received enough conversion treatment and physical strength or liver, kidney, or bone marrow function is not sufficient to continue, the maintenance treatment can be selected in light of the failed conversion therapy.
(3) Conversion therapy successful and radical resection	Surgery is still the core treatment for patients with HCC to obtain the best survival benefit.

therapies as long as patients tolerate them. If conversion and resection are successful, then a subtractive approach is adopted as much as possible, using fewer effective therapies as maintenance postoperative adjuvant therapy based on a full analysis of preoperative therapies with the best response (Table 1).

5. Conclusion

Surgery remains the core treatment for patients with HCC to achieve the best survival benefit. With advances in targeted immunotherapy as well as radiotherapy interventions, multimodal conversion therapies are being explored to improve the proportion of inoperable HCCs that are potentially resectable and to reduce the risk of recurrence with postoperative adjuvant maintenance therapy, thereby improving the long-term prognosis for patients with advanced HCC (shown in Table 1). However, the role of these treatment options needs to be further investigated due to the lack of high-grade evidence. Future research on conversion therapy and successive maintenance treatment should focus more on scientifically designed randomized controlled trials with large samples to identify biomarkers of effective response and mechanisms of drug resistance and to obtain sufficient data to ensure the optimal combination regimen and sequence of therapies.

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Original Article

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Value of multidisciplinary team (MDT) in minimally invasive treatment of complex intrahepatic bile duct stones

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SUMMARY This study aimed to investigate the value of multidisciplinary team (MDT) management in minimally invasive treatment of complex intrahepatic bile duct stones (IHDs) by laparoscopy, choledochoscopy and percutaneous choledochoscopy. The characteristics, perioperative index, complication rate and minimally invasive rate of patients in MDT group (n = 75) and non-MDT group (n = 70) were compared. The members of MDT include doctors in ultrasound, imaging, hepatobiliary and pancreatic surgery, anaesthesia and intensive care medicine. The results showed that minimally invasive surgery reduced the incidence of postoperative residual stones, OR (95% CI) = 0.365 (0.141-0.940) (p = 0.037). MDT reduced the operation time, OR (95% CI) = 0.406 (0.207-0.796) (p = 0.009). Minimally invasive surgery significantly reduced intraoperative bleeding, OR (95% CI) = 0.267 (0.133-0.534) (p < 0.001). Minimally invasive surgery also reduced hospitalization time, OR (95% CI) = 0.295 (0.142-0.611) (p = 0.001). The stone clearance rates of MDT group and non-MDT group were 81.33% and 81.43% respectively. In the MDT group, the operative time was less than that in the non-MDT group (p = 0.010); the intraoperative bleeding volume was significantly less than that in the non-MDT group (p < 0.001); the hospitalization time was less than that in the non-MDT group (p = 0.001). Minimally invasive operation rate:48 cases (64.00%) in MDT group were significantly higher than 17 cases (24.29%) in non-MDT group (p < 0.001). In conclusion, minimally invasive procedures can be selected more through MDT. MDT can shorten the operation time, and minimally invasive surgery can reduce the incidence of residual stones, reduce intraoperative bleeding, and may shorten hospital stay. Therefore, MDT management model can provide personalized and minimally invasive surgical protocol for patients with complex IHD, which has high application value.

Keywords multidisciplinary team, minimally invasive surgery, laparoscopy, choledochoscope, percutaneous choledochoscope

1. Introduction

Complex intrahepatic bile duct stones (IHDs) usually refer to multiple intrahepatic stones, sometimes combined with extrahepatic bile duct stones. It is a difficult disease to treat because of its complicated etiology, large number of stones and wide distribution, high residual rate and recurrence rate. For patients with IHDs, open hepatectomy (OH) combined with intraoperative choledochoscopy is usually chosen for the convenience of operation and stone eradication (*1*). With the development of laparoscopy and choledochoscopy, the choice of surgical methods for complex IHDs tends to be diversified. However, there is still no standard on how to select minimally invasive procedures for patients. Multidisciplinary team (MDT) is a kind of structural mode to optimize patient management, including holding group meetings regularly and setting up multidisciplinary forums. MDT is usually emphasized in the clinical management of complicated diseases. The aim is to provide more complete and accurate diagnosis and more favorable treatment methods (*2,3*). On the basis of MDT, combined with the techniques of laparoscopy, choledochoscopy and percutaneous choledochoscopy, this study made decisions on treatment methods for patients to evaluate the value of MDT in minimally invasive treatment of complex IHDs.

2. Patients and Methods

2.1. Patients

Patients included in this study received surgical treatment at our hospital from July 2017 to November 2020. The

data of patients with IHDs are usually discussed by MDT in the second department of hepatobiliary and pancreatic surgery in our hospital. We divided 145 patients who met the inclusion criteria into two groups. The patients in MDT group (n = 75) were from the second department of hepatobiliary and pancreatic surgery, while those in non-MDT group (n = 70) were from the first department of hepatobiliary and pancreatic surgery. In the MDT group, 27 cases were treated with OH combined with choledochoscopy, 33 cases were treated with laparoscopic hepatectomy (LH) combined with choledochoscopy, and 15 cases were treated with percutaneous transhepatic cholangioscopic lithotripsy (PTCSL). In the non-MDT group, 53 cases were treated with OH combined with choledochoscopy, 16 cases were treated with LH combined with choledochoscopy, and 1 case was treated with PTCSL. The inclusion criteria for this study were as follows: (*i*) diagnosis of IHDs with (or without) extrahepatic bile duct stones; and (*ii*) patients undergoing at least one procedure. The exclusion criteria for this study were as follows: (*i*) high suspicion or diagnosis of cholangiocarcinoma; (*ii*) poor general condition, intolerance to surgery; and (*iii*) patient rejection. Patients in the MDT group were informed that their case data were discussed with MDT. All patients finally agreed to the operation.

2.2. Preoperative evaluation

All patients underwent liver function tests, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance cholangiopancreatography (MRCP), which provided important information about the location and size of the stone, and anatomy of the biliary tract. Preoperative selective percutaneous transhepatic biliary drainage (PTCD) was performed in patients with severe jaundice and intrahepatic bile duct (IHD) dilation to improve liver function. When stones cause serious infection, the patient is treated with anti-infective treatment to improve the basic condition of the patient. After the completion of the auxiliary examination, the data of patients in MDT group were discussed with the doctors of ultrasound, imaging, hepatobiliary and pancreatic surgery, anaesthesia and intensive care medicine, and the minimally invasive treatment scheme was finally determined. In addition, patients undergoing hepatectomy were subjected to an indocyanine green 15 minute retention rate test (ICG-R15) to estimate the volume of residual liver and determine the specific segment of the liver to be resected.

2.3. Surgical procedure

OH combined with choledochoscopy: A right subcostal inverted L-shaped or arc-shaped incision was used, the midline extended to xiphoid process, and the length was about 25-45 cm. During the procedure, the exact location of IHDs was determined again by the operator's palpation. The liver parenchyma was resected using ultrasonic knife clamping. The portal vein and hepatic artery were blocked according to the results of preoperative MDT and intraoperative conditions (Figure 1B). We opened the IHD or common bile duct (CBD) and performed choledochoscopy, we repeatedly flushed the bile duct or removed the stone with a basket. After choledochoscopy confirmed that the bile duct was free of stone and severe stenosis, the abdominal drainage tube and T tube were placed. Roux-en-Y cholangiojejunostomy was performed to drain bile if necessary.

LH combined with choledochoscopy: Five-hole method was used. Laparoscopy was used to detect abdominal adhesions and liver atrophy. Intraoperative ultrasound was used to further determine the location of stones, the condition of intrahepatic vessels and bile ducts (Figure 2A). Severe stenosis of IHD and severe atrophy of liver parenchyma were removed. Liver parenchymal resection was performed with ultrasonic knife clamping, and the left or right portal vein and hepatic artery were blocked if necessary to reduce intraoperative bleeding (Figure 2B). IHD or CBD was explored during the operation, and stones were removed with a choledochoscope and basket (Figure 2C). Repeated exploration and flushing of the bile duct was conducted, if necessary, and reuse of intraoperative ultrasound to determine whether the stone was removed. We used 4-0 absorbable sutures to close IHD or CBD. Drainage tubes were placed at the liver section, winslow hole and pelvic cavity, and T tubes were placed in patients with CBD exploration.

PTCSL: The procedure was performed under general anesthesia. To facilitate stone extraction, the stone extraction channel should be parallel to the target bile duct as much as possible. Therefore, surgery is performed in the left or right lying position depending on the stone location. The relationship between hepatic vascular system and target bile duct was studied by intraoperative ultrasound, preoperative MRI and MRCP (Figure 3A). An ultrasound-guided puncture needle was inserted into the target bile duct and a passage was established with a 16 F fascia dilator and 14 F outer sheath. Choledochoscopy was used to explore the bile duct, holmium laser shattered the stones and were removed with basket (Figure 3B). Patients with bilateral IHDs underwent similar procedures on the other side. After confirming that there was no stone in the bile duct within the visual range of choledochoscopy, we placed the biliary drainage tube (Figure 3C). We chose whether to place biliary stent to dilate the narrow bile duct according to the situation.

2.4. Statistics

The normality of metrological data was expressed

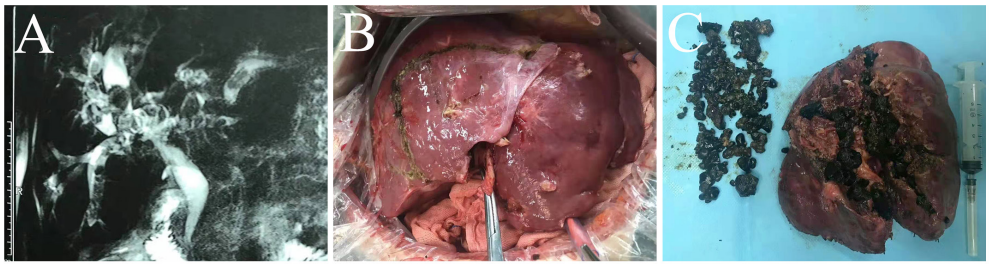

Figure 1. OH procedure. (A) MRCP of patient before OH. **(B)** Block the left hepatic artery and left branch of portal vein to determine the extent of hepatectomy. (C) The liver specimens were dissected and a large number of IHDs were found.

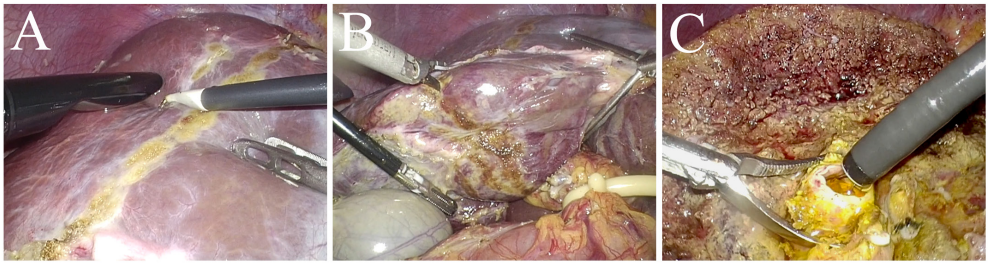

Figure 2. LH procedure. (A) Intraoperative ultrasound was used to determine the location of stone and middle hepatic vein. **(B)** The liver parenchyma was resected with ultrasonic knife clamping after setting the blocking band. **(C)** Intraoperative choledochoscope was used to explore the right hepatic duct and remove the stone with basket.

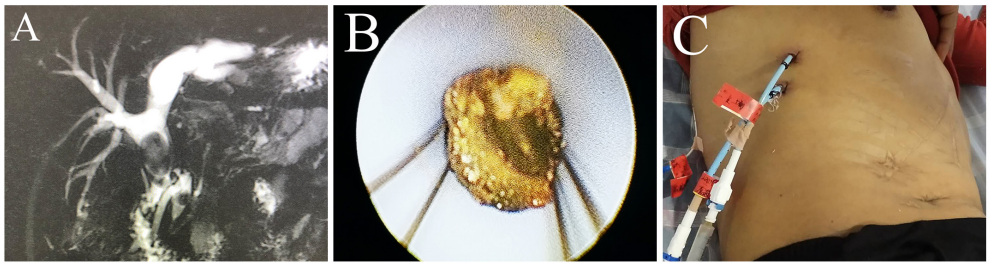

Figure 3. PTCSL procedure. (A) MRCP of patient before PTCSL. **(B)** Basket for stone removal during PTCSL. **(C)** A biliary drainage tube was placed to preserve the tract for stone removal. Abdominal surgical scars caused by multiple biliary operations.

by Shapiro-Wilk test, if the normal distribution was satisfied, it was expressed by $\overline{x} \pm s$, and if the variance homogeneity was satisfied, the independent sample t test was used for group comparison. If the metrological data did not satisfy the normal distribution, it was expressed by inter-quartile range [M (P_{25}, P_{75})], and the Mann-Whitney U test was used for group comparison. The counting data were expressed as the rate, and the Pearson Chi-Square test and Fisher's exact test were used in the group comparison. Some studies suggest that intrahepatic bile duct stones can be classified into simple and complex types based on the presence or absence of biliary stricture, infection, sepsis and liver abscess (*1,4*). These indicators were closely followed in this study. When a patient has the characteristics of both presentations and concomitant conditions, it is considered as a severe stone. Transforming the history of biliary surgery and minimally invasive surgery into dichotomous variables. The operation time, intraoperative bleeding, and hospital stay data were converted into dichotomous variables based on the mean or median values in 145 patients. The dependent variables were residual stone, operation time, intraoperative bleeding and hospitalization time, and other related indexes were independent variables for logistic regression analysis. $p < 0.05$ was allowed for statistical significance. SPSS 26.0 was used for statistical analysis.

3. Results

3.1. Characteristics of patients

The data results are shown in Table 1. The main clinical symptoms of both groups were abdominal pain, fever and jaundice. There were 29 males and 46 females in MDT group, aged 58.00 (50.00, 65.00) years (range: 18-85 years), 26 males and 44 females in non-MDT group, aged 56.00 (49.00, 65.00) years (range: 20-79

years). Forty-three patients (57.33%) in MDT group (range 0-5 times) and 35 patients (50%) in non-MDT group had history of biliary operation (range 0-6 times). There was no significant difference in history of biliary operation between groups (p = 0.376). Patients with cirrhosis and extrahepatic bile duct stones in the MDT group were fewer than those in the non-MDT group (p = 0.024 and p = 0.021).

