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# THE SOCIETY OF PHYSICIANS OF HONG KONG

57th Anniversary Scientific Meeting (Free admission for doctors)
November 10, 2013 (Sunday)

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4:00 – 4:30 Q & A Enquiry Tel: 2526 2626 (No telephone registration)
Place: The Langham Hotel, 8 Peking Road, TST, Kowloon (尖沙咀北京道朗廷酒店)

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Web registration and further details: [www.SOPHYSICIANSHK.org](http://www.SOPHYSICIANSHK.org)

☐ I wish to attend Scientific Meeting and lunch on November 10, 2013 at 10 am. (Free)

Name of Doctor (surname first): 
Tel: ____________________
This issue will review current updates in the management of chronic hepatitis B (HBV) and C (HCV) virus infection and examine the role of endoscopic submucosal dissection in early gastrointestinal tumours.

The first article will discuss the efficacy and effects of long-term tenofovir treatment for chronic hepatitis B on the development of liver fibrosis and hepatocellular carcinoma. Long-term tenofovir monotherapy has resulted in virological suppression in the vast majority of patients with a high viral load (HBV DNA>10⁹ copies/mL) at baseline. The second article will review recent breakthroughs in the management of HCV, with a particular focus on boceprevir and telaprevir. When combined with pegylated interferon/ribavirin combination therapy, these novel direct-acting antiviral agents confer an improved sustained virological response in both treatment-naïve and prior relaper patients with HCV genotype 1. Factors that predict treatment response will also be discussed. The final article will look into the role of endoscopic resection techniques in the management of early gastrointestinal cancers. New techniques, including submucosal tunnelling endoscopic resection, will also be reviewed.

In Greek mythology, centaurs were half–man, half-horse mythical beasts. They were notorious for being uncultured, wild and lusty, overly indulgent drinkers, and given to violence when intoxicated. In contrast with the rest of the centaurs, Chiron was civilized, kind and wise. He was a teacher and mentor to some of Greek mythology’s greatest heroes. Apollo placed Asclepius under the tutorship of Chiron, who was distinguished for his knowledge of medicine. Asclepius was a gifted and studious student. He soon acquired the great art of healing, and went on to become an outstanding healer.

An amphora vase painted by Oltos, late Greek archaic period, circa 480 BC, Musée du Louvre, Paris.
Introduction

Hepatitis B virus (HBV) infection is a global public health problem. Up to 40% of those with chronic hepatitis B (CHB) may develop complications, including cirrhosis, decompensated liver disease and hepatocellular carcinoma (HCC).1 Viral suppression by means of HBV polymerase/reverse transcriptase inhibition has demonstrated clinical benefits, such as reduction in the risk of hepatic decompensation and lower rates of HCC in cirrhotic patients.2

Tenofovir disoproxil fumarate (TDF) is a potent inhibitor of HBV polymerase/reverse transcriptase that has activity against the hepatitis B (HBV) and HIV viruses. Two international, multicentre, randomized, double-blind phase III studies (NCT00117676 and NCT00116805) evaluated the efficacy and safety of once-daily tenofovir versus once-daily adefovir for 48 weeks. Tenofovir was more effective than adefovir in suppressing viral load and reducing histological inflammation.3 Studies have also shown that long-term use (3–5 years) of tenofovir maintains viral suppression and biochemical improvements.4,5

This review will present updated information on the efficacy of tenofovir in patients with high baseline viral load and its beneficial effects on regression of liver cirrhosis and for the prevention of HCC. The emergence of HBV resistance to nucleos(t)ide analogues will also be discussed.

High viral load and its implications for the treatment of CHB

Higher levels of HBV DNA are associated with an increased risk of HCC and cirrhosis.6 CHB patients with a high viral load (HVL) are less likely to respond to some nucleos(t)ide analog treatment. Mean baseline HBV DNA is a factor that predicts virological response to entecavir therapy.7 In a study of treatment-naïve patients receiving entecavir for 3 years, only 75% of patients with baseline HBV DNA >8 log copies/mL had undetectable HBV DNA (<12 IU/mL), compared with the 100% of patients with baseline HBV DNA <8 log copies/mL.8 Although many patients with undetectable HBV DNA have a relatively low HBV DNA (<3 log copies/mL), it is unknown whether longer treatment with entecavir will achieve further reductions in HBV DNA.

