PAPERS AND SHORT REPORTS

Large hepatocellular cancers: hepatic resection or liver transplantation?

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Abstract

Thirteen patients with primary hepatocellular cancer were studied to outline criteria for resectability in patients with large liver tumours. The mean age was 34 and the mean tumour diameter 13 cm (range 7-18 cm). Five of the tumours had a diameter of 15 cm or more. Extensive radiological investigations showed that seven of the patients had tumours of both right and left lobes of the liver, 10 had evidence of vascular invasion, and three had evidence of extrahepatic spread. Only two of the patients underwent a classically described formal hepatic resection, the rest having extensive resections crossing major anatomical planes. In no instance did the vascular invasion preclude resection, and extrahepatic spread could be verified in only one patient.

The traditional criteria of resectability—that is, tumours located to one main lobe of the liver without vascular invasion and extrahepatic spread—can and should be extended. Resection may be preferable to transplantation even in patients with large primary liver tumours.

Introduction

Primary hepatocellular carcinoma is generally considered to be a highly malignant tumour with an extremely poor prognosis. Mean survival time for untreated patients rarely exceeds three or four months,[1-4] although survival times of up to two years have been reported.[5] On the other hand, survival after hepatic resection for primary liver cell cancer varies considerably. Critical analyses indicate that the main reason for the variation in results is probably variation in the characteristics of the patient populations—that is, differences between Asian and African patients on the one hand and, on the other, Western populations, in whom underlying liver cirrhosis is less common.[6] Whereas survival after resection is low in most Asian reports[1 7 8] it is improving in Western studies.[9-12]

The identification of the fibrolamellar variant of hepatocellular carcinoma in recent years is also important. This type of tumour usually occurs in young patients and in non-cirrhotic livers, and the tumour is often large. This carcinoma has several unusual characteristics, the most important of which is that the prognosis is probably better than that for other variants of primary hepatocellular cancer.[13-16]

Thus in Western patients several factors indicate that an aggressive surgical approach should be advocated, particularly for fibrolamellar hepatocellular cancer. The problem is that few authors have given guidelines on the resectability of liver tumours. Specification of the criteria for resectability is even more important now that liver transplantation is a possible option. Patients, particularly young ones, with irresectable primary liver cell cancers are often said to be ideal candidates for liver transplantation.[17] Although definitions of irresectability can be found in reports on transplantation, such definitions are often related to multicentric cancer and there is little precise information about extensive, apparently solitary lesions. Results after transplantation for primary liver cancer are not uniformly good, with survival times rarely exceeding two years.[18-20] Despite this many physicians and surgeons see liver transplantation as the only alternative in young patients with large liver tumours. This view seems to be supported by the National Institutes of Health consensus development conference statement on liver transplantation.[21]

In view of these factors, and the fact that most patients with primary liver tumours are usually seen by physicians, medical gastroenterologists, or surgeons with relatively limited experience in hepatic surgery, we believe that it is important to show that potentially curative surgery can be carried out for patients with very large primary hepatocellular cancer, and that tumours that seem irresectable on clinical and radiological grounds can in fact be safely resected.

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Patients and methods

Thirty six patients with primary liver cancer have been evaluated in the hepatobiliary unit at this hospital since May 1979. All were referred from other hospitals in the United Kingdom or abroad. Twenty three patients were found to have irresectable tumours, mostly because of multicentric disease shown at laparotomy or laparoscopy or by extensive radiological evaluation. Histopathological diagnosis was obtained in all patients. Thirteen of these patients (five men, eight women; mean age 34, range 16-64) underwent hepatic resection and form the basis of this report. Four of the patients were admitted to hospital because of an abdominal mass and three because of abdominal pain. A further three patients were admitted complaining of anorexia, breathlessness, and tiredness. One patient was thought to have hepatitis, and another presented with a paraneoplastic syndrome (a tumour producing adrenocorticotrophic hormone). Pregnancy was suspected in one girl owing to amenorrhoea, vomiting, and tiredness.

TABLE I—*Laboratory results in patients with resectable liver cancer*

Test	Mean	No of abnormal or positive results (n = 13)
Haemoglobin (g/l)	132	3
Albumin (g/l) (normal 35-55)	42	1
Liver function tests:		
Bilirubin (μmol/l) (normal 2-14)	13	3
Alkaline phosphatase (IU/l) (normal 30-130)	231	7
Alanine aminotransferase (IU/l) (normal 30-130)	66	6
Hepatitis B surface antigen		0
α Fetoprotein		2

Conversion: SI to traditional units—Bilirubin: 1 μmol/l ≈ 0·06 mg/100 ml.

Scrupulous preoperative investigations were performed in all the patients using ultrasonography, computed tomography, selective coeliac and superior mesenteric angiography, indirect or direct splenoportography, and inferior venacavography. Endoscopic retrograde cholangiography was performed in patients with a history of jaundice.

The anatomical description of the liver followed the classification of Couinaud.[22] The division between the left and right lobes of the liver (the principal scissura or Cantlie's line) was assessed by drawing a line through the gall bladder and inferior vena cava on a computed tomogram that permitted visualisation of both markers.[23] The angiographic and phlebographic findings were as reported by the radiologist.