3.2. Results of logistic regression analysis

Logistic regression analysis was performed with residual stones, operation time, intraoperative bleeding volume and hospitalization time as dependent variables (Table 2), with statistically significant results as follows. A history of biliary surgery increased the incidence of postoperative stone residue, OR (95% CI) = 2.702 (1.106-6.600) (p = 0.029). Minimally invasive surgery reduced the incidence of postoperative residual stones, OR (95% CI) = 0.365 (0.141-0.940) (p = 0.037). MDT reduced the operation time, OR (95% CI) = 0.406 (0.207-0.796) (p = 0.009). Minimally invasive surgery significantly reduced intraoperative bleeding, OR (95% CI) = 0.267 (0.133-0.534) (p < 0.001). Minimally invasive surgery also reduced hospitalization time, OR (95% CI) = 0.295 (0.142-0.611) (p = 0.001). An increase in intraoperative

Table 1. Patient characteristics

	MDT group	Non-MDT group	*P*
Age (years)	58.00 (50.00,65.00)	56.00 (49.00,65.00)	0.638
Gender			
Male	29 (38.67%)	26 (37.14%)	0.850
Female	46 (61.33%)	44 (62.86%)	
Presentation			
Acute cholangitis	32 (42.67%)	23 (32.86%)	0.224
Liver abscess	5 (6.67%)	2 (2.86%)	0.444
Jaundice	8 (10.67%)	5 (7.14%)	0.458
History of biliary operation	43 (57.33%)	35 (50%)	0.376
Cholecystectomy	30 (40%)	33 (47.14)	0.386
Exploration of bile duct	2 (2.67%)	1 (1.43%)	1.000
Bilioenteric anastomosis	8 (10.67%)	5 (7.14%)	0.458
Hepatectomy	8 (10.67%)	4 (5.71%)	0.279
PTCSL	0	1 (1.43%)	0.483
Concomitant condition			
Bile duct stricture	20 (26.67%)	15 (21.43%)	0.461
Liver atrophy	23 (30.67%)	13 (4.29%)	0.092
Cirrhosis	0	5 (7.14%)	0.024
Extrahepatic bile duct stone	35 (46.67%)	46 (65.71%)	0.021

Table 2. Logistic regression analysis of outcome indexes and related factors

		OR (95%CI)	*P*
Residual stone	Age	-	0.139
	MDT	-	0.278
	History of biliary operation ≥1 (time)	2.702 (1.106-6.600)	0.029
	Stone severity	-	0.413
	Minimally invasive surgery	0.365 (0.141-0.940)	0.037
Operation time > 325 (min)	Age	-	0.336
	MDT	0.406 (0.207-0.796)	0.009
	History of biliary operation ≥1 (time)	-	0.697
	Stone severity	-	0.425
	Minimally invasive surgery	-	0.375
Intraoperative bleeding ≥ 400 (mL)	Age	-	0.255
	MDT	-	0.121
	History of biliary operation ≥1 (time)	-	0.849
	Stone severity	-	0.427
	Minimally invasive surgery	0.267 (0.133-0.534)	< 0.001
Hospitalization time ≥ 20 (day)	Age	-	0.450
	MDT	-	0.115
	History of biliary operation ≥1 (time)	-	0.578
	Stone severity	-	0.265
	Minimally invasive surgery	0.295 (0.142-0.611)	0.001
	Operation time > 325 (min)	-	0.262
	Intraoperative bleeding ≥ 400 (mL)	2.281 (1.105-4.712)	0.026

Table 3. Perioperative data results

	MDT group	Non-MDT group	*Z* or *t* value	*P*
Operation time (min)	300.09 ± 125.41	352.81 ± 116.05	-2.614	0.010
Intraoperative bleeding volume (mL)	225.00 (137.50, 500.00)	500.00 (300.00, 900.00)	-3.848	< 0.001
Length of stay (days)	18.00 (15.00, 24.00)	22.00 (17.75, 29.25)	-3.181	0.001

Table 4. Postoperative complications and minimally invasive surgery

	MDT group (*n* = 75)	Non-MDT group (*n* = 70)	Value	*P*
Liver failure	0	0	-	-
Biliary fistula	0	4 (5.71%)	-	0.052
Residual stone	14 (18.67%)	13 (18.57%)	0.000	0.988
Minimally invasive surgery	48 (64%)	17 (24.29%)	23.090	< 0.001
Stone recurrence	6 (8%)	3 (4.29%)	-	0.496

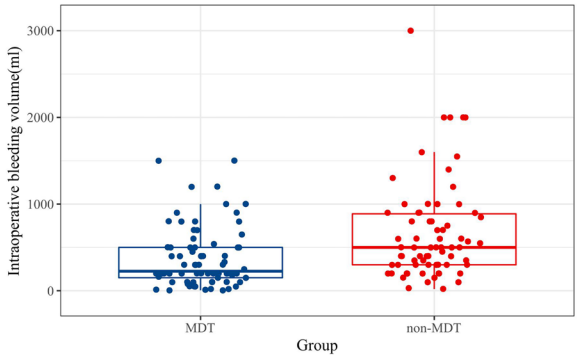

Figure 4. Intraoperative bleeding volume comparison.

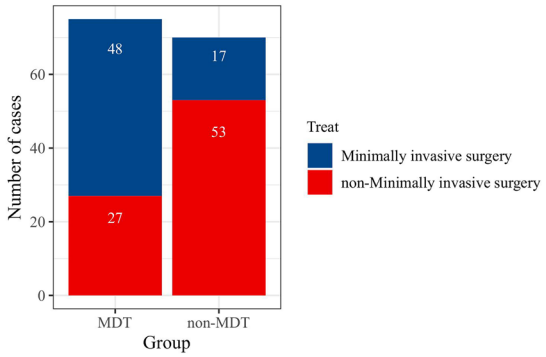

Figure 5. Comparison of minimally invasive surgery.

bleeding increased hospitalization time, OR (95% CI) = 2.281 (1.105-4.712) ($p = 0.026$).

3.3. Perioperative outcomes

The data results are shown in Table 3. The operation time was 300.09 ± 125.41 min in MDT group and 352.81 ± 116.05 min in non-MDT group. Intraoperative bleeding volume was 225.00 (137.50, 500.00) mL in MDT group and 500.00 (300.00, 900.00) mL in non-MDT group. The box diagram of intraoperative bleeding volume is shown in Figure 4. The hospital stay was 18.00 (15.00, 24.00) days in MDT group and 22.00 (17.75, 29.25) days in non-MDT group. In comparison, the operation time in MDT group was less than that in non-MDT group ($p = 0.010$), the intraoperative bleeding volume in MDT group was significantly less than that in non-MDT group ($p < 0.001$), and the hospitalization time in MDT group was less than that in non-MDT group ($p = 0.001$).

3.4. Postoperative complications

The data results are shown in Table 4. Postoperative liver failure did not occur in either group according to criteria presented in the International Study Group of Liver Surgery (ISGLS)2011 (*5*). Postoperative biliary fistula was identified by T-tube or biliary drainage tube angiography. There were 4 cases (5.71%) in non-MDT group and no biliary fistula in MDT group. There was no statistical difference between groups ($p = 0.052$). Postoperative CT, T-tube or biliary drainage angiography was used to confirm the presence of residual stones. Postoperative residual stones were found in 14 patients (18.67%) in MDT group and in 13 patients (18.57%) in non-MDT group. There was no statistical difference between the two groups ($p = 0.988$).

3.5. Stone clearance rate and minimally invasive surgery rate

The data results are shown in Table 4. The stone clearance rates of MDT group and non-MDT group were 72.00% and 81.43%. 48 Patients (64.00%) in the MDT group were successful in minimally invasive surgery (LH combined with choledochoscopy or PTCSL) and 17 patients (24.29%) in the non-MDT group were successful in minimally invasive surgery (Figure 5). The success rate of minimally invasive surgery in MDT group was significantly higher than that in non-

MDT group ($p < 0.001$). Patients with residual stones underwent PTCSL or T-tube sinus choledochoscope for removal of stones 8-10 weeks after surgery. Some patients with residual stones received conservative treatment. After the first PTCSL in the MDT group, 8 patients had residual stones (Table 5). All 8 patients underwent PTCSL again, but one patient still had residual stones. This patient ended up with conservative

Table 5. Stone location and operation method

Items	Cases	Segment of lobectomy or operation method	Number of patients with residual stones
MDT group			
OH combined with choledochoscopy	27		
LIHD	13	S2 and S3 (7)	3
		S2, S3 and S4 (5)	
		S4b (1)	
RIHD	4	S5 (1)	0
		S6 and S7 (1)	
		S5 and S8 (1)	
		S5, S6, S7 and S8 (1)	
BIHD	10	S2 and S3 (2)	6
		S2, S3 and S4 (2)	
		S2, S3, S4 and S6 (1)	
		S2, S3, S6 and S7 (1)	
		S2, S3, S4 and S8 (1)	
		S2, S3, S7 and S8 (1)	
		S2, S3, S7 and S8 (1)	
		S2, S3, S4, S6 and S7 (1)	
LH combined with choledochoscopy	33		
LIHD	26	S2 and S3 (16)	3
		S2, S3 and S4 (10)	
RIHD	3	S7 (1)	0
		S5 and S8 (1)	
		S5, S6, S7 and S8 (1)	
BIHD	4	S2, S3 and S4 (1)	1
		S2, S3 and S7 (1)	
		S2, S3, S6 and S7 (2)	
The first PTCSL	15		
LIHD	3	PTCSL	1
RIHD	5	PTCSL	3
BIHD	7	Double-channel PTCSL	4
The second PTCSL	8		
LIHD	1	PTCSL	0
RIHD	3	PTCSL	0
BIHD	4	PTCSL	1
Non-MDT group			
OH combined with choledochoscopy	53		
LIHD	22	S2, S3 (7)	0
		S2, S3 and S4 (15)	
RIHD	18	S6 (4)	4
		S7 (1)	
		S5 and S6 (2)	
		S6 and S7 (3)	
		S5, S6, S7 and S8 (8)	
BIHD	13	S2, S3 (5)	7
		S2, S3 and S4 (2)	
		S2, S3 and S6 (1)	
		S5, S6, S7 and S8 (3)	
		S2, S3, S6 and S7 (1)	
		S2, S3, S4, S6 and S7 (1)	
LH combined with choledochoscopy	16		
LIHD	13	S2 and S3 (2)	1
		S2, S3 and S4 (11)	
RIHD	2	S6 (2)	0
BIHD	1	S2, S3 and S4	0
PTCSL	1		
RIHD	1	PTCSL	1

Distinguishing liver segment by Couinaud method. LIHD: left intrahepatic bile duct; RIHD: right intrahepatic bile duct; BIHD: bilateral intrahepatic bile duct.

treatment for asymptomatic stones. The final stone clearance rate of 15 patients in MDT group was 93.33% after the second PTCSL. Due to the advantages and characteristics of the PTCSL, the stone clearance rate and stone residual rate were used as data after the second PTCSL. One patient in the non-MDT group had residual stones after a single PTCSL and was eventually treated conservatively.

3.6. Follow-up

The data results are shown in Table 4. After operation, the patients were followed up every 3 months for the first year, and once a year thereafter. The bile duct fistula was successfully closed after prolonging the drainage time of drainage tube, T tube or placing nasobiliary tube under endoscope. Abdominal ultrasound was done in outpatient clinic, and CT, MRI and MRCP were performed in patients with clinical symptoms. By February 2021, all patients completed at least one follow-up and collected stone recurrence data through retrospective medical data and telephone interviews. The mean follow-up period was 21.73 months (range: 3-43 months) in MDT group and 20.51 months (range: 3-38 months) in non-MDT group. Recurrence of stones is defined as the formation of new stones in the liver or outside the liver after surgical removal of stones. The overall stone recurrence rate was 6.21% in 145 patients. 6 patients (8%) in MDT group, and 3 patients (4.29%) in non-MDT group had stone recurrence. There was no significant difference between the two groups in the recurrence rate of stones ($p = 0.496$). The residual stone rate and stone recurrence rate of different operation modes in the two groups are shown in Figure 6. Specific treatment of patients with stone recurrence is as follows. In MDT group, 5 patients were treated with PTCSL again and 1 patient with asymptomatic calculus was treated conservatively. In the non-MDT group, 2 patients were treated with PTCSL again and 1 patient was treated conservatively.

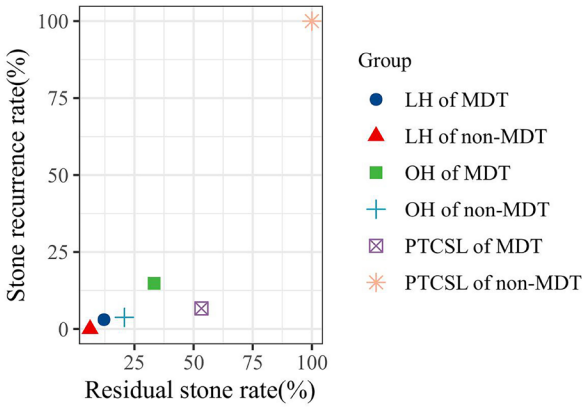

Figure 6. Comparison of residual stone rate and stone recurrence rate.

4. Discussion

Biliary calculus is associated with women, age, pregnancy, BMI, alcohol consumption, eating habits, hyperlipidemia, and diabetes. As a result of these factors, IHDs are more common in Asia than in the West, but there is also a trend of increased incidence in the West (*6-9*). Because of stone obstruction and repeated infection, IHDs can cause bile duct stenosis and segmental liver atrophy, which can be transformed into cholestatic cirrhosis. And because of recurrent cholangitis and even pyogenic cholangitis, the possibility of cholangiocarcinoma is greatly increased (*10*). Treatment of IHDs is generally targeted at the removal of stones, drainage, eradication of narrow bile ducts and atrophic liver parenchyma, so hepatectomy for IHDs has been widely accepted (*1*). In recent years, more studies have shown that LH is a better choice for the treatment of IHDs than OH. LH has the advantages of less bleeding, less trauma, less complications and shorter hospital stay (*11-13*). In the past, LH was often limited to the treatment of IHDs in the left lateral lobe of the liver. However, with the progress of laparoscopy and choledochoscopy, laparoscopic major hepatectomy for large-scale IHDs (*14*) and LH combined with choledochoscopy for bilateral IHDs have also achieved good results (*1,4*). In this study, 15 patients in the MDT group and 12 patients in the non-MDT group underwent laparoscopic major hepatectomy (3 or more Couinaud segments). It is worth mentioning that, after MDT discussion, 3 patients in MDT group underwent laparoscopic resection of bilateral liver segments (Table 5). However, in the non-MDT group, there were no cases of laparoscopic bilateral hepatectomy. This suggests that MDT may benefit more patients with bilateral IHDs from LH. In addition, 33 patients in the MDT group and 16 patients in the non-MDT group underwent LH combined with choledochoscopy, and achieved good stone clearance outcomes (stone clearance rates were 87.88% and 93.75%).