In contrast, long-term treatment with tenofovir in CHB patients with HVL (defined as having HBV DNA ≥9 log copies/mL) at baseline was evaluated after 240 weeks of tenofovir treatment.9 By week 240, 98.3% of HVL and 99.2% of non-HVL patients on treatment achieved HBV DNA negativity (<400 copies/mL). HVL patients generally took longer to achieve HBV DNA <400 copies/mL than did non-HVL patients; however, by week 96, the probability of achieving HBV DNA <400 copies/mL were similar in both groups (Figure 1).

In conclusion, long-term tenofovir monotherapy can lead to virological suppression in the vast majority of CHB patients with HVL, regardless of HBeAg status, and may be the preferred option for this group of patients.

Regression of liver cirrhosis with tenofovir

Treatment for CHB aims to maximize viral suppression with the objectives of controlling liver fibrosis and preventing progression to clinical complications associated with hepatic decompensation and HCC.

Previous studies with entecavir have demonstrated low rates of resistance in treatment-naïve patients, and a clear reversal of fibrosis in patients who participated in an amended roll-over protocol after receiving a median of 6 years of therapy. However, these observations are not conclusive in view of the small sample size; only 57 patients (8% of the randomized and treated population) were analyzed, and that only four of them had cirrhosis at entry.10,11

Recent evidence confirms that potent viral suppression with long-
Long-term use of tenofovir is associated with improved histological response and regression of fibrosis. Long-term tenofovir therapy results in fibrosis regression, even when the patient has developed cirrhosis due to hepatitis B. In two randomized double-blind comparative trials of tenofovir versus adefovir (NCT00117676 and NCT00116805), participants with a positive or negative HBeAg were included in a 7-year open-label study of tenofovir treatment, with a pre-specified repeat liver biopsy at week 240 (Figure 2). A total of 348 patients (54%) had biopsy results at both baseline and week 240. Of these, 304 (87%) had histological improvement, and 176 (51%) had regression of fibrosis at week 240 (p<0.0001). Of the 96 (28%) patients with cirrhosis (Ishak score 5 or 6) at baseline, 71 (74%) no longer had cirrhosis (≥1 unit

**Figure 1.** Time to viral negativity on the basis of baseline viral load. The proportion of HBV patients with high baseline viral load (≥9 log10 copies/mL) versus non-high baseline viral load (<9 log10 copies/mL) who achieved HBV DNA <400 copies/mL during long-term TDF treatment. (Figure adapted from Gordon SC, Krastev Z, Horban A, et al, 2013)

**Figure 2.** Distribution of Ishak fibrosis score over 5-year treatment phase. (Figure adapted from Marcellin P, Gane E, Buti M, et al, 2012)
Recommended first-line treatment for chronic hepatitis B 1-3

Sustained virologic suppression maintained through 6 years 4

0% resistance detected through 6 years 4

Proven efficacy in regressing fibrosis and cirrhosis 5

Presentation: Film-coated tablet containing 300 mg of tenofovir disoproxil fumarate (TDF). Indications: 1. Treatment of chronic hepatitis B (CHB) in adults. 2. In combination with other antiretroviral medicinal products for treatment of HIV-1 infected adults. Dosage: Adults: One tablet once daily taken orally, without regard to food. The dosing interval of VIREAD should be adjusted in patients with baseline creatinine clearance <50 ml/min. Children and adolescents: Not recommended. Insufficient data to make dose recommendations for patients <16 years. Contraindications: Known hypersensitivity to tenofovir, TDF, or any of the excipients. Warnings and Precautions: Lactic acidosis/severe hepatomegaly with steatosis; exacerbation of hepatitis after discontinuation of treatment; new onset or worsening renal impairment; patients coinfected with HIV-1 and HBV, decreases in bone mineral density; fat redistribution; immune reconstitution syndrome; early virologic failure. Interactions & Side effects: refer to Package Insert.