Results

LABORATORY FINDINGS

Table I shows the mean values and the proportion of patients with abnormal test results. Although the results of liver function tests were abnormal in most patients, the mean values indicated that the abnormalities were modest. No patient was positive for hepatitis B antigen, and only two had a raised α fetoprotein concentration. Plasma neurotensin concentrations were raised in five of seven patients in whom they were measured preoperatively.

RADIOLOGY

Table II summarises the combined radiological findings for each patient related to the location of the tumour, its maximal diameter, and whether it was single or multiple. Seven of the tumours affected both the right and left lobes of the liver. Invasion of the main portal vein was suspected in two patients while two patients had invasion or severe compression of the right branch of the portal vein and seven patients of the left branch of the portal vein. Seven patients had severe compression or displacement, or both, of the inferior vena cava. Six patients had invasion or compression, or both, of one main branch of the portal vein and of the inferior vena cava. Extrahepatic spread was suspected in three patients. As an example of the radiological features in this group the figure shows the findings in one of the patients (case 5).

The mean diameter of the tumours was 13 cm (range 7-18 cm). Many of the tumours had a clear cut margin separating them from the normal liver tissue, suggesting that they were growing by pushing and by compressing and displacing adjacent structures rather than by invading them.

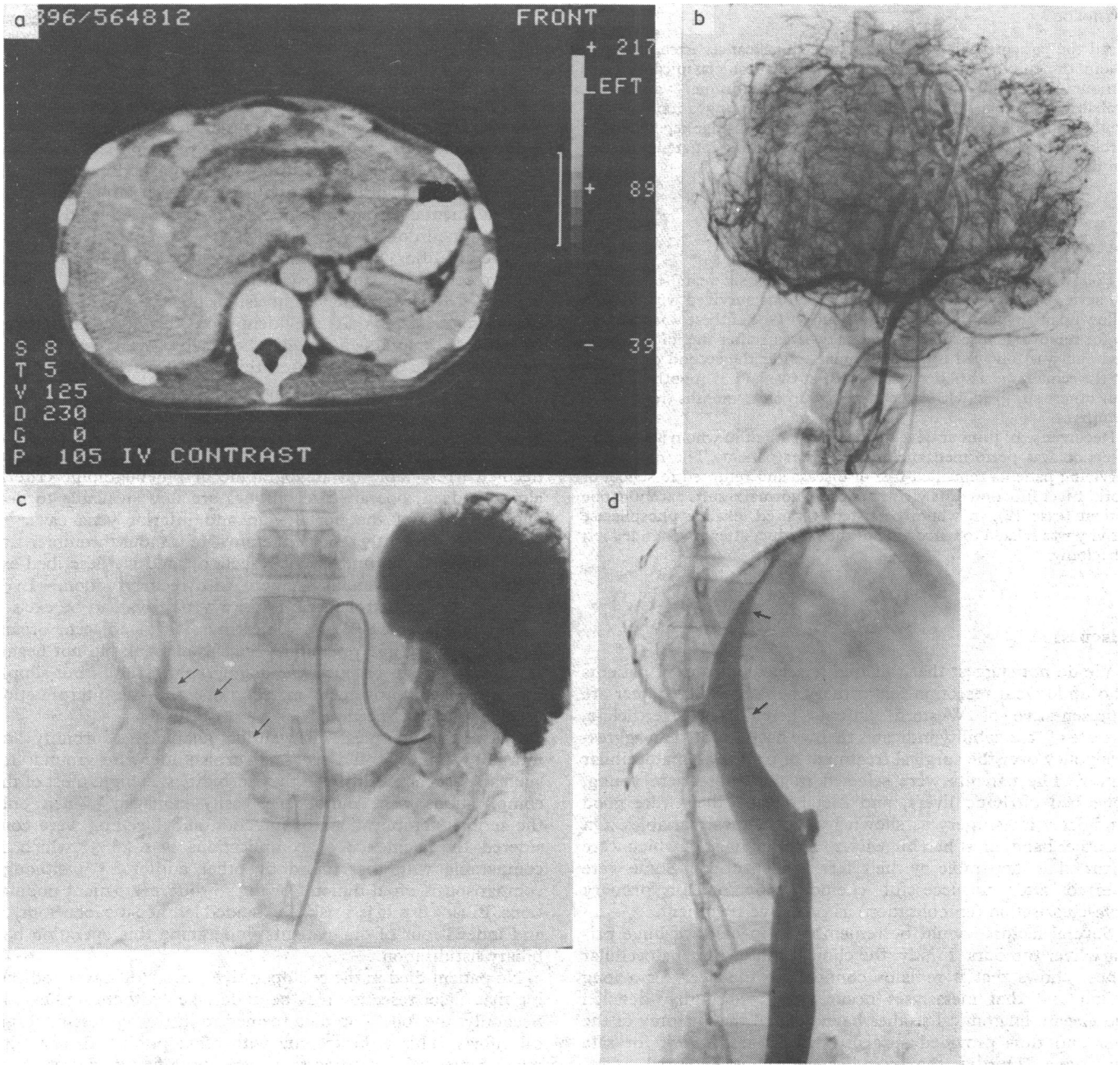
TABLE II—*Summary of radiological findings related to some macroscopic features of the tumour*