Some patients with IHDs have biliary anatomic abnormalities, metabolic diseases and other factors, leading to recurrence of stones. Some of these patients had a history of recurrent infection and multiple biliary operations, which resulted in severe adhesions in the abdominal tissue and prevented reoperation (*15*). Multiple history of biliary surgery often indicates that patients with stones are prone to recurrence, and this type of patient is more likely to have these factors. Our study also showed that having a history of biliary surgery would increase the occurrence of postoperative residual stones (Table 2). In other patients, due to poor general conditions, hepatectomy was not tolerated and ERCP failed to clear large IHDs (*16*). In the above cases, PTCSL is considered as a good alternative because of less hepatic parenchyma injury, low complication rate, high removal rate of target stones

and strong repeatability (*17-19*). Although PTCSL has a limited clearance rate for multiple IHDs, there have been studies in which single-step multi-channel PTCSL surgery is used to treat bilateral IHDs with increased stone clearance (*20*). In this study, 7 patients with bilateral IHDs were treated with single-step double-channel PTCSL, but the stone clearance rate was not significantly increased in a single operation (Table 5). Fifteen (20%) patients in the MDT group underwent one or two PTSSL (final stone clearance was 93.33%). One patient in the non-MDT group received PTCSL due to a history of 6 biliary operations. In this study, the rate of stone residue (56.25%) remained high in 16 patients after first PTCSL. In practice, however, after the first PTCSL, the major stones causing the symptoms were removed. After the first PTCSL, access to stones was retained by placing a drainage tube, and the patient with residual stones could usually have PTCSL again. And the second PTCSL was acceptable because of the minimally invasive features of PTCSL. Moreover, some studies have shown that, even if the rate of residual stones is high after a single PTCSL, the residual stones are almost completely removed by another PTCSL (*15*). In 16 patients in this study, the residual stone rate of the first PTCSL was up to 56.25%, but after the second PTCSL, the final stone residual rate was 87.5%. Therefore, for the patients with complex IHDs, after MDT discussion, the MDT group chose more PTCSL. PTCSL is often used in patients who are difficult for hepatectomy, but after discussion of MDT, PTCSL was still selected for the initial diagnosis of IHDs in 3 patients in the MDT group (2 left IHDs,1 right IHDs). This was mainly due to dilatation of the target bile duct and limited stone location. It should be noted that PTCSL does not address the problem of dilated IHD, which is still at risk of conversion to cholangiocarcinoma.

MDT is a structure designed to optimize the clinical management of patients. Due to the serious harm of tumors and the variety of treatment methods, MDT has been developed rapidly in the field of tumors (*21,22*). Although IHD is a benign disease, there is a risk of conversion to cholangiocarcinoma. In addition, the surgical treatment of IHDs with (or without) extrahepatic bile duct stones is diversified. Therefore, it is necessary to explore the value of MDT in the treatment of complex IHDs.

In the specific decision-making process of MDT, all patients continued to need liver function tests, MRI, MRCP and CT after the initial diagnosis of IHDs by ultrasound. The doctors of ultrasound and imaging department have preliminarily understood the patient's condition during the preoperative examination. At the MDT meeting, the hepatobiliary surgeons summarized and reported the patient data in detail, and initially proposed an alternative procedure. Subsequently, the ultrasound and imaging doctors analyzed the specific location of the stones, dilatation or atrophy of the bile duct, and proposed treatment for the stones and liver segments. ICG-R15 was further accepted to assess the safety of hepatectomy when the MDT considered that the patient could undergo hepatectomy. According to the CT and MRI images, the target liver and bile duct were confirmed again, and whether the operation under laparoscopy was possible. The anesthesiologist evaluates the patient's ability to tolerate general anesthesia based on the patient's general condition, operation time, and other indicators. At the same time, anesthesiologists and hepatobiliary surgeons consider whether to block the portal vein and hepatic artery or reduce the central venous pressure during the operation to reduce bleeding. All patients were pre-discussed whether they would enter the ICU after surgery by the doctors of anesthesiology, intensive care medicine, and hepatobiliary surgery.

If the patient's condition is more suitable for PTCSL, then the ultrasound doctor suggests how to establish the stone extraction channel. The PTCSL is often faced with refractory bile duct stones, and the PTCSL is often limited to the removal of the target stones determined by preoperative discussion. Although intraoperative ultrasound can be very helpful, it is difficult to remove all bile duct stones at once (*17*). In addition, if the IHD is not dilated, the difficulty of establishing stone extraction channels is significantly increased and PTCSL is unable to eradicate the dilated bile duct. With the consent of all MDT members, the doctor obtains the operation consent based on full explanation of the above information to the patient, and actively prepares the equipment such as intraoperative ultrasound and choledochoscopy. The MDT discussion allows patients to be more prepared for surgery. For example, a better preoperative design, as well as more frequent intraoperative use of ultrasound, will make the procedure smooth, reducing the time of the procedure. Therefore, the surgical decision through MDT will be more beneficial to the patient. In addition, a comparison between the two groups showed that more patients underwent minimally invasive surgery after MDT. According to logistic regression analysis in this study, minimally invasive surgery can significantly reduce the occurrence of residual stones and the amount of intraoperative bleeding (Table 2). In fact, this is related to the use of ultrasound, and choledochoscope in minimally invasive surgery. Combined use of choledochoscope, transdermal choledochoscope and ultrasound avoids the disadvantage that traditional open surgery can only determine the location of stones by the touch of the hand. At the same time, ultrasound-guided liver resection and percutaneous choledochoscopy are safer. Moreover, intraoperative bleeding will prolong the hospital stay, and minimally invasive surgery indirectly reduces the hospital stay. More patients in the MDT group received minimally invasive surgery

and intraoperative ultrasound-guided hepatectomy, with less intraoperative bleeding than in the non-MDT group (Figure 4). At the same time, the hospitalization time of MDT group was less than that of non-MDT group. So we believe that minimally invasive surgery is also beneficial for patients with intrahepatic bile duct stones.

Two patients in the non-MDT group had difficulty in the operation, which was transferred from LH to OH. One patient had more bleeding when the first hepatic portal was separated, and the other patient had severe adhesion between the target hepatic lobe and abdominal wall. In the MDT group, 75 patients were successfully operated on after the discussion of MDT, and more patients were successfully operated on with personalized and minimally invasive surgery.

In conclusion, it is necessary to establish the MDT model in the clinical management of complex IHDs. Minimally invasive procedures based on laparoscopy, choledochoscope and percutaneous choledochoscope can be selected more easily through MDT. MDT can shorten the operation time, and minimally invasive surgery can reduce the incidence of residual stones, reduce intraoperative bleeding, and may shorten hospital stay. Therefore, MDT management model can provide a personalized and minimally invasive surgical protocol for patients with complex IHD, which has high application value.

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Original Article

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Role of a multidisciplinary team (MDT) in the diagnosis, treatment, and outcomes of inflammatory bowel disease: A single Chinese center's experience

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SUMMARY The incidence of inflammatory bowel disease (IBD) with a poor prognosis is increasing, and a single field is not capable of fully diagnosing and comprehensively treating IBD. The purpose of the current study was to explore the role of a multidisciplinary team (MDT) in the diagnosis and treatment of IBD. Subjects were 55 patients with IBD who underwent surgery at this hospital before the establishment of a MDT (before June 2016) and 276 patients who were discussed by a MDT; 72 of the latter patients underwent surgery. The preoperative rate of diagnosis, preoperative basic nutritional status, frequency of emergency surgery, and surgical complications in the two groups were compared to determine whether the MDT significantly affected the diagnosis and treatment of IBD and to explore trends in the types of patients with IBD and treatment decision-making since the establishment of MDT. Results revealed that the MDT significantly improved preoperative diagnostic accuracy for patients with IBD who underwent surgery ($p < 0.005$), and the frequency of elective surgery decreased significantly ($p < 0.005$). There were significant differences in the rate of clinical recurrence ($p < 0.005$) and the rate of additional surgery ($p < 0.01$) between the two groups, with higher rates in the control group. In terms of preoperative nutritional status, the proportion of decreased serum albumin and hemoglobin in the experimental group was significantly lower than that in the control group ($p < 0.05$). MDT plays a positive role in accurate preoperative diagnosis, improvement of preoperative preparations, and a reduction in postoperative adverse events for patients with IBD undergoing surgery.

Keywords Crohn's disease, ulcerative colitis, multidisciplinary team, diagnosis, prognosis

1. Introduction

Inflammatory bowel disease (IBD) is a group of chronic nonspecific inflammatory diseases, including Crohn's disease (CD) and ulcerative colitis (UC), whose etiology and pathogenesis have not been elucidated. Its onset may be related to dietary habits, environment, genes, infection, intestinal flora, and immune disorders. IBD is developing into a global epidemic. The highest annual incidence of UC is 24.3 cases per 100,000 population-years in Europe, with 6.3 cases per 100,000 population-years in Asia. The highest annual incidence of CD is 12.7 per 100,000 population-years in Europe, with 5.0 cases per 100,000 population years in Asia (*1*). As the incidence increases, so does the chance of complications and poor outcomes (*2*).

As the level of China's economic development, diet, and lifestyle have changed and the average life expectancy of the population has increased, the number of cases of IBD has increased yearly and is approaching numbers in Europe and North America (*3*). The incidence of IBD in China is increasing yearly, and an indeterminate or incomplete diagnosis is often common. Although the incidence of postoperative complications and in-hospital mortality of patients with IBD has significantly decreased in recent years, a retrospective analysis of the epidemiology and surgical management of IBD in China conducted in 2016 indicated that the frequency with which patients with CD were misdiagnosed with conditions such as appendicitis before surgery was as high as 50.8%. The rate of postoperative complications in both CD and UC

is higher than 20%. Moreover, there were significant differences in the rate of emergency surgery and in-hospital mortality among IBD centers of different grades and levels (*4*). This is due to a lack of diagnostic capacity, but a factor that cannot be ignored is that gastrointestinal surgeons at small medical facilities lack experience in surgically treating IBD. In addition to staff and team differences, diagnostic equipment is unevenly distributed among large and small medical facilities. Large facilities have great difficulty specifically diagnosing IBD, and the same is true for small medical facilities with much less staff collaboration and equipment. Given these circumstances, the ability to diagnose and treat IBD desperately needs to be improved at many national, provincial, municipal, and even county medical facilities in China. The aim of the current study was to explore the role of a multidisciplinary team (MDT) in the diagnosis and treatment of IBD over the past five years.

Core members of the MDT work as a group to diagnose and treat a given disease through conferences. This increases the accuracy of the diagnosis, helps to identify the best treatment plan, helps to determine the best form of management, and facilitates the coordination of personalized care and outpatient services. The key is how teams are set up and work in practice and how they affect patient care and prognosis (*5*). According to a large retrospective study in Denmark, there is an increased risk of death in the near and long term, and especially in the near term, following a diagnosis of IBD (*6*). IBD has a high incidence and involves many complications. Conventional drug therapy may have difficulty treating the multiple and serious complications of IBD (*7*). Surgery, Radiology, and Pathology are often involved when these complications develop (*8*).

As technology to diagnose and treat IBD continues to advance, more medical treatments and various new types of bio-targeted agents have been developed, and temporary relief of inflammation and infection control can often be achieved with medical therapy. Nevertheless, bio-targeted treatments still involve many contraindications and complications (*9*), and multiple specialists are still needed for diagnosis and treatment of the disease. Gastroenterologists, pathologists, imaging specialists, and surgeons regularly monitor disease activity *via* fecal and serum biomarkers, imaging, endoscopy, and histology. This information is used to tailor medical therapy, identify surgical options, and determine the patient's diagnosis. As early as 1995, the Calman-Hine report identified significant deficiencies in the preparation, structure, and organization of cancer care in the UK, including inconsistencies in specialist care, disjointed referral systems, outcomes, and wide variations in the use of specific treatments. The key to solving these problems is more teamwork among those providing treatment and care, so multidisciplinary management and consultation are needed to diagnose and treat complex refractory diseases (*10*). Multidisciplinary teamwork has been widely used to diagnose and treat cancer, and it has been proven to have a significant positive effect on outcomes for patients with cancer (*11*). The same drawbacks the Calman-Hine report identified in the treatment of tumors also exist in IBD, such as delayed diagnosis and surgery.

2. Methods

2.1. The multidisciplinary approach used in this study

Established in June 2016, the multidisciplinary center at the Second Xiangya Hospital, Central South University is one of the largest IBD centers in China that meets international standards. Approximately 300 patients with IBD were potential subjects of a multidisciplinary conference during the past 5 years. Experts in various specialties at the center are all skilled in the diagnosis and treatment of IBD.

A MDT conference on diagnosis and treatment of IBD includes gastroenterologists, gastrointestinal surgeons (geriatric surgeons), pathologists, radiologists, and non-core members, including nutritionists, psychiatrists, and nurses. A MDT conference on patients with IBD is held once a week. The conference is conducted as follows: By reviewing the patient's history, clinical phenotypes, imaging characteristics, and histological findings, the best diagnosis and the most appropriate treatment plan are defined. This includes determining the stage of the disease, the type of disease, and whether surgery is necessary.

The circumstances for convening a MDT conference for patients with IBD at this hospital include: 1) IBD should have been considered first during diagnosis, but other diseases could not be ruled out or direct evidence of IBD could not be found, leading to difficulties in diagnosis and influencing the physician's selection of appropriate treatment options; 2) The treatment the patient received in Gastroenterology is unable to alleviate symptoms, or an intestinal obstruction, intestinal fistula, severe malnutrition, severe anemia, or some other condition develope during the treatment process, necessitating the involvement of other specialties, and especially surgery, in treatment; and 3) The patient's condition is so serious that surgery is required. The basic steps for convening a MDT conference for the diagnosis and treatment of IBD at the Second Xiangya Hospital, Central South University are shown in Figure 1.

2.2. Study population and design

This study was conducted at the Second Xiangya Hospital, Central South University in the City of

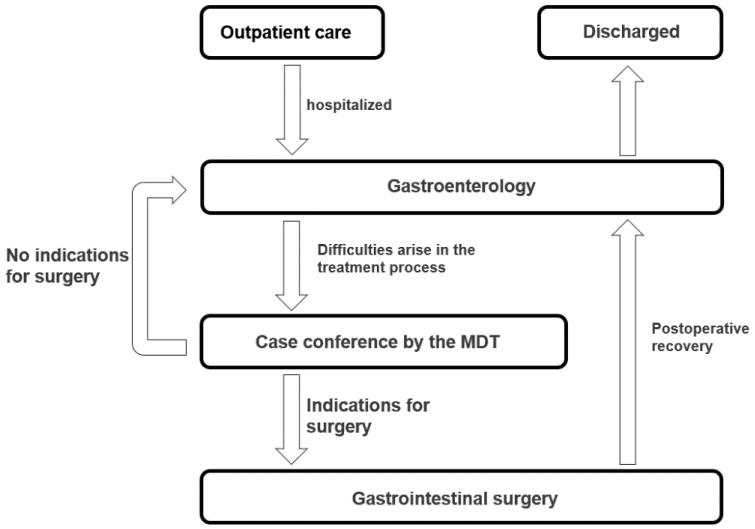

Figure 1. The basic steps for diagnosis and treatment of IBD by a MDT at the Second Xiangya Hospital, Central South University.