Before prescribing, please consult full prescribing information which is available upon request.

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Prevention of HCC with tenofovir

The beneficial effect of nucleos(t)ide analogue treatment in the prevention of HBV-related HCC is well established. The study on the long-term effect on lamivudine was the only prospective, placebo-controlled study involving HBV patients with biopsy-proven cirrhosis or advanced fibrosis (n=651). The study was terminated early (at 32.4 months) due to the significant beneficial effects observed in the treatment group, in which 7.8% patients developed cirrhosis-associated complications versus 17.7% in the placebo group (hazard ratio [HR], 0.45; p<0.001). The effect on HCC prevention was less obvious, probably due to the early termination of the trial. HCC occurred in 3.9% of patients in the lamivudine group and 7.4% in the placebo group (hazard ratio, 0.49; p=0.047). However, this beneficial effect was blunted by the development of resistance.

The efficacy of tenofovir in the prevention of HCC has been recently examined using predictive mathematical models. As such, further randomized, placebo-controlled study on nucleos(t)ide analogue treatment for the prevention of HBV-related HCC may become unethical. Using 6-year follow-up data from registration trials of 641 CHB patients, the estimated risk of HCC in these individual patients was predicted using a model validated in both cirrhotic and non-cirrhotic patients (the REACH-B model). Beyond the study period of 3.3 years, there was a progressive divergence between the predicted and observed number of HCC cases. The standardized incidence ratio was 0.55 (95% CI=0.32–0.94) at the latest follow-up (median 5.52 years). These data concluded that in contrast to the predicted risk, the incidence of HCC was shown to decrease after long-term tenofovir therapy.

HBV resistance to nucleos(t)ide analogues

Tenofovir-resistant HBV mutations have not been reported. No resistance mutations were detected after up to 5 years of treatment in two studies. Most cases of virological breakthrough were attributed to patient non-adherence to therapy. In both studies, most patients at the highest risk of antiviral drug resistance (ie, those who had detectable serum HBV DNA after 72 weeks treatment) received additional treatment with emtricitabine. Therefore, the risk of antiviral drug resistance in patients receiving long-term tenofovir monotherapy remains unknown.

Resistance to entecavir is generally rare in nucleoside-naïve patients, (~1% after 5 years of treatment). On the contrary, resistance is common in lamivudine-refractory patients (~50% after 5 years of treatment). A preliminary report indicated a high incidence of tyrosine-methionine-aspartic acid-aspartic acid (YMDD) motif mutations in antiviral treatment-naïve CHB patients in China. A total of 1,042 antiviral treatment-naïve (including lamivudine-naïve) CHB patients in the past year were recruited from the outpatient and inpatient departments of six centres in China from December 2008 to June 2010. Using a line probe assay detecting drug-resistant HBV strains (Inno-Lipa HBV-DR), YMDD variants were detected in 243 (23.3%) patients. YMDD mutation was accompanied by L180M mutation in 154 (76.9%) patients. Wild-type and YMDD variant HBV were present in 231 of 243 patients, respectively. Further studies are required to determine the incidence of YMDD mutation in treatment-naïve CHB patients in the community.

Conclusion

- Long-term tenofovir monotherapy can lead to virological suppression in the vast majority of CHB patients with high viral load (HBV DNA >10^6 copies/mL) at baseline regardless of HBsAg status.
- Long-term tenofovir treatment can result in a favourable histological response and regression of fibrosis due to its potent viral suppression. In addition, it has been shown to reduce the incidence of HCC.
- Tenofovir-resistant HBV mutations have not been reported. Tenofovir is the first-line treatment for patients with lamivudine-/telbivudine-resistant HBV. A recent report showed a high incidence of YMDD motif mutations in treatment-naïve CHB patients in China.
Introduction

Infection with the hepatitis C virus (HCV) can result in both acute and chronic hepatitis. Acute HCV is most often asymptomatic, and typically leads to chronic infection in 60–80% of cases. Chronic HCV infection is usually slowly progressive and asymptomatic, with approximately 20–30% of patients developing cirrhosis over a 20- to 30-year period.1 As patients develop advanced fibrosis, the risk of progression to cirrhosis is about 10% per year. This article reviews the disease course of HCV during glucocorticoid use and pregnancy, as well as updates on the management and treatment of HCV infection.

Disease course during glucocorticoid use

Patients with chronic HCV may have co-existing conditions that require treatment with glucocorticoids. HCV viral load has been found to be significantly increased in non-transplant HCV patients exposed to short-term glucocorticoid use.2,3 On the contrary, serum levels of aminotransferases have been shown to be reduced, although they tend to rebound after discontinuation. HCV RNA levels generally increase during therapy (by about 1 log) before decreasing to pretreatment values within 1–5 weeks after stopping therapy. No significant histological changes in the liver have been observed.

Disease course during pregnancy

There is some evidence that chronic HCV has adverse effects on fetal outcomes. In a population-based cohort study, infants born to HCV-positive mothers were more likely to have low birth weight, and require assisted ventilation or neonatal intensive care.4

Serum aminotransferase concentrations have been shown to decrease during pregnancy,5 and increase 6 months after delivery. Pregnancy may decrease a mother’s immune responses against HCV.6 Further complicating the matter is the teratogenic effect of ribavirin (RBV), and thus the contraindication of antiviral treatment in pregnancy.

Mother-to-infant transmission occurs in only 5–10% of deliveries;7 however, the risk of infection is three-fold higher in infants born to mother co-infected with HCV and HIV.8 Such a transmission is only possible when the mother is positive for HCV-RNA and that the risk of transmission is related to the level of viraemia at the time of birth. Prolonged rupture of membranes for more than 6 hours increases this risk. Caesarean delivery does not reduce the risk of transmission.

Early diagnosis of HCV in newborns requires HCV-RNA testing as anti-HCV antibodies are passively transferred from the mother. Breastfeeding is not a risk for infection among infants born to HCV-infected women.9

Management of chronic HCV

Goal of antiviral therapy

The goal of antiviral therapy for chronic HCV is complete eradication, which is measured by sustained virologic response (SVR). SVR is defined as HCV RNA negativity at 24 weeks after completion of therapy. The antiviral treatment regimen and duration of therapy are determined by the genotype of HCV, which correlates with the rates of SVR. Achievement of SVR has been associated with decreases in all-cause mortality, liver-related death, the need for liver transplantation, the incidence of hepatocellular carcinoma,
and liver-related complications in HCV patients, including those patients with advanced liver fibrosis.10

**Treatment protocol**

**Treatment regimens for HCV genotype 1**

For chronic HCV genotype 1 patients who are candidates for therapy, treatment with pegylated interferon (PEG-IFN) and weight-based RBV for 48 weeks results in SVR rates of 40–50%.

PEG-IFN-α2a (PEGASYS®, Roche) and PEG-IFN-α2b (PEG-Intron®, MSD) differ in their pharmacokinetic profiles. One of the largest trials comparing the two types of PEG-IFN – the Individualized Dosing Efficacy versus Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) study – showed that PEG-IFN-α2a and -α2b (standard dose or low dose) had comparable efficacy in the treatment of chronic HCV.11 In this study, patients with treatment-naïve HCV genotype 1 infection were randomly assigned to receive 48 weeks of treatment with one of three regimens: (1) standard dose PEG-IFN-α2b at a dose of 1.5 μg/kg/week or (2) low-dose PEG-IFN-α2b at a dose of 1.0 μg/kg/week, each plus RBV at a dose of 800–1400 mg per day, or (3) PEG-IFN-α2a at a dose of 180 μg/week plus RBV at a dose of 1000–1200 mg per day. Based on the 3070 patients evaluated, the rates of SVR were similar among the three arms: 39.8%, 38.0%, and 40.9%, respectively (p=0.20 for standard-dose vs low-dose PEG-IFN-α2b; p=0.57 for standard-dose PEG-IFN-α2b vs α2a). The comparable results between standard-dose and low-dose PEG-IFN-α2b allow an individualized response-guided approach to treatment, without compromising clinical efficacy. Safety profiles were similar across the treatment arms. Serious adverse events were observed in 8.6–11.7% of patients. In a subgroup analysis of patients with low body weight, PEG-IFN-α2a caused significantly more neutropenia and thrombocytopenia compared with standard-low-dose PEG-IFN-α2b.