Changsha, Hunan Province. A total of 276 patients were discussed at a MDT conference at the Second Xiangya Hospital from June 2016 to February 2021. The basic information on all of the patients, including clinical symptoms and imaging and pathological findings, was obtained by the researchers from an electronic medical records system. MDT conferences on patients conducted from June 2016 (inception) to February 2021 were retrospectively examined. This study was approved and overseen by the ethics committee of Central South University, and conducted in accordance with the Declaration of Helsinki. All patients who underwent surgery signed a surgical consent form beforehand. An audit was commenced in June 2016. Although some patients were discussed more than once, only the initial MDT conference was assessed for each patient.

Demographic data obtained included age, sex, course of the disease, treatment options, whether to undergo surgery, and the IBD subtype. The groups that underwent surgery before and after the establishment of the MDT for IBD were compared. The experimental group (n = 72) consisted of patients who were discussed by a MDT and who underwent surgery between June 2016 and February 2021, and the surgical indications were confirmed by the MDT. All patients diagnosed with IBD upon discharge from the hospital after surgery between September 2006 and May 2016 served as the control group. Patients hospitalized for less than 1 day and patients with incomplete information were excluded. In total, 55 patients served as the control group for this study. The role of a MDT was examined by comparing the accuracy of preoperative diagnosis, the frequency of emergency surgery, preoperative nutritional status, and the treatment outcomes between the two groups. All MDT conferences conducted between June 2016 and February 2021 were reviewed. Subjects were a total of 276 patients who were diagnosed with IBD. To reflect the involvement of the MDT in the diagnosis and treatment of IBD since 2016, the period from June 2016 to February 2021 was divided into three phases.

2.3. Standards and endpoints

When the 276 patients were discussed by a MDT, the histological findings from patients with CD were defined as characteristic when they were deep mucosal longitudinal ulcers covering necrotic tissue or noncaseating necrotic granulomas in the intestinal wall. The histological findings from patients with UC were defined as characteristic when they were extensive ulcers with atypical hyperplasia. Imaging findings of CD were defined as characteristic when one of the following features was evident: 1) significant intestinal wall thickening; 2) significant intestinal mucosal enhancement; 3) intestinal stenosis and deformation; 4) a vascular "comb sign;" 5) enlarged mesenteric lymph nodes; and 6) fibroadipose hyperplasia. A "full diagnosis" was defined as the patient's diagnosis at discharge that included the disease stage, type, disease activity, and complications, and a "partial diagnosis" was defined as the patient's diagnosis at discharge that consisted of only "CD" or "UC." Preoperative diagnosis often determines surgical options, accurate diagnosis is closely related to determination of the disease stage and subsequently guides treatment and prediction of prognosis, and diagnosis is based on a combination of symptoms and laboratory, imaging, endoscopy, and histopathology findings (*12*). Adequate preoperative preparations are known to be closely related to postoperative recovery; there is less time for

preoperative preparations in the event of emergency surgery, hampering full preoperative preparations. Moreover, postoperative recovery of surgical patients is closely related to their preoperative nutritional status, and relevant indicators include serum albumin and hemoglobin. In the current study, patients preoperatively diagnosed with intestinal tuberculosis, an intestinal tumor, appendicitis, or simply an intestinal obstruction or intestinal perforation were deemed to have been misdiagnosed. Postoperative complications in this study included a surgical site infection and postoperative intestinal fistulae; other adverse events included clinical recurrence and additional surgery. Clinical recurrence referred to the recurrence of symptoms after surgery, such as abdominal pain, blood in the stool, and vomiting, resulting in readmission to the hospital, Additional surgery refers to undergoing further surgery due to recurrence or serious complications and excludes elective stoma reduction. In patients who underwent an intestinal resection, an intestinal colostomy and abscess removal were defined as "surgery" while perianal surgery was excluded.

2.4. Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics 25 package. $P < 0.05$ was considered statistically significant, and categorical variables were expressed as a percentage. The rate of preoperative diagnosis, the rate of postoperative complications, and preoperative nutritional status were compared between the experimental group and the control group using the chi-square (χ^2) test.

3. Results

3.1. Clinical characteristics of patients discussed by a MDT

From June 2016 to February 2021, 276 patients with IBD were discussed by a MDT at the Second Xiangya Hospital, Central South University, including 256 patients (92.8%) with CD and 20 (7.2%) with UC. Of the 256 patients with CD, 50 (19.5%) were female, with a mean age of 34 years, and the youngest patient was 14 years old. Of the 20 patients with UC discussed by a MDT, 10 were female (50%), with an average age of 45 years.

In order to explore demographic trends in IBD and the status of the MDT conference, the period from June 2016 to February 2021 was divided into three phases: June 1, 2016 to December 31, 2018 (Phase 1), the whole of 2019 (Phase 2), and January 1, 2020 to February 28, 2021 (Phase 3). A total of 42 patients were discussed by a MDT in Phase 1, 78 were discussed by a MDT in Phase 2, and 156 were discussed by a MDT in Phase 3. Unlike neoplastic disease, IBD is characterized by a low age of onset, and the age of onset is closely related to disease behavior and symptoms (*13*). IBD has significant disease heterogeneity depending on the age of onset.

Of the 42 patients in Phase 1, only 4 (9.3%) were female, with an average age of 34.2 years. Of the 78 patients in Phase 2, 22 (28.2%) were female, with an average age of 36.1 years. Of the 156 patients in Phase 3, 34 (21.8%) were female, with an average age of 34.1 years (Figure 2A).

Since the duration of the disease can reflect the impact of the disease on the quality of life to some extent, the course of the disease was divided into three phases: less than 1 year, 1-5 years, and longer than 5 years (from initial onset to the first MDT conference). Of the total patients, 23.8% in Phase 1 had IBD for less than 1 year, 20.5% in Phase 2 had it for less than 1 year, and 26.9% in Phase 3 had it for less than 1 year. Of the total patients, 28.6% in Phase 1 had IBD for 1 to 5 years, 48.7% in Phase 2 had it for 1 to 5 years, and 44.9% in Phase 3 had it for 1 to 5 years. Of the total patients, 47.6% in Phase 1 had IBD for longer than 5 years, 30.8% in Phase 2 had it for longer than 5 years, and 28.2% in Phase 3 had it for longer than 5 years (Figure 2B). Demographic data on patients who

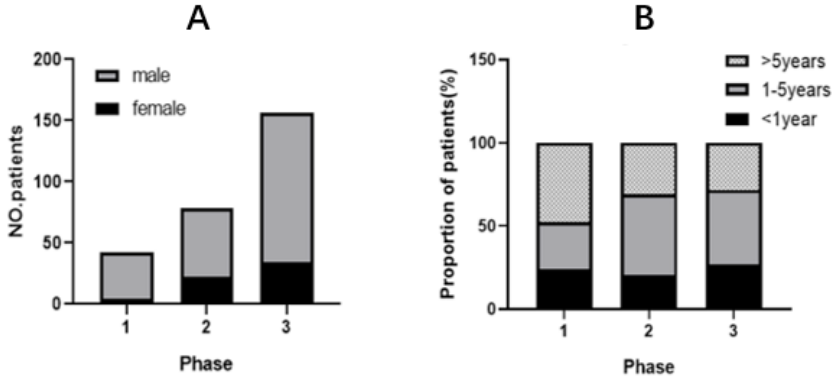

Figure 2. (A) The course of disease was divided into three phases (less than 1 year, 1 to 5 years, and longer than 5 years), and the sex distribution of patients with disease in a given phase is shown in the figure. (B) Percentage of patients in each phase.

Table 1. Demographic data on 276 patients discussed by MDT conferences during each phase of the study

Patient characteristics and no.	Phase 1, 42 (%)	Phase 2, 78 (%)	Phase 3, 156 (%)
Sex			
Female	4 (9.5)	22 (28.2)	34 (21.8)
Male	38 (90.5)	56 (71.8)	122 (78.2)
Course of the disease			
< 1 year	10 (23.8)	16 (20.5)	42 (26.9)
1-5 years	12 (28.6)	38 (47.7)	70 (44.9)
> 5 years	20 (47.6)	24 (30.8)	44 (28.2)
Diagnosis			
Partial	14 (33.3)	10 (12.8)	20 (12.8)
Full	28 (66.7)	68 (87.2)	136 (87.2)
Decisions by the MDT			
Surgery	22 (52.4)	26 (33.3)	24 (15.4)
Targeted therapy	6 (14.3)	28 (35.9)	46 (29.5)
Supplemen-tary examinations/studies			
Pathology (+)	10 (23.8)	24 (30.1)	56 (35.9)
Imaging (+)	26 (61.9)	62 (79.5)	134 (85.9)

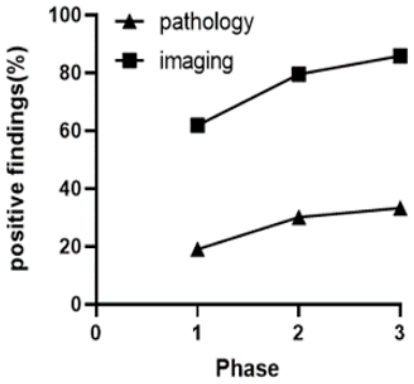

Figure 3. From June 2016 to February 2021, the proportion of pathological examinations yielding characteristic findings increased from 23.8% to 30.1% to 35.9%, and the proportion of imaging-positive findings continued to increase from 61.9% to 79.5% to 85.9%.

were discussed by a MDT are shown in Table 1. Of 276 patients with IBD, 14 (33.3%) were only partially diagnosed in Phase 1, 10 (12.8%) were only partially diagnosed in Phase 2, and 20 (12.8%) were only partially diagnosed in Phase 3 (Table 1).

The role of Pathology in the diagnosis of IBD gradually increased from Phase 1 to Phase 3. A characteristic pathological diagnosis was made in 10 patients (23.8%) in Phase 1; this number increased to 24 (30.1%) in Phase 2 and 56 (35.9%) in Phase 3.

The characteristic imaging findings of CD include intestinal wall thickening, enhanced mucosal enhancement during active disease, increased mesenteric lymph nodes, and complications such as intestinal fistulae and abscesses (*14*). An intestinal CTE examination is crucial to determining diagnosis, staging, and complications. Imaging findings indicated CD in 26 patients (61.9%) during Phase 1, but this number increased to 62 (79.5%) in Phase 2 and 134 (85.9%) in Phase 3 (Figure 3). Of the 276 patients who were discussed by a MDT, 14.3% received targeted therapy in Phase 1, 35.9% received that therapy in Phase 2, and 29.5% received that therapy in Phase 3 (Table 1).

3.2. Preoperative diagnosis and nutritional status

There were no significant differences in sex between the experimental group and the control group ($p > 0.05$). In the experimental group consisting of 72 patients with IBD, 3 (4.2%) were misdiagnosed preoperatively. Of the 55 patients in the control group, up to 45 (81.8%) were misdiagnosed preoperatively. Most of those misdiagnoses were lymphoma, intestinal tuberculosis, or a tumor. The rate of misdiagnosis was significantly higher than that in the 3 misdiagnosed patients in the experimental group ($p < 0.005$) (Table 2).

In the experimental group, 12 patients (16.7%) had preoperative serum albumin levels below 30g/L, and the rate of a preoperative decrease in albumin was significantly lower than that in 20 patients (36.3%) in the control group. The same was also true when the preoperative hemoglobin level was compared. A total of 28 patients (38.9%) in the experimental group had a hemoglobin level below 100 g/L, which was significantly lower than that in 41 patients (74.5%) in the control group ($p < 0.001$) (Table 2).

3.3. Emergency surgery rate and postoperative adverse events

Of the 72 patients in the experimental group who underwent surgery, only 2 (2.8%) underwent emergency surgery while 70 (97.2%) underwent elective surgery. In contrast, 15 patients (27.2%) in the control group underwent emergency surgery while 40 (72.8%) underwent elective surgery. A significantly lower proportion of patients in the experimental group

Table 2. Statistical analysis of the preoperative diagnosis, preoperative nutritional status, emergency surgery rate, and postoperative adverse events in the experimental group and the control group

Surgical characteristics of patients	Exp group, 72 (%)	Con group, 55 (%)	*P* value
Sex			
Female	20	23	> 0.05
Male	52	32	
Preop diagnosis			
Accurate	69 (95.8)	10 (18.2)	< 0.005
Misdiagnosis	3 (4.2)	45 (81.8)	
Necessity for surgery			
Elective surgery	70 (97.2)	40 (72.8)	< 0.005
Emergency surgery	2 (2.8)	15 (27.2)	
Postop complications			
Surgical site infection	10 (13.9)	14 (25.5)	> 0.05
Clinical recurrence	5 (6.9)	20 (36.3)	< 0.005
Additional surgery	0	5 (9.1)	< 0.01
Intestinal fistula	4 (5.6)	4 (7.3)	> 0.05
Total number of patients	17 (23.6)	38 (69.1)	< 0.005
Preop nutritional status (g/L)			
Albumin < 30	12 (16.7)	20 (36.3)	< 0.05
Hemoglobin < 100	28 (38.9)	41 (74.5)	< 0.001

underwent emergency surgery compared to the control group ($p < 0.005$) (Table 2).

Postoperative adverse events included a surgical site infection, intestinal fistulae, additional surgery, and clinical recurrence. In the experimental group, a total of 17 patients (23.6%) experienced postoperative adverse events, including 10 (13.9%) who developed a surgical site infection, 5 (6.9%) who experienced clinical recurrence, and 4 (5.6%) who developed an intestinal fistula; none of the patients in the experimental group underwent additional surgery. In the control group, a total of 38 patients (69.1%) experienced postoperative adverse events, including 14 (25.5%) who developed a surgical site infection, 20 (36.3%) who experienced clinical recurrence, 5 (9.1%) who underwent additional surgery, and 4 (7.3%) who developed an intestinal fistula. The proportion of patients who experienced adverse events differed significantly between the two groups. Significantly fewer patients in the experimental group experienced adverse events ($p < 0.005$), and the rate of clinical recurrence ($p < 0.005$) and the rate of additional surgery ($p < 0.01$) in the experimental group were significantly lower than rates in the control group. However, there were no significant differences between the two groups in terms of the development of intestinal fistula and surgical site infections ($p > 0.05$) (Table 2).

4. Discussion

As the incidence of IBD has increased in China and elsewhere around the world and the course of the disease has been prolonged in recent years, the number of patients who need surgery has also increased yearly (*15*). Improving the diagnostic accuracy, treatment, and outcomes of IBD relies not only on the ability of gastroenterologists but also requires multidisciplinary cooperation, and particularly cooperation by pathologists, imaging specialists, and surgeons (*16*). Therefore, the current study investigated whether MDT could improve the diagnostic accuracy, treatment, and outcomes of IBD. The above considerations emphasize the need for an IBD center to have an IBD team in the form of a MDT including gastroenterologists, pathologists, imaging specialists, and surgeons.

Today, China's economy is developing rapidly, and the incidence and prevalence of IBD are rising sharply. According to some researchers, that rise is associated with urbanization and industrialization. The burden of IBD is heavier in economically developed areas, but the purported association is unlikely considering population migration. Nowadays, population migration in China mainly involves the middle-aged and younger people who migrate from underdeveloped areas to developed areas, and this group happens to have a high incidence of IBD. Therefore, one can reasonably assume that the burden of IBD in underdeveloped areas or rural areas of China is much more serious than expected (*17*). IBD has a long course, is extremely difficult to cure, and is accompanied by many complications that affect one's quality of life, so the disease presumably poses a great burden to the families of the patients with IBD and society as a whole. Often one person gets sick, and the quality of life and economic status of family members also decline. Therefore, improving the ability to diagnose IBD early and to provide standardized treatment is crucial to each patient's family and society as a whole, and that was also a goal of this study. IBD is a non-specific chronic bowel disease with no gold standard for its diagnosis, unlike an ordinary intestinal disorder such as a perforation, obstruction, or tumor. The existing diagnosis of IBD is exclusive, so it needs to be differentiated from intestinal tuberculosis, intestinal lymphoma, and other diseases when making a diagnosis. Therefore, the accurate and early diagnosis

of IBD should be based on a comprehensive evaluation of radiology , endoscopy, and histopathology findings (*18*).

All patients discussed by a MDT between June 2016 and February 2021 were retrospectively examined, and demographic data included sex and age distribution, duration of disease, the rate of correct diagnosis, and treatment plans were comprehensively analyzed. Unlike a peptic ulcer, tumor, or other common gastrointestinal diseases, IBD has complex clinical manifestations, hidden symptoms, a high degree of variation, and involves many complications, such as an intestinal obstruction, perforation, dilation, tumor, abdominal abscess, or malnutrition. Misdiagnosis of CD and UC is common. Therefore, the accuracy with which these diseases are diagnosed needs to be improved *via* a MDT conference. Although the medical treatment of IBD has improved greatly, Gastroenterology, Gastrointestinal Surgery, Pathology, and Radiology are crucial to the accurate diagnosis and treatment of IBD.

A MDT for IBD was established at this hospital in June 2016. Gastroenterology is still the core of the team and is mainly responsible for outpatient consultations regarding IBD, hospital admission, preliminary diagnosis, and follow-up after discharge. Colonoscopies and enteroscopies performed by Gastroenterology play a vital role in the diagnosis of IBD, determination of disease activity, identification of complications, and as a guide for follow-up treatment. Endoscopy is also an important way for Pathology to obtain biopsy specimens from non-surgical patients. Routine antibiotics, steroids, immunomodulatory drugs, biologically targeted therapy drugs, and nutritional support in Gastroenterology can roughly meet the routine treatment needs of patients with IBD. Gastroenterology is responsible for the initial diagnosis of patients with IBD. If Digestive Internal Medicine encounters difficulties in the diagnosis and treatment process or it notes poor efficacy, it will request a MDT conference to discuss a patient with other team members in order to reach the most accurate diagnosis and to determine if a further examination is required or which subsequent treatment is best.

In addition to Internal Medicine, Surgery is also indispensable to alleviate the complications of IBD since surgery will directly affect the survival rate of and long-term prognosis for patients (*19*). Gastrointestinal Surgery has been involved in the treatment of IBD for decades, and there is a marked difference in surgical management between CD and UC. Although CD is still a type of incurable intestinal disease, and it is mainly treated medically, Gastrointestinal Surgery has a proven role in the management of the complications of IBD. Surgical indications for CD include intestinal stenosis or an obstruction, abdominal abscesses, intestinal fistulae or external fistulae, an intestinal perforation, uncontrollable intestinal bleeding, cancer, and inefficacious medical treatment. Surgical indications for UC include toxic megacolon, a perforation, bleeding, poorly tolerated parenteral nutrition, and malignant transformation. During a MDT conference, the team will refer a patient with surgical indications for IBD to Gastrointestinal Surgery for surgery as appropriate. Patients who undergo elective surgery should be adequately prepared preoperatively in Gastrointestinal Surgery, and the appropriate procedure should be selected in conjunction with the opinions of pathologists and imaging specialists. After surgery and once the patient recovers sufficiently, the patient will be returned to Gastroenterology for postoperative rehabilitation.

The core members of the MDT also include Pathology and Radiology, which play a key role in providing more diagnostic methods and criteria, improving diagnostic accuracy, identifying complications, determining disease activity and lesion sites, and guiding treatment. The histological findings of CD are mucosal erosions and deep ulcers covered with necrotic tissue, noncaseating necrotic granulomas in the intestinal wall, lymphocyte, plasma cell, and macrophage aggregation in the submucosa, and lymphatic follicular proliferation. The typical histological appearance of UC is extensive ulceration with infiltration of neutrophils, lymphocytes, plasma cells, and eosinophils in the lamina propria, and dysplasia. Pathological changes are even more suggestive than endoscopic changes when predicting the prognosis for some patients (*20*) (Figure 4). Imaging also plays an important role in the supplementary diagnosis of CD. Computed tomography (CT) and magnetic resonance (MR) intestinal imaging can indicate inflammatory changes in the intestinal wall, lesion location and extent, the presence of stenosis, and various complications such as fistula formation and abdominal abscess. These modalities can be used as a routine examination for CD in the small intestine (*21*). Imaging plays a unique role in assessing the condition of patients with IBD before surgery, as well as in determining the procedure and perioperative drug therapy. The typical computed tomography enterography (CTE) findings of active CD have been described in detail in the Methods (Figure 5). When three of the six criteria above are met, imaging is crucial to the diagnosis of CD.

This retrospective study has compared an experimental group and a control group, and results revealed that the ability to diagnose and treat IBD increased significantly at the Second Xiangya Hospital, Central South University after the establishment of a MDT. Preoperative diagnostic accuracy has improved for patients undergoing surgery, preoperative preparations are more extensive, tolerance of surgery has significantly improved, and the risk of postoperative adverse events has decreased significantly.

A MDT has numerous advantages over the conventional general medical and surgical consultation approach for the following reasons. First, there are

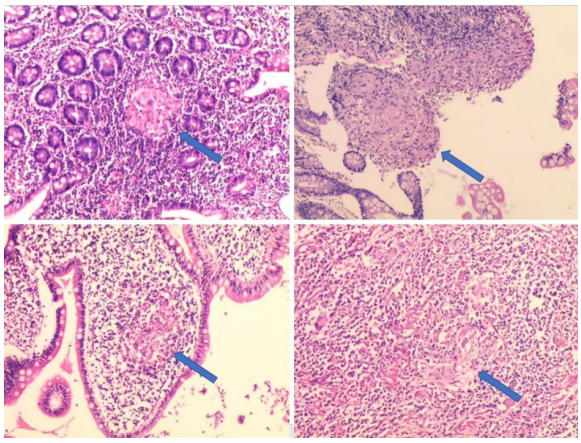

Figure 4. The three upper images depict the typical histological finding in CD, a noncaseating granuloma (arrows).

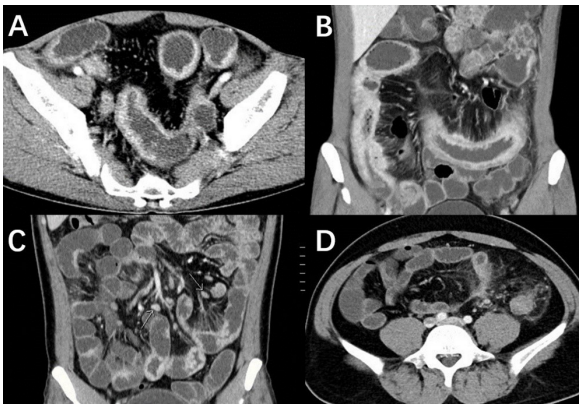

Figure 5. The typical radiographic appearance of CD: (A) thickening and enhancement of the intestinal wall, (B) the "comb sign" of CD, (C) enlarged lymph nodes around the bowel, (D) fibroadipose hyperplasia.

multidisciplinary conferences such as hospital-wide conferences in the conventional medical approach, but the personnel and time are not fixed, and team members lack sufficient understanding and experience cooperating, so the efficiency of such a multidisciplinary conference is often limited. In contrast, a multidisciplinary approach to IBD seems to be effective in assisting the complex decision-making involved in diagnosing and treating IBD (*22*). Second, in the conventional approach to consultation, physicians lack experience surgically treating a disease, so they often consider seeking a consultation once the disease has progressed to a point where the patient's infection status, nutritional status, and ability to tolerate surgery have significantly worsened and may be accompanied by economic concerns due to excessive reliance on medication. Third, there were differences between the experimental group and the control group in terms of the diagnostic and treatment modalities as well as in terms of the patient visits, so the development of drug therapies, procedures, and supplementary examinations or studies for patients of different ages may also have a positive effect on diagnosis and treatment.

The current study revealed that a MDT conference can improve the rate of correct diagnosis and outcomes, and the ability of this multidisciplinary center to diagnose IBD has improved between June 2016 and February 2021. This has contributed to a greater understanding of IBD and it has improved ability of physicians, surgeons, pathologists, and radiologists to manage the disease. In addition, results revealed that MDT conferences on patients with IBD had a significant effect and are necessary not only at national and provincial centers but also at municipal and county hospitals.

5. Conclusion

IBD is a chronic disease that is difficult to cure. Diagnosis and treatment of IBD relies not only on the ability of gastroenterologists but it also requires a MDT throughout the course of the disease. A MDT conference plays an important role in the diagnosis and treatment of IBD. In addition, a MDT can enhance the overall level of clinical treatment and the level of teamwork.

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Communication

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Using a multidisciplinary team for the staged management and optimally minimally invasive treatment of severe acute pancreatitis

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SUMMARY Severe acute pancreatitis (SAP) is a common critical disease with a high mortality rate that involves a complex, rapid change in condition and multiple organ systems. Therefore, a multidisciplinary team (MDT), including staff from the emergency department, intensive care unit, pancreatic surgery, gastroenterology , and imaging, is necessary for the early diagnosis, evaluation, and treatment of patients with SAP. This involves managing the systemic inflammatory response and maintaining organ function in the early stage and managing systemic infection and treatment of peripancreatic complications in the middle-to-late stages. The MDT should be led by departments corresponding to the clinical characteristics of each stage, and those departments should be responsible for the coordination and implementation of treatment by other relevant departments. In the late stage, pancreatic surgery and gastroenterology are the main departments that should manage peripancreatic complications. In line with the principle of minimally invasive treatment, the timely and reasonable selection of endoscopic or minimally invasive surgical debridement can achieve good therapeutic outcomes. Open surgery is also an effective method for treating an intractable massive hemorrhage in the abdominal cavity or necrotic cavity, intractable abdominal compartment syndrome, visceral perforation, and fistulae.

Keywords multidisciplinary team; staged management, severe acute pancreatitis, optimally, minimally invasive

1. Introduction

Severe acute pancreatitis (SAP) is a critical disease involving multiple organ dysfunction or even failure and is characterized by peripancreatic lesions and a systemic inflammatory response (*1*). SAP is a major concern because of its prevalence, unpredictable onset, rapid progression, and high mortality rate. Due to the complexity of SAP, the close relationship between peripancreatic local lesions and systemic inflammation, and the interaction between various organs, the diagnosis and treatment of SAP must involve timely and accurate assessment of the disease. In addition, the function of multiple important organs must be maintained, nutritional support and fluid treatment must be provided, infection must be controlled, drainage must be performed, and peripancreatic complications must be treated endoscopically or surgically. These efforts must involve the emergency department, intensive care unit (ICU), and emergency treatment unit. This multidisciplinary team (MDT) must, therefore, include departments such as hepatobiliary and pancreatic surgery, gastroenterology, medical imaging (ultrasound, computed tomography [CT], and interventional radiology), microbiology, nutrition, and traditional Chinese medicine (*2*) (Figure 1). Depending on the clinical characteristics in different stages of the development of SAP, different departments will be involved; however, the most important aspect is to provide timely and accurate assessment of the disease at all stages and to formulate the best treatment plan accordingly (*3*).

2. Management during the first visit

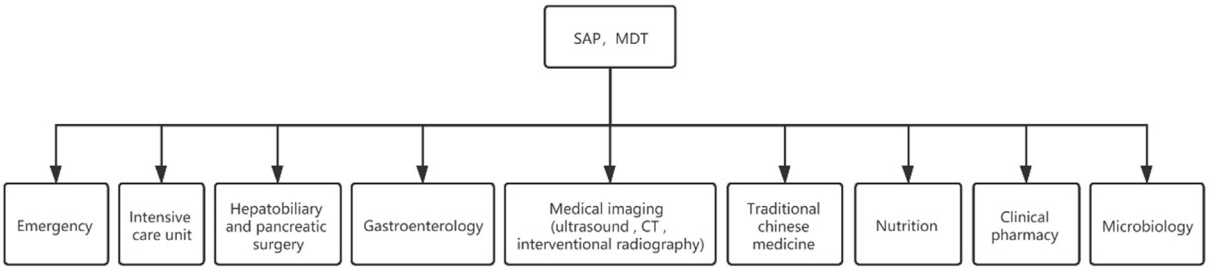

Figure 1. Multidisciplinary team for severe acute pancreatitis.

The onset of SAP is unpredictable, sudden, and often occurs first in the emergency department; therefore, proper anticipation and timely diagnosis of SAP and its complications in the emergency department are particularly important. SAP occurs in 15-25% of cases of acute pancreatitis (*4*). In the early stage of acute pancreatitis, inflammatory mediators and cytokines are transmitted and amplified in a "cascade." Systemic inflammatory response syndrome (SIRS) occurs rapidly, and then multiple organ dysfunction syndrome (MODS), which includes the heart, lungs, and kidneys, can occur (*5*). Prolonged MODS affects the respiratory, circulatory, digestive, renal, and coagulation systems (*5-7*). Therefore, within the MDT framework, a practical and feasible protocol must be formulated that involves the training of emergency doctors to closely monitor the blood oxygen, blood pressure, and renal function of patients recently diagnosed with acute pancreatitis and to evaluate cardiopulmonary and renal function with the improved Marshall scoring system to detect and diagnose SAP early. The emergency department should call for an MDT conference, manage SAP in a timely and appropriate manner according to standards, reduce the inflammatory response, maintain tissue and organ perfusion, and protect the organ function environment (*8*).

2.1. Scoring systems

At the authors' facility, SAP was diagnosed when patients had a bedside index for severity in acute pancreatitis (BISAP) score > 3. The BISAP score was evaluated repeatedly during the course of the disease, allowing for any changes to be monitored dynamically. Patients with organ failure for more than 48 h (defined according to the revised Atlanta classification standard) were transferred to the ICU for treatment (*9,10*).

The initial diagnosis and management of SAP was mostly done in the emergency department. Therefore, the development of an MDT process is conducive to timely and accurate evaluation and appropriate treatment. Doctors from relevant departments with extensive experience in treating SAP can be contacted for treatment advice and protocols. When patients need to be transferred to the ICU, they can be transferred smoothly *via* the MDT path.

3. Early management

The initial phase of SAP may last 1-2 wks, and early SIRS and persistent (≥ 48 h) dysfunction of more than two organs are the main clinical manifestations. The first peak in mortality occurs at this time (*10*). The management of this stage should be led by the ICU or internal and external departments that are capable of providing intensive care, and treatment should focus on fluid resuscitation, respiratory and circulatory support, improvement in ventilation and tissue perfusion, and maintenance of organ function (*11*).