In 2011, the US FDA approved two oral direct-acting antiviral (DAA) agents for the treatment of genotype 1 HCV. Boceprevir and telaprevir are both NS3/4A
protease inhibitors, used in combination with PEG-IFN and RBV. Triple therapy with boceprevir demonstrated superior efficacy over the standard PEG-IFN/RBV dual therapy in treatment-naïve patients in the HCV Serine Protease Inhibitor Therapy-2 (SPRINT-2) trial (SVR 67–68% vs 40%, p<0.0001), and in patients failing previous treatment in the Retreatment with HCV Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol 2 (RESPOND-2) study (59–66% vs 21%, p<0.0001).12,13 Similar SVR results were observed with triple therapy with telaprevir compared with the standard dual therapy in treatment-naïve patients in the A New Direction in HCV Care: A Study of Treatment-Naïve Hepatitis C Patients with Telaprevir (ADVANCE) trial (69–75% vs 44%, p<0.0001), and in those who have relapsed after previous treatment in the Telaprevir Study C216 (REALIZE) (83–88% vs 24%, p<0.0001).14,15 The improvements in SVR for triple therapy in treatment-naïve patients are shown in Figure 1. The most common side effects associated with triple therapy were anemia, neutropenia, leucopenia, gastrointestinal symptoms and skin rashes.

DAAs are indicated for HCV genotype 1 infection, and used in combination with PEG-IFN and RBV in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy. The use of boceprevir requires a lead-in phase, during which PEG-IFN/RBV therapy is given alone for 4 weeks prior to starting boceprevir. This lead-in phase assesses the patient’s tolerability to PEG-IFN/RBV therapy before starting boceprevir, and this could potentially reduce the risk of resistance.

Treatment regimens for HCV genotypes 2, 3, 4 and 6
Patients with HCV genotype 2 or 3 should be treated with PEG-IFN and RBV for 24 weeks, while those with genotype 4 should receive PEG-IFN and weight-based RBV for 48 weeks. Protease inhibitors are not recommended for patients with genotype 2, 3 or 4.16

Besides genotype 1, genotype 6 is particularly prevalent in Hong Kong (~27% of chronic HCV cases). The SVR rates for genotype 6 have been shown to be higher compared with that for genotype 1.17,18 In addition, there was no statistically significant difference in SVR rates with 24 versus 48 weeks of treatment (70% vs 79% respectively, p=0.45).19

“Besides genotype 1, genotype 6 is particularly prevalent in Hong Kong”

Predictors of treatment response to PEG-IFN and RBV
Combination therapy with PEG-IFN/RBV with or without the newly approved DAAs is the standard treatment for chronic HCV infection. Achieving SVR following treatment with PEG-IFN/RBV relies on viral-, patient-, and treatment-related factors.

HCV genotype and baseline viral
load are the two most important predictors of SVR. SVR rates have been shown to be higher in patients with genotypes 2 or 3, as well as those with lower baseline viral loads (≤600,000 to 800,000 IU/mL).