3.1. Fluid resuscitation

Fluid resuscitation is essential for maintaining circulation stability and ensuring organ perfusion and should be implemented as soon as possible after diagnosis (*12*). The decrease in mortality associated with acute pancreatitis in recent years has been attributed to an improvement in microcirculation during fluid resuscitation, which has helped prevent pancreatic necrosis (*5*). Early fluid resuscitation can be performed to optimize tissue perfusion before hemodynamic deterioration. The first 12-24 h of active intravenous rehydration is the most beneficial, and isotonic crystalloid solution is the preferred fluid. The goal-directed fluid therapy recommended in the American Gastroenterological Association treatment guidelines for acute pancreatitis in 2018 includes quickly supplementing isotonic crystalloid solution (0.9% sodium chloride or lactate Ringer's solution) in order to restore end organ perfusion (*13*). Initially, a bolus of 20 mL/kg of fluid is administered within 30 minutes at a rate of 5-10 mL/kg/h, and then continuous intravenous fluid is added at a rate of 3 mL/kg/h for 8-12 h. Indications that fluid therapy has been effective include a central venous pressure of 8-12 cmH_2O, a mean arterial pressure ≥ 65 mmHg, urine volume ≥ 0.5 mL/kg/h, oxygen saturation ≥ 0.70, central or mixed venous hematocrit > 0.3, and decreased blood urea nitrogen (*14*). However, excessive fluid therapy can increase the burden on the heart, affect the lungs,

and increase intra-abdominal pressure. Therefore, blood volume responsiveness and blood volume status should be evaluated, and the infusion volume and infusion rate should be dynamically adjusted as necessary. In addition, invasive hemodynamic monitoring may be indicated (*11*).

3.2. Analgesia

Patients with SAP may have abdominal pain and pain associated with other diseases (various invasive surgeries or bed rest). Therefore, appropriate analgesics and sedatives should be administered within 24 h of admission to improve comfort and reduce clinical symptoms associated with increased oxygen consumption and stress (*15*).

3.3. Lung protection

The lungs are the main target of inflammatory mediators and toxins. The increase in pulmonary capillary permeability, the decrease in alveolar surface-active substances, and the decrease in pulmonary perfusion lead to ventilation dysfunction. The sharp increase in intra-abdominal pressure associated with SAP also raises the diaphragm, thus affecting ventilation. Therefore, symptoms of acute respiratory distress syndrome, such as chest tightness, respiratory distress, and progressive hypoxemia, may appear in the early stage of SAP (*16*). A persistent hypoxic state can lead to hypoxia in tissues and organs throughout the body, potentially worsening MODS if it is not corrected quickly. When oxygen therapy is ineffective, noninvasive or invasive ventilation is often indicated. When, however, the removal of bronchial secretions is ineffective or the patient is exhausted, tracheal intubation should be performed and positive pressure ventilation should be used to improve oxygenation and ventilation. The strategy of using ventilation to protect the lungs should be adopted during invasive ventilation. The tidal volume should be 6 mL/kg, plateau pressure should be 30 cm H2O, and positive end expiratory pressure should be titrated accordingly. Pleural effusion should also be drained promptly (*17*).

3.4. Renal protection

Acute kidney injury (AKI) is a common complication of SAP. Approximately 70% of patients with SAP develop AKI (*18*). The main causes of AKI are hypoperfusion and inflammatory mediator toxin attack. The first manifestation is oliguria or even anuria (*19*). The diagnostic criteria for AKI include an increase ≥ 0.3 mg/dL in serum creatinine (SCR) within 48 h, a 1.5-fold or greater increase in SCR from baseline, or a continuous urine volume < 0.5 mL/kg/h over 6 h (*20*). Sodium retention and the accumulation of water and toxic substances can lead to a disturbance in the acid-base balance. In addition, dysfunction of organs such as the lungs and the respiratory center in the brain can also occur. Therefore, continuous renal replacement therapy should be performed in patients with SAP who develop AKI when adequate fluid resuscitation is ineffective or abdominal compartment syndrome occurs (*21*).

3.5. Antibiotics

The prophylactic use of antibiotics has not been found to reduce mortality in patients with acute pancreatitis. Therefore, the routine use of antibiotics is not recommended for all patients with acute pancreatitis. However, antibiotics should be promptly administered to patients with acute cholangitis or extrapancreatic infections (*2*).

3.6. Enteral nutrition

Early enteral nutrition is helpful at maintaining the intestinal barrier and reducing bacterial translocation and the incidence of multiple infections. Patients should be encouraged to eat early; however, enteral nutrition (oral, nasogastric, and jejunal) and nutritional support should be tailored individually depending on the patient's intra-abdominal pressure and gastrointestinal function (*13*).

4. Interim management

4.1. Infection control

Once the systemic inflammatory response has subsided in patients with SAP, the functioning of the lungs, kidneys, heart, liver, and other organs will recover; effective circulating blood volume increases; tissue perfusion improves, tissue hypoxia diminishes, and respiratory function improve; and urine output volume increases. Ten to fourteen d after the onset of the disease, however, some patients have obvious symptoms of infection and enter a period of systemic infection (*10*). The causes of SAP infection are as follows: 1) translocation of intestinal flora; 2) a retrograde infection caused by percutaneous catheter drainage; 3) biliary calculi and obstruction complicated by infection; 4) respiratory insufficiency and hypoxemia; and 5) reduced immunity (*22*). Most of the pathogens responsible are Gram-negative bacteria, and Escherichia coli is the most common (*23*). Currently, MDT management requires close cooperation between the ICU, pancreatic surgery, and gastroenterology. Systemic infections may cause the disease to recur; therefore, a broad-spectrum antibiotic that can treat a wide range of bacteria and pass through the blood-pancreatic barrier must be selected while keeping respiratory, circulatory, and renal function stable, the etiological cause must be quickly diagnosed, and more sensitive drugs must then be administered either

immediately or after symptom control (*24,25*). SAP has a long course, so clinicians should be alert for multi-drug resistant bacteria or fungal infections (*26,27*). The optimal use of antibiotics can be determined under the guidance of microbiologists and clinical pharmacists on the MDT (Figure 2).

4.2. Invasive surgery

A local infection should be treated with minimally invasive, safe, and effective drainage. Percutaneous catheter drainage should be performed immediately in case of definite local infection or high pressure. Surgical treatment needs to be carefully considered during the early stage and is preferably performed 4 wks after onset (*28*). Biliary SAP with a biliary obstruction should be treated with CT or B-ultrasound-guided percutaneous transhepatic cholangial drainage and percutaneous transhepatic gallbladder drainage. Alternatively, endoscopic retrograde cholangiopancreatography, endoscopic sphincterotomy, or nasobiliary drainage can also be selected (*29,30*).

4.3. Reducing abdominal pressure

Gastrointestinal emptying disorders and abdominal hypertension are common in the early stage of SAP. Abdominal hypertension, digestive and absorption disorders, intestinal barrier damage, and bacterial translocation lead to acid-base disorders and abdominal compartment syndrome and can aggravate respiratory and circulatory dysfunction, infection, and the systemic inflammatory response, all of which play an important role in the progression of the disease and its prognosis (*31*). However, relieving pressuring of the small intestine using a conventional gastric tube is difficult and open surgery is rarely used because of the associated trauma and complications (*32,33*). In traditional Chinese medicine, acute pancreatitis is categorized as abdominal pain and epigastric pain. Its etiology and pathogenesis are mainly related to the accumulation of heat and toxins, obstruction of the viscera, blood stasis, or stagnation of qi in the liver (*34*). Because of its "cold and bitter" properties, rhubarb is believed to treat diarrhea by relieving "heat and fire;" combined with rhubarb, mirabilite is believed to "moisten dryness" and increase the "heat-relieving" effect of rhubarb (alleviating diarrhea) (*35*). A mixture of rhubarb and mirabilite can promote intestinal peristalsis, accelerate the recovery of intestinal function, regulate inflammatory mediators, promote the elimination of oxygen free radicals, and reduce systemic inflammation (*36*). Guided by B-ultrasound, X-ray, or gastroscopy and in consultation with traditional Chinese medicine, an indwelling nasogastric intestinal catheter can be placed by manually at the bedside. This catheter

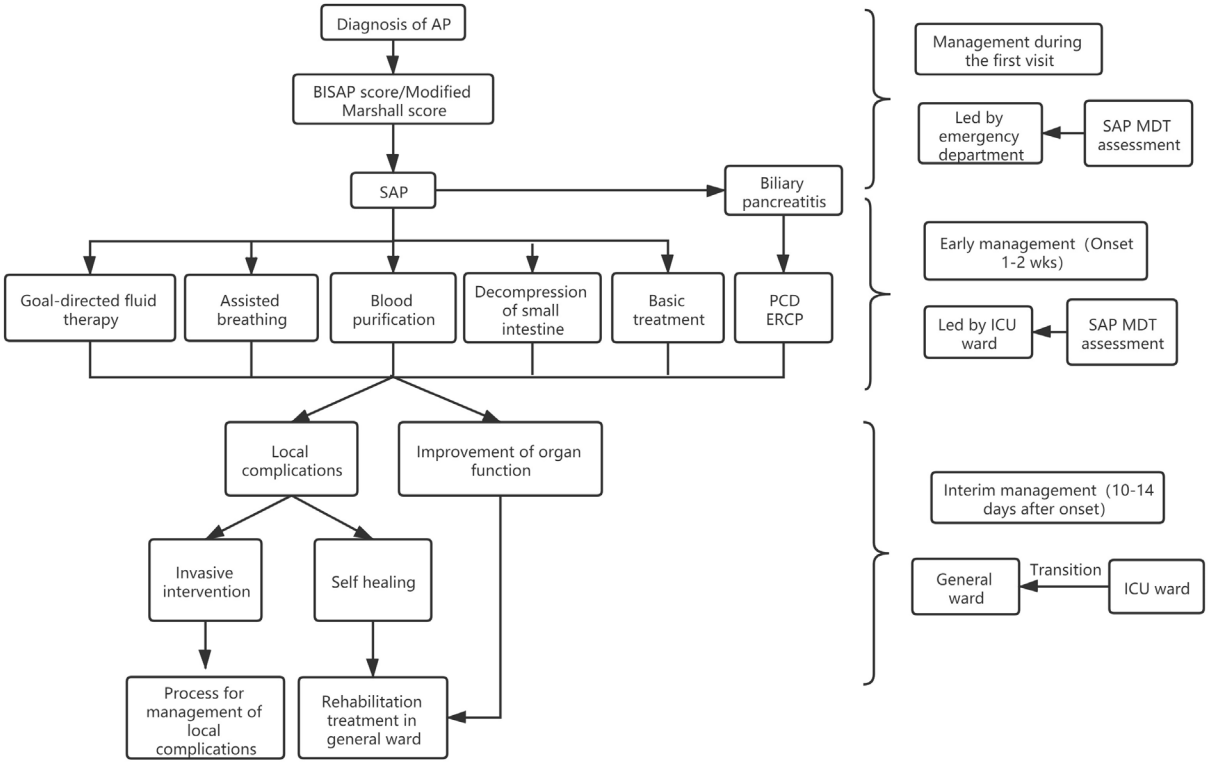

Figure 2. SAP phased management

can reach the distal part of the small intestine and effectively drain intestinal effusion and gas at the same time and, when combined with rhubarb, the external application of mirabilite, and an enema, can quickly reduce the pressure on the gastrointestinal tract and abdominal cavity (*37,38*). It is safe, noninvasive, simple, and effective. After the recovery of intestinal function, the catheter can also be used for enteral nutrition.

4.4. Nutritional support

Gastrointestinal dysfunction, high energy consumption, and anabolic disorders often lead to malnutrition in patients with SAP. The goal of nutritional support is to provide energy and metabolic substrates, maintain the function of cells, tissues and organs, correct a negative nitrogen balance, reduce the inflammatory response, and avoid energy depletion. Nutrition should be administered through the whole process of SAP treatment (*13*). Due to a dysfunction in gastrointestinal absorption and emptying and a high abdominal pressure, total parenteral nutrition must be administered in the early stage of SAP. To avoid high fat input, glucose is generally the main form of energy administered. Albumin as a colloidal supplement is helpful in correcting hypoproteinemia (*39*). Glutathione, polyunsaturated fatty acids, nucleotides, and other therapeutic nutrients are also used (*40*). Once intestinal function has recovered, enteral nutrition should be promptly started. This helps to protect the intestinal mucosal barrier, maintain the balance of intestinal microorganisms, and reduce the translocation of intestinal flora (*41*).

5. Late management and optimally minimally invasive treatment of peripancreatic complications

Four wks after the onset of SAP, the inflammatory response in some patients is effectively reduced, and the function of the heart, lungs, kidneys, and other important organs gradually recover and stabilize. The main problem at this stage is infectious necrosis of the pancreas and retroperitoneum, which leads to the second peak in mortality. In this stage, the MDT should be led by gastroenterology or pancreatic surgery (*10,42*). The pancreas is a retroperitoneal organ. Activated pancreatic juices are placed under increased pressure and erode the adjacent portal vein, causing necrotic pancreatic tissue to spread along the left and right retroperitoneum. Necrosis can span from the diaphragm to the sacroiliac joint. Therefore, acute peripancreatic fluid collection, acute necrotic collection, pancreatic pseudocyst, walled-off necrosis, and infectious pancreatic necrosis are the main causes of mortality (*2*).