In addition to viral factors, host factors have also been shown to predict antiviral response. The IL28B gene encodes interferon lambda, which contributes to viral resistance and is upregulated by interferons. IL28B polymorphisms are strong independent predictors of viral responsiveness to PEG-IFN and RBV. Patients with IL28B CC genotype tend to have higher SVR rates than those with CT or TT genotypes. The differences in IL28B genotype may also explain differences in SVR rates across the different ethnic groups. Other factors that have been found to be associated with higher SVR rates include age, body mass index and insulin resistance.

Use of weight-based dosing of RBV, maintenance of full therapeutic dose, treatment adherence, and on-treatment response are treatment-related factors influencing SVR. Early virological response (EVR), defined by undetectable HCV RNA or ≥2 log drop from baseline at week 12 of therapy, has been shown to predict SVR. Patients without an EVR have less than a 2% chance of achieving SVR, in contrast to the 65% observed in patients with an EVR. Failure to achieve EVR is a powerful negative predictor of SVR in dual therapy. There is also evidence to demonstrate the predictive value of rapid virological response (RVR), defined by an undetectable HCV RNA by PCR at week 4, with maintenance of negativity at weeks 12 and 24. Patients with an RVR have more than a 90% percent chance of achieving SVR. Using RVR may help identify patients most likely to benefit from a shorter duration of treatment.

“It is anticipated that newer DAAs will become available in the near future, bringing the promise of an interferon-free treatment regimen for patients with HCV”

Summary

Combined PEG-IFN/RBV therapy has been the standard of care for chronic HCV for more than a decade. The recent approval of boceprevir and telaprevir for the treatment of HCV genotype 1 patients was long-awaited, and has led to improved SVR rates in both treatment-naive and prior relapse patients. Predictors of treatment response include HCV genotype, baseline viral load, on-treatment viral response and IL28B polymorphisms, all of which could be effectively incorporated into antiviral treatment strategies for HCV. The comparable efficacy between the standard and low-dose PEG-IFN-α2b allows an individualized response-guided approach to treatment, without compromising clinical efficacy. It is anticipated that newer DAAs will become available in the near future, bringing the promise of an interferon-free treatment regimen for patients with HCV. Of note, DAAs simprevir and sofosbuvir have recently been submitted to the US FDA for review.

References

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Lam Tat Chung Paul (林達聰醫生)
President
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Update on Endoscopic Submucosal Dissection for Early GI Tumours

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Specialist in Gastroenterology and Hepatology

Key words:
Early gastrointestinal tumours (早期腸胃腫瘤), endoscopic submucosal dissection (內視鏡黏膜下層剝離術)

Introduction

With the increasing use of endoscopy for the diagnosis of gastrointestinal (GI) diseases, and the screening of GI cancers in high risk areas, early GI tumour diseases are being more frequently diagnosed. In Japan, approximately 50–70% of gastric cancer cases were detected at an early stage, through a GC screening program. It is estimated that 50% of these lesions can be resected using endoscopy techniques. It is very important for endoscopists and physicians to be informed on the latest developments of endoscopic resection techniques for managing these patients.

Endoscopic detection and characterization of early GI tumours

Early GI tumour is difficult to detect. Published literature from the western world and Japan suggests that 7–23% of upper GI cancers have been left undiagnosed in patients who had a negative oesophago-gastroduodenoscopy up to 3 years prior to their cancer diagnosis. Based on population-based colonoscopy studies, the rate of missed colonic cancer is up to 6% in non-inflammatory bowel disease (IBD) patients and 15% in IBD patients. Latest image-enhancing technologies, such as chromoendoscopy, magnifying endoscopy, narrow-band imaging (NBI), autofluorescence imaging and confocal endomicroscopy, have led to improved diagnosis of GI cancers, particularly small depressive and flat lesions. Once the lesion is detected, the endoscopist should characterize the lesion according to the: appearance (protruded, flat, depressed); margin; pit patterns; microvasculature changes to predict the histology (neoplastic vs non-neoplastic); and depth of invasion (mucosal vs submucosal invasion). Ideally, video of the lesion should be recorded to determine the site of the lesion and inform further treatment decisions. If a lesion is deemed a candidate for subsequent endoscopic resection, multiple biopsies, especially those for flat lesions, or endoscopic tattooing of the lesion, are best avoided since they may induce irreversible submucosal fibrosis that can hinder future endoscopic resection. For small lesions, it can be resected by endoscopic mucosal resection (EMR). However, for large-size lesions, ESD is more effective for en-bloc resection, whereas EMR may result in piecemeal resection, which is associated with a high rate of local recurrence.

Basic ESD procedures

The border of the lesion is often first identified with NBI and white light endoscopy. The intended cutting site, including an adequate circumferential resection margin from the lesion, is marked with an endo-knife. Submucosal injection of a mixture of solution (usually saline, mixed with indigo carmine and adrenaline) is used to lift up the lesion. Hyaluronic acid, which provides a longer cushioning effect, is sometimes used for submucosal injection. The procedure is followed by circumferential mucosal incision of the lesion margin, and finally, gradual ESD to dissect the lesion from the GI wall.

ESD for early oesophageal tumour

ESD is indicated for the treatment of high-grade intraepithelial neoplasm, including non-invasive squamous cell carcinoma (SCC) (carcinoma in situ), and intramucosal invasive SCC limited to the lamina propria mucosa without vessel infiltration, lymph nodes or distant metastases. Once the tumour penetrates deeper to 200 μm, the probability of lymph node metastases may increase to 10–15%. In such a case, ESD may not be able to clear the tumour.

Oesophageal ESD is indicated for circumferential lesion that is less than two-third of the circumference of the oesophageal lumen. For a complete circumferential excision, there is a high risk of stricture formation. Studies are ongoing to test the use of steroid injection or cultured autologous epidermal cell sheets to prevent stricture formation.

Based on the current literature, the rates of en bloc resection in oesophageal ESD are 90–100%, and the rates of curative resection are 88–97%. Reported major complications include perforation (0–6%) and bleeding (0%). With the latest submucosal tun-
nelling endoscopic resection (STER) technique, selected deep submucosal lesions and tumours arising from the muscularis propria layer can be removed from the oesophagus. In a recent report from China, 15 tumours originating from the muscularis propria were resected with STER. The en bloc resection rate was 100%. The size of the tumours ranged between 1 and 3 cm. Pathology showed 12 leiomyoma and three gastrointestinal stromal tumours. Perforation occurred in three patients, and all patients recovered with conservative treatment.\(^\text{14}\)

### ESD for early gastric tumour

Early GC (EGC) limited to the mucosa or submucosa can be managed with ESD, thereby obviating the need for surgery. ESD is indicated for differentiated mucosal cancer without ulceration, irrespective of the tumour size; differentiated mucosal cancer with ulceration if the size is less than 3 cm; and differentiated lesions less than 3 cm in size that invade less than 500 \(\mu\)m into the submucosa and with no evidence of lymphovascular invasion on computed tomography or endoscopic ultrasound. The reported en bloc resection and complete resection rates are 83–95% and 73–92%, respectively. Perforation occurs in 2–10% of patients, the majority of whom are treated endoscopically.\(^\text{15}\)

In a local retrospective cohort study of patients with EGC or severe dysplasia, 40 patients received gastrectomy (T1m, 47.5%; T1sm, 52.5%), and 74 underwent ESD (T1, 89.2%; T1sm, 10.8%). When compared with those in the ESD group, patients in the surgery group had a longer operative time (median 265 vs 90 min), prolonged hospital stay (median 9.9 vs 3.0 days), and a higher overall complication rate. The 3-year survival rate was comparable between treatment arms (89.7 vs 94.6%). Therefore, in appropriately selected patients, ESD may obviate the need for an extensive gastrectomy.\(^\text{16}\)

When the tumour has invaded to the submucosa, ESD alone may not be an effective treatment. In a retrospective study, 38 patients with operable EGC with submucosal invasion (T1sm 86.8%) were treated with ESD. The en bloc resection rate was 84.2% and the complete (R0) resection rate was 63.2%. Non-curative resection rate was high (n=34, 89.5%), and procedure-related perforation occurred in up to 13% of patients. A total of 22 patients required subsequent gastrectomy for lymph node clearance. The 5-year cause-specific survival rate for ESD was found to be lower than that reported for gastrectomy (91.8 vs 96.7%).\(^\text{17}\) Therefore, patients with submucosal EGC should undergo formal gastrectomy and lymph node dissection, unless the patient is deemed unfit for, or refuses surgery.