5.1. Minimally invasive approach

For the treatment of peripancreatic lesions (Figure 3), the MDT needs to be led by pancreatic surgery and gastroenterology. The "3D" principle (delay, drainage, and debridement) should be followed with the help of imaging and interventional radiology. Debridement is a minimally invasive treatment with ascending steps (*43,44*). In the early stage (within the first 4 wks), acute peripancreatic fluid collection and acute necrotic collection mainly occur. If the disease requires treatment, CT or B-ultrasound-guided percutaneous catheter drainage can be performed. Abscesses are liquefied. This can both reduce the inflammatory response and the abdominal and retroperitoneal pressure and promote the recovery of gastrointestinal function (*45*). In the middle and late stages of the

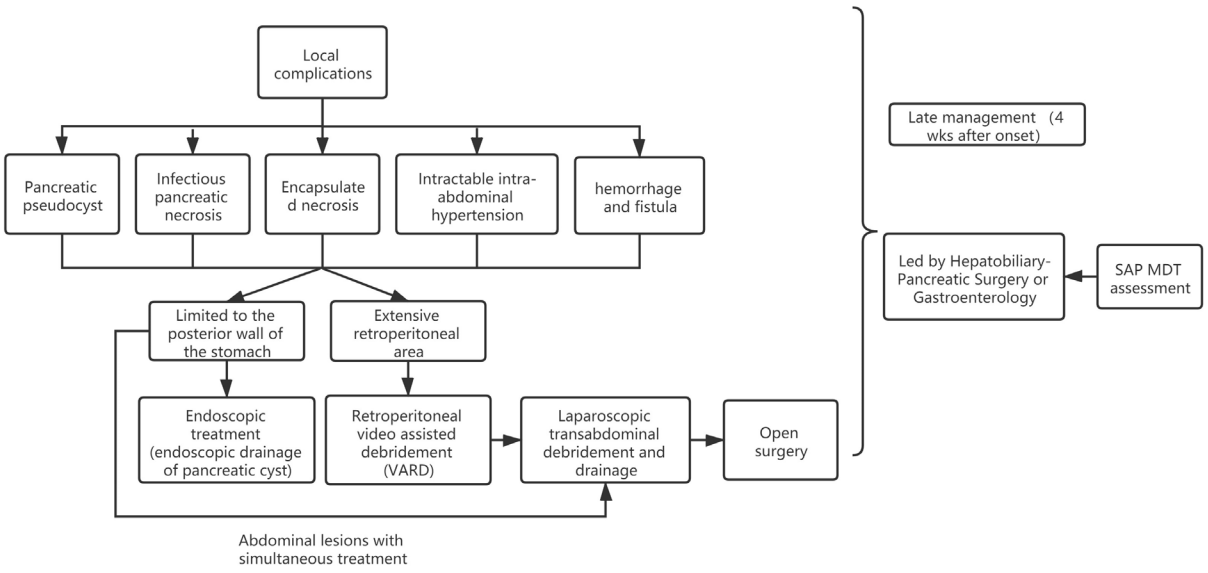

Figure 3. Process for management of local complications.

disease (4 wks after onset), necrotic tissues around the pancreas and retroperitoneum gradually liquefy and form a boundary, and the following manifestations may appear: 1) temperature ≥ 38.5ºC and elevated C-reactive protein and other inflammatory markers, 2) persistent organ failure or new onset of organ failure, 3) CT and other imaging findings indicating that the extent of necrosis has increased and a "bubble sign" evident in the necrotic focus, 4) fine-needle aspiration of necrotic tissue and positive Gram staining or culture (*46*). When pancreatic surgery is needed to treat tissue necrosis and an infection, minimally invasive debridement and drainage should be performed at the appropriate time. Common surgical techniques include video-assisted retroperitoneal debridement (VARD), endoscopic transmural drainage (ETD), laparoscopic debridement and drainage, and open surgery (*47*). VARD allows a direct view as the surgeon clears the necrotic tissue around the pancreas and pelvis under direct vision, so it is suitable for retroperitoneal necrosis that has not invaded the abdominal cavity. Gastroscopic debridement is suitable for peripancreatic cysts close to the posterior wall of the stomach and involves minimal surgical trauma. Stent placement can provide drainage to an extent, but it is not effective at debridement, plastic stents provide limited drainage, and metal stents need to be replaced regularly (*48*). Most cases of acute pancreatitis are treated with open surgery when there is a massive hemorrhage in the abdominal cavity or necrosis that cannot be readily controlled by conservative or interventional treatment, when compartment syndrome cannot be readily relieved, and when a visceral perforation or fistula is present (*49*). Each method of debridement and drainage has its advantages and disadvantages.

5.2. Timing and indications

The key to the treatment of peripancreatic lesions is to determine the timing and indications. Early inflammation, hyperemia, and exudation are the main causes. Patients with a severe systemic inflammatory response and multiple organ dysfunction should undergo percutaneous catheter drainage or some other minimally invasive method. Blindly expanding the surgery will only backfire, aggravate the trauma, and even lead to death. In the later stage, the patients with retroperitoneal infection and necrosis should be treated promptly, and appropriate debridement and drainage should be performed.

In short, SAP is a common surgical emergency with a high mortality rate. Its diagnosis and treatment involves multiple organ systems and portions of the pancreas. SAP should be treated by an MDT consisting of experts from relevant departments who are proficient in the latest techniques to diagnose and treat SAP. The MDT should effectively coordinate during the diagnosis and treatment process. Depending on the different stages of the disease, the departments in charge should provide the patient with a standardized and optimal treatment plan. The treatment of peripancreatic complications should follow the principle of least invasiveness and provide the best form of treatment in a timely manner.

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What is always necessary throughout efforts to prevent and control COVID-19 and other infectious diseases? A physical containment strategy and public mobilization and management

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SUMMARY The COVID-19 pandemic continues to ravage the world. As many countries have entered the post-pandemic period, current efforts to prevent and control COVID-19 have gradually been normalized in many countries. Although the focus is on vaccines to achieve herd immunity, conventional physical containment strategies should be reassessed as part of efforts to prevent and control infectious diseases. Continued respiratory protective measures such as social distancing and the wearing of masks have been extensively accepted by the public in most countries. A point worth noticing is that the activities of influenza and other respiratory diseases have decreased as these strategies have been implemented. Public mobilization and large-scale campaigns to promote health are also important to interrupting the transmission of pathogens. A good example can be found in the achievements of China's Patriotic Public Health Campaign. These practices underscore the importance of enhancing physical containment strategies and public mobilization and management, with support from the legal system, to respond to any potential emerging infectious diseases.

Keywords physical containment strategy, public mobilization, COVID-19, infectious disease

Though we are halfway through 2021, the COVID-19 pandemic continues to ravage the world (Figure 1). Many countries have implemented interventions to control the disease. Vaccines have been seriously considered to achieve herd immunity in order to control the COVID-19 pandemic (*1*), and different types of vaccines have proven effective (*2*). Under real-world conditions, vaccines still face many challenges to protecting the public against COVID-19 and other infectious diseases.

Without sufficient testing, vaccines may fail to fully eliminate or halt the spread of viral infections. Generally, the preparation phase takes too long to respond to outbreaks and other public health emergencies. Although COVID-19 vaccines have been developed rapidly in comparison to conventional vaccines and various approaches to evaluating vaccine efficacy have been devised, testing to evaluate safety and efficacy still takes time, and trials must assess the rate of protection afforded to multiple subpopulations, the reduction in the incidence or spread of infection, the severity of the resulting disease, and the duration of protection (from new variants) (*4*).

The availability of vaccines should be considered for them to be accepted and received by a large majority of the population. Availability includes sufficient storage, and especially in developing countries. Attention should also be paid to the willingness of the public to be vaccinated (*5*).

Vaccine breakthrough infections are expected. In one study, a small percentage of subjects (2 female subjects) who received the second dose of the NHT162b2 (Pfizer–BioNTech) or mRNA-1273 (Moderna) vaccine underwent viral testing weekly (*6*). Two female subjects were identified as vaccine breakthrough infections (infection was identified In Subject 1 19 days after the second dose and in Subject 2 36 days after that dose). According to surveillance by the US CDC, a total of 10,262 SARS-CoV-2 vaccine breakthrough infections had been reported from 46 US states and territories as of April 30, 2021. Those vaccine breakthrough infections included 2,725 asymptomatic patients (27%), 995 patients who were hospitalized (10%), and 160 patients who died (2%) (*7*).

Although the focus is on vaccines, conventional physical containment strategies should be reassessed as part of efforts to prevent and control infectious diseases. Physical containment strategies can be divided into four levels based on the target and scale. Personal protections include the wearing masks, handwashing, and social distancing. Epidemiological measures include patient

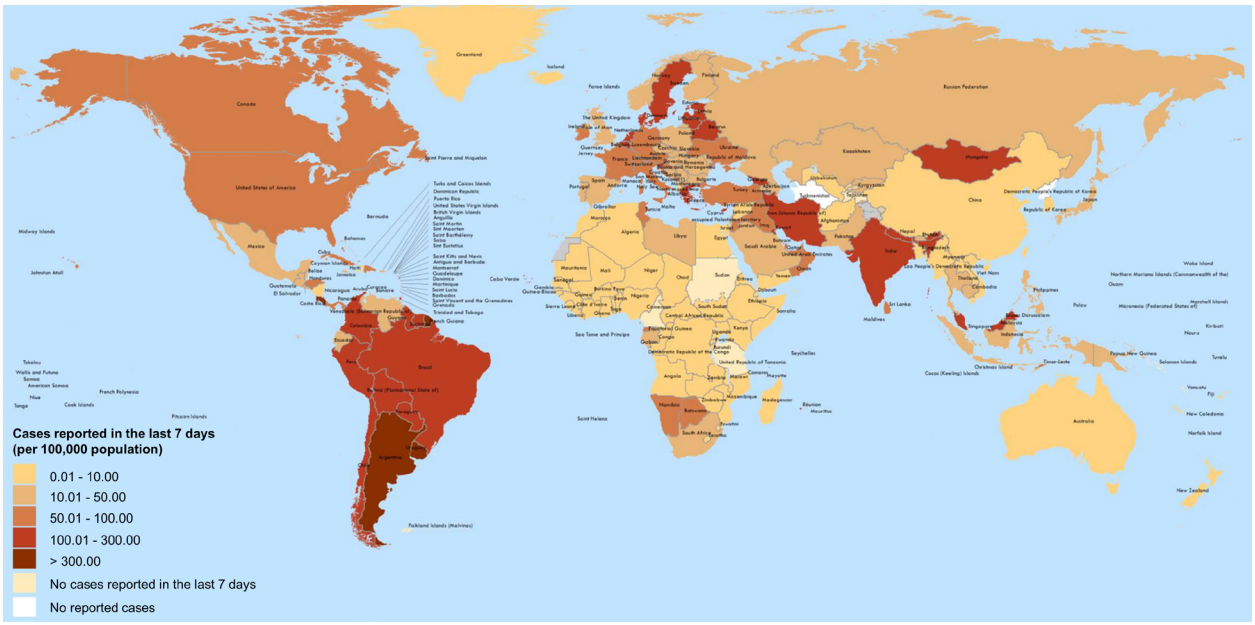

Figure 1. COVID-19 cases per 100,000 population reported by countries, territories, and areas, 17 May-23 May 2021. Figure is from the COVID-19 Weekly Epidemiological Update (*3*). Data presented are based on official laboratory-confirmed COVID-19 case and deaths reported to the WHO by country/territories/areas, largely based upon WHO case definitions and surveillance guidance.

isolation and contact tracing. Environmental measures include environmental disinfection and standard operating procedures in clinics and other key locations. Public mobilization and lockdown measures include cancelling of large gatherings, locking down of areas where a disease is likely to spread, and traffic control (*8*).

Due to continued concerns about controlling COVID-19, at a minimum, personal respiratory protection has been extensively accepted by the public in most countries. A point worth noticing is that the activities of influenza and other respiratory diseases have decreased while these strategies have been implemented. According to a report by the World Health Organization (WHO), seasonal influenza activity has decreased: influenza A(H1N1) pdm09, A(H3N2), and influenza B viruses circulated in very low numbers and the relative proportions of the viruses circulating varied among global reporting countries between September 2020 and January 2021 (*9*) (Figure 2). In Europe, only sporadic outbreaks of influenza A or B viruses were detected. In comparison to previous years, the number of specimens tested decreased 20%.

Similar reductions in influenza and other respiratory infections have also been noted in Asian countries. According to the Tokyo Metropolitan Infectious Disease Surveillance Center, there have been fewer than 5 reported cases at each designated medical facility per week during the past year (week 36 of 2020 to week 36 of 2021) compared to a peak (64 cases/sentinel site) from week 36 of 2018 to week 36 of 2019 during the past 5 years (*11*). Based on a weekly database, a Japanese study clearly demonstrated that summer influenza disappeared in Okinawa Prefecture in 2020 (*12*). Physical containment strategies that seek to interrupt the transmission of pathogens are effective at preventing and controlling COVID-19, influenza, and other infectious diseases.

As many countries have entered the post-pandemic period, the current efforts to prevent and control COVID-19 have gradually been normalized in many countries. However, the global public health system should aware that emerging infectious diseases (EIDs) require continuous vigilance. Since 2003, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), Zika virus disease, and other EIDs have rapidly developed and caused a series of serious public health incidents. Governments and public health agencies should emphasize research and practical implementation of conventional physical containment strategies. To prevent and control sexually transmitted diseases, personal behaviors such as condom use and remaining monogamous should be emphasized; to control the spread of infectious diseases of the digestive tract, environmental disinfection should be emphasized, such as preventing the contamination of drinking water and food, sanitary waste disposal, and eradication of flies. Many EIDs appear to be caused by zoonotic pathogens and involve interaction between humans and wildlife (*13*). To avoid infection with vector-borne diseases, entry into wildlife habitats should be limited, and wildlife should not be regularly consumed. Surveillance and elimination of vectors should also be emphasized. In Eastern China, an evaluation system with four indices was created: control of mosquito density, village administration, health education and public attitudes, and control of mosquito density via

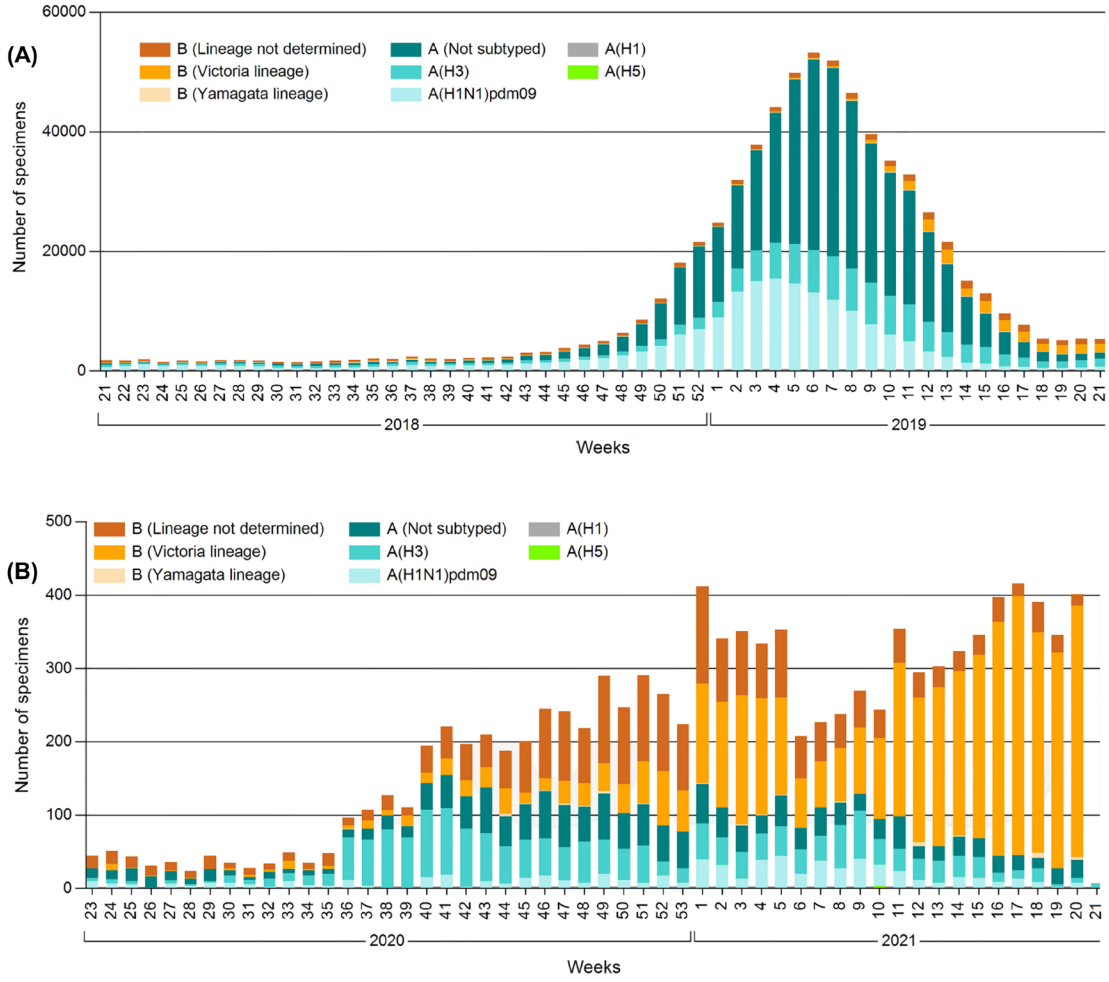

Figure 2. (A), Number of specimens positive for influenza by subtype from week 21 of 2018 to week 21 of 2019. (B), Number of specimens positive for influenza by subtype from week 21 of 2020 to week 21 of 2021. Figures are from the global influenza surveillance and response system (GISRS), WHO. Data presented are based on influenza laboratory surveillance information (*10*)