**“In appropriately selected patients, ESD may obviate the need for an extensive gastrectomy”**

The reported rates of incomplete ESD resection range from 7.4% to 26.3%, and the reported rates of local recurrence after ESD are between 0% and 3%. Factors associated with local recurrence include tumour size >3 cm, U-shaped lesion at initial presentation, and incomplete resection.\(^\text{18}\) When GC recurs at previous ESD site, performing second ESD would be challenging due to the scarring at the site of previous resection. In a series of 12 patients who underwent second ESD for residual or recurrent GC, the average operating time was longer (152 ± 47 min), and the rate of en bloc resection was lower (91.2%) when compared with those reported for the ESD series. The bleeding risk is also higher (25%), although only one patient required salvage surgery for tumour removal.\(^\text{18}\)

Published literature on colorectal ESD outcomes reveals that the rates of en bloc resection (endoscopic) and complete en bloc resection (histological) were 88.8% and 83.8%, respectively. Perforation rates were 3.3–14%, and delayed...
perforation rates were 0.4–0.7%. Postoperative bleeding occurred in 1.5–2.1% of patients.19

ESD is gaining ground for treating early colorectal cancer diseases. In a retrospective analysis of 589 patients with T1 colorectal cancer, 297 patients received ESD treatment while 292 patients underwent laparoscopic assisted colectomy (LAC). The rates of en bloc resection and curative resection for ESD were 87% and 80%, respectively. There were 14 perforations (4.7%) and five post-procedure bleeding (1.7%). Only one patient required emergency surgery, while other patients were managed endoscopically. In the LAC group, there were 31 wound infections, two cases of pelvic abscesses, three cases of anastomotic leakage, and one case of anastomotic bleeding. Stomas creation was required in 93% of patients who underwent LAC for rectal cancers located below the peritoneal reflection. In conclusion, ESD may be a useful treatment option for patients with lesions predicted to have a low risk of lymph node metastases (mucosal or superficial submucosal lesions).20

In another retrospective study, the efficacy of ESD was compared with transanal endoscopic microsurgery (TEM) in 63 patients with nonpolypoid rectal high-grade dysplasia (HGD) or submucosa-invading cancer. For ESD and TEM, respectively, the rates of en bloc resection were 96.7% and 100%, and the rates of R0 resection were 96.7% and 97%. No patients in either group had local recurrence or distant metastases. Antibiotic use was higher in the TEM group than in ESD group. When compared with TEM, ESD was associated with a shorter procedure time and hospital stay. There was no difference between both treatment arms in terms of complication rate. In conclusion, ESD is as safe as TEM for treating nonpolypoid rectal HGD and superficial submucosa-invading cancers (Figures 1–4).21

**ESD for duodenal tumour**

Performing ESD on a lesion in the duodenum is considered to be most difficult due to the narrow lumen and thin wall. In a recent report of 14 cases of sessile, non-ampullary duodenal neoplasm resected with ESD, the rate of en bloc resection was 78.6%, and the rate of complete (R0) resection was 85.7%. These rates were lower compared with other GI indications for ESD. Perforations were seen in five patients (35.7%), while two patients needed surgical repair. Therefore, duodenal ESD should be performed with care and in appropriately selected cases.22

**Conclusion**

ESD is a rapidly developing field, and its application is likely to expand, particularly with the development of new technologies. One example is the incorporation of robotics into endoscopic treatment of EGC.23 Such an advance will enable easier learning of the procedure and wide clinical application.

**References**

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