elimination of mosquito breeding grounds (*14*). After just one year, the mosquito density in a pilot village had decreased more than 90% (*15*). These measures demonstrate that physically separating vulnerable populations from potential pathogens is always an essential but economical and effective method of controlling infectious diseases. Public mobilization and large-scale campaigns to promote health are important to spreading those concepts and providing that health knowledge. The decades-long Patriotic Public Health Campaign in China is a good example of improving environmental health in urban and rural areas, and it has greatly improved public health. In Eastern China, local governments have combined efforts to prevent and control infectious diseases (such as vector-borne diseases) with rural revitalization in order to create a more comfortable and safer environment in rural villages (*16*). In July 2017, the WHO awarded the Chinese Government for its efforts and achievements during its Patriotic Public Health Campaign (*17*).

To ensure the effectiveness of prevention and control measures, a complete public health system should be envisioned and implemented. This means not just facilities but also science-based prevention and control efforts. Legal regulations ensure that the public health system functions legally and effectively. The World Health Assembly (WHA) adopted the new International Health Regulations (IHR) on May 23, 2005, and the purpose of the new IHR is "to prevent, protect against, control, and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks and which avoid unnecessary interference with international traffic and trade" (*18*). Moreover, legal regulations help improve the public health system's response. A more resilient and responsive public health system needs support from the legal system. A study in the Netherlands retrospectively compared the effects of legislative changes and increased awareness on the timeliness of notification (of local public health authorities) and reporting (to national public health authorities) during 10 outbreaks (*19*). Results indicated that the average delay in notification decreased from 1.4 to 0.4 day once the changes took effect (six diseases; $p < 0.05$), and the delay in reporting mainly decreased right after the changes took effect (from 0.5 to 0.1 day, six

diseases; $p < 0.05$).

The role of legislation should be emphasized to enhance the WHO's emergency response to acute infectious diseases or public health emergencies. This means that the previous IHR (2005) needs to be modified. The legal status of measures to prevent and control infectious diseases should be enhanced, and new IHR (2022) may be adopted to enhance public mobilization and management.

As globalization continues, the threat of infectious diseases is ever-present. Governments should always prepare to implement a containment strategy and mobilize the public. The public health system and related support from the legal system should both be seriously considered. During the formulation of physical containment strategies, their advantages and disadvantages should be fully evaluated to identify the most effective strategies to protect public health, with due consideration to personal freedom of movement. Lastly, positive aspects can be maximized to promote both global public health and economic development.

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Impact of China's COVID-19 prevention and control efforts on outbreaks of influenza

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SUMMARY The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a serious public health burden. As the COVID-19 epidemic in China would coincide with a seasonal outbreak of influenza, there were serious concerns about whether influenza would be aggravated by the SARS-CoV-2 infection and COVID-19 pandemic. This article provides a brief overview of the impacts of the COVID-19 epidemic on influenza activity in China. The percentage of positive influenza tests decreased during the COVID-19 pandemic. During the first stage of the COVID-19 outbreak, the percentage of positive influenza tests reached to a peak of 47.7%. At the second stage, the percentage of positive influenza tests was dramatically decreased from 40.4% to 14.0%. Thereafter, it remains at a low level of less than 6.2%. In addition, the possible causes of this phenomenon have been summarized, including prevention and control measures and ecological competition. Lastly, this article suggests that the public health approach to preventing COVID-19 may also help to control other respiratory infectious diseases. Public health measures need to be maintained even in the later stages of the COVID-19 epidemic.

Keywords COVID-19, SARS-CoV-2, influenza, co-infection, vaccines

1. Introduction

Outbreaks of influenza result in almost 650,000 respiratory-related deaths and millions of hospitalizations annually, and seasonal influenza has a significant impact on healthcare systems worldwide (*1*). In China, there were 88,100 annual deaths due to influenza in 22 provinces in 2010-11 and 2014-15 (*2*). To make matters worse, the outbreak of COVID-19, another respiratory infection that is causing a huge public health crisis in China, coincided with a seasonal outbreak of influenza in 2020. One study mentioned that influenza viruses might exacerbate COVID-19 *(3*). Thus, the question of whether a COVID-19 pandemic would exacerbate influenza has garnered attention worldwide.

2. Controversy on how the COVID-19 pandemic might affect the flu season

During the early stages of the COVID-19 pandemic, questions about how the COVID-19 pandemic might affect the flu season stirred up considerable controversy. Experts on one side argued that the COVID-19 pandemic might worsen influenza activity and, vice versa, that influenza might exacerbate the COVID-19 pandemic. Support for this view comes from evidence that patients infected with both COVID-19 and influenza A have more severe disease progression and higher mortality (*4,5*), and recent experiments in mice have validated the ability of influenza A viruses to accelerate SARS-CoV-2's infection of the upper respiratory tract (*6*). In addition, the impaired host immunity, decreased influenza vaccination rates, and limited medical resources caused by the COVID-19 pandemic may all aggravate influenza.

Experts on the other side contend that public health measures such as social distancing, wearing masks, diligent hand washing, and measures taken to mitigate COVID-19 may help prevent influenza and reduce the burden of the upcoming flu season. In addition, they believe that effective public health measures to prevent COVID-19 could also help control other respiratory diseases, and not just influenza (*7,8*).

3. Influenza activity during the winter season in China from 2018-2021

A previous study that examined influenza activity during the COVID-19 pandemic noted a decline in

that activity in many regions, including the United States, Australia, Chile, and South Africa (*9*). Other studies compared influenza activity during the 2019-2020 flu season (from the outbreak of COVID-19 to March 29, 2020) and during the 2011-2019 flu season, and they found that non-pharmaceutical interventions reduced influenza activity in southern China by 79.2% in northern China by 79.4%, and in the United States by 67.2% (*10,11*). An abrupt subsidence of seasonal influenza was also observed in Hong Kong, China during the COVID-19 pandemic (*12*). Together, these findings indicate that influenza activity declined during the COVID-19 pandemic (*13,14*).

To further shed light on this result, the number of respiratory specimens tested for influenza in China during the winter season (December to the end of March) in 2018-2019, 2019-2020, and 2020-2021 has been summarized (*15*). Consistent with the previous findings, data from influenza surveillance sites in China indicated a clear decrease in the percentage of laboratory tests positive for influenza after the outbreak of COVID-19. Figure 1 shows that during the winter of 2020-2021, the percentage of positive influenza tests declined sharply during the winter flu season in China, almost 4 weeks earlier than the winter flu season of 2018-2019. Since then, the percentage of positive influenza tests has been zero. Even though the percentage of positive influenza tests declined sharply at the end of December and even in the first 4 weeks of 2020, the number of respiratory specimens tested for influenza during this period is on par with the number tested previously (Figure 2).

4. Possible explanations for the abrupt subsidence of outbreaks of influenza after the COVID-19 epidemic

The following are possible explanations for the abrupt subsidence of influenza outbreaks after the COVID-19 pandemic. According to the timeline for the spread of COVID-19 (*16*), influenza activity remained at a high level during the first stage of the COVID-19 outbreak before the outbreak of the disease in Wuhan, China. The percentage of positive influenza tests was fluctuated from 45.3% to 44.9%, and even reached to the peak of 47.7% one week after the appearance of COVID-19 cases. Even though respiratory specimen testing remained at the same levels in the first month after the appearance of pneumonia cases, the rate of positive results declined rapidly from 47.7% to 35.8%. One can reasonably assume that the decline in influenza activity may be related to ecological competition between the two respiratory viruses in the human upper respiratory epithelium, which may give rise to the emergence of COVID-19 as the dominant virus, thus reducing the rate of influenza virus infection (*17-19*).

More importantly, public health measures are thought to have been effective in reducing the burden of an influenza outbreak. Figure 1 shows that influenza activity declined dramatically. The percentage of positive influenza tests was decreased from 40.4% to 14.0% during the second stage of the COVID-19 outbreak in China, which is when prevention and control measures were implemented in response to COVID-19. During this period of time, individuals took basic COVID-19 prevention and control measures, including handwashing, wearing a mask, social distancing, and avoiding crowded places. Local governments implemented different policies depending on the level of risk of a COVID-19 outbreak in different areas. For example, high-risk areas were ordered to shut down cities, close schools and workplaces, and ban social gatherings to avoid large crowds and close contact settings while areas with a mid-level or low risk were advised to reduce public activities and to self-isolate (Figure 3) (*19*). Even though the basic reproduction number (R0) of COVID-19 may be higher

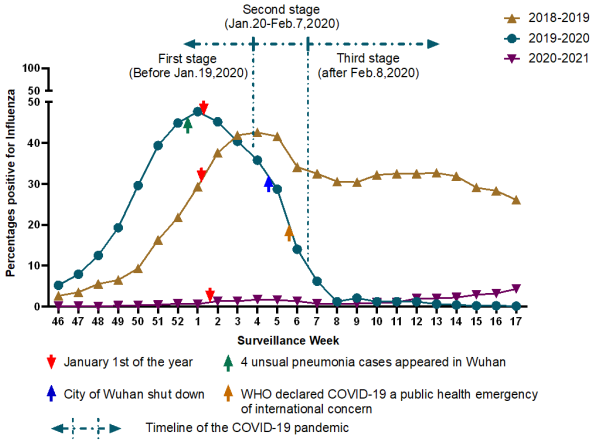

Figure 1. The percentage of positive influenza tests in China during the winter seasons (December to the end of March) from 2018-19, 2019-20, and 2020-21. Source: *http://www.chinaivdc.cn/cnic/en/*

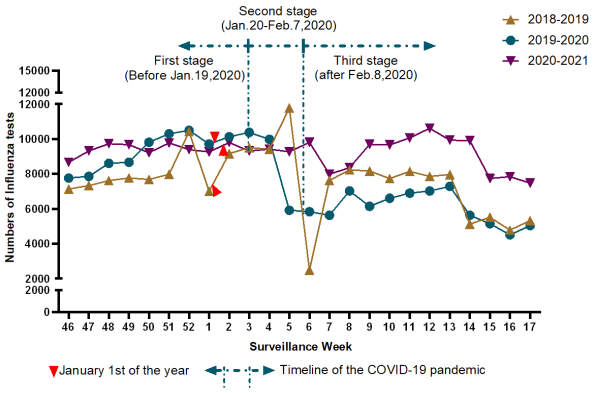

Figure 2. Number of respiratory specimens tested for influenza at Southern and Northern surveillance sites in China during the winter season (December to the end of March) from 2018-19, 2019-20, and 2020-21. Source: *http://www.chinaivdc.cn/cnic/en/*

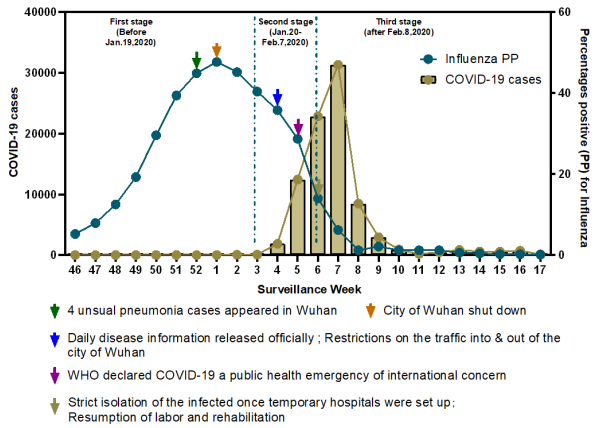

Figure 3. The percentage of positive influenza tests and COVID-19 cases in China during the winter season from 2019-2020. Key public health measures for the management of COVID-19 are indicated with arrows. Source: *https://covid19.who.int/region/wpro/country/cn*

than that of seasonal influenza, a substantial decrease in transmission could prevent excess deaths from the COVID-19 pandemic (*20*) since respiratory viruses are transmitted in similar ways and by similar routes. Thus, even if prevention and control measures may not have definitively reduced transmission, these findings greatly substantiate the hypothesis that public health interventions implemented to limit COVID-19 can reduce the burden of influenza pandemics.

The absence of influenza activity after the third stage of COVID-19 outbreak and the winter flu season of 2020-2021 further suggested that non-pharmaceutical interventions implemented to tackle COVID-19 also prevented influenza. Behavioral changes adopted in response to COVID-19, such as the weaking of a mask, social distancing, travel restrictions, and better personal hygiene, are still evident. Moreover, experience tracking COVID-19 has increased awareness of infectious disease prevention and control. Enhanced education and training for both healthcare personnel and the general public regarding personal hygiene and the public response to infectious diseases will also help to tackle the COVID-19 pandemic (*21*). In addition, the rate of influenza vaccination is on par with the previous rate, so vaccine efficacy and vaccination coverage may reduce the genetic drift or transfer of the dominant strain of influenza (*21*). Moreover, the surveillance of influenza was not inhibited by the COVID-19 pandemic but rather increased after COVID-19 was adequately controlled (Figure 2) (*22*).

In conclusion, the decline in influenza activity appears to be closely associated with public health measures that were implemented to control the COVID-19 pandemic. Public health measures taken by individuals, such as frequent hand washing, wearing of a mask, social distancing, and isolation of the infected, as well as policies adopted by governments, including stronger laws on infectious diseases, stricter quarantines, and restrictions on public activities in high-risk areas, have played a crucial role not only in defending against COVID-19, but also in combating influenza activity. This finding prompts careful consideration of the positive role of effective public health measures during the COVID-19 pandemic or even in the management of respiratory infectious diseases in the future. Thus, public health measures need to be maintained even in the aftermath of the COVID-19 pandemic.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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