Case No	Tumour	Maximal diameter of tumour (cm)	Radiological findings: Liver affected	Invasion/compression: Main portal vein	Right portal vein	Left portal vein	Inferior vena cava	Extrahepatic spread
1	Single	8	Left			Compressed		
2	Single	12	Left			Obstructed		
3	Single	12	Right					
4	Single	15	Both			Obstructed	Obstructed	
5	Single	13	Both		Invasion		?Invasion	
6	Single	16	Both			Obstructed	Compressed	+
7	Single	18	Both	Compressed		Compressed	Compressed	+
8	Single	13	Right					
9	Multiple	11	Both			Obstructed		
10	Single	7	Left					
11	Multiple	14	Both		Invasion		Compressed	+
12	Single	17	Right				Compressed	
13	Multiple	18	Both	?Invasion		Obstructed	Invasion	

*Right and left liver refers to division of parenchymal image by Cantlie's line, confirmed at operation.

TABLE III—*Treatment, complications, and follow up*

Case No	Procedure	Remaining liver segments	Complications	Follow up: Time (months)	Follow up: Condition
1	Left hepatic lobectomy	I, V-VIII	Pneumothorax	70	Free of disease
2	Embolisation, extended left hepatic lobectomy	VI, VIII	Biliary fistula	41	Free of disease
3	Right hepatic lobectomy, excision of segment I and part of IV	II, III, part of IV	Pleural effusion	35	Dead
4	Extended left hepatic lobectomy	I, VI-VII	None	20	Free of disease
5	Right hepatic lobectomy, excision of segment I and part of IV	II, III, part of IV	Infection, pleural effusion	16	Recurrent disease
6	Extended left hepatic lobectomy	I, VI, VII	None	15	Recurrent disease
7	Extended left hepatic lobectomy	I, VI, VII	Biliary fistula	16	Free of disease
8	Partial hepatectomy	I, III, VII, VIII	None	13	Free of disease
9	Extended left hepatic lobectomy	VI, VII, part of I	Bleeding, biliary fistula	8	Free of disease
10	Left hepatic lobectomy	I, V-VIII	None	8	Free of disease
11	Extended right hepatic lobectomy	I-III	None	2	Dead
12	Partial hepatectomy	I-III, VII, VIII	None	7	Free of disease
13	Embolisation, extended left hepatic lobectomy, local excisions	VI, VII	Biliary fistula	6	Free of disease



Typical radiological findings (case 5). (*a*) Computed tomogram showing mainly left sided tumour but extending into right liver. (*b*) Hepatic arteriogram showing highly vascular tumour with arterial supply from both left and right hepatic arteries. (*c*) Indirect portal venography showing displacement of main and right portal veins and obstruction (middle arrow) of left portal vein. (*d*) Extrinsic displacement and obstruction (arrows) of inferior vena cava at level of liver with established collateral circulation.

SURGICAL TREATMENT

Table III shows the type and extent of the resections performed. Interestingly, only two of the 13 patients underwent a classically described formal hepatic resection, the rest having extensive resections crossing Cantlie's line and necessitating some form of extended resection. In particular, seven of the patients had primarily left sided lesions, and six of these underwent extended left hepatic lobectomy as suggested by Couinaud.[22] (There are few records of this operation, which has been rarely carried out.[24 25]) Two of the patients had their tumours embolised before surgery to reduce vascularity and size.

All but three of the operations were performed through a bilateral subcostal abdominal incision. Of the remaining three patients, one had a right chest extension and two a midline sternotomy. One patient was operated on during liver vascular exclusion using cardiopulmonary bypass. In no instance did the vascular invasion apparent during the preoperative investigations preclude hepatic resection. No patient in whom invasion of the inferior vena cava was suggested preoperatively actually had direct invasion, although severe compression was apparent in all cases. Spread to the branches of the portal vein as suggested in preoperative studies was confirmed in all cases, and in two cases the tumour extended into the main lumen of the portal vein at its bifurcation. No direct spread to the main portal vein was found, the changes observed preoperatively being due to compression rather than invasion. Extrahepatic spread was verified in two cases, and in a third the preoperative findings could not be confirmed.

Twelve of the 13 patients had curative resection—that is, macroscopic clearance of all tumour. In one patient (case 6) with a fibrolamellar hepatoma extended resection was performed despite regional lymph node metastases.

MORBIDITY AND MORTALITY

Seven of the patients had complications related to the operation, two of whom required a second laparotomy (one for bleeding and one for drainage of an infected collection). Four patients had a biliary fistula, but in all it closed spontaneously within six weeks. There were no intraoperative deaths or deaths in hospital within 30 days.

PATHOLOGY

All the patients had primary hepatocellular cancer except one, in whom difficulty was experienced in histological classification: the tumour presented with a paraneoplastic syndrome, which was probably a primary hepatocellular cancer secreting adrenocorticotrophic hormone. Seven of the patients had fibrolamellar hepatocellular carcinoma and the rest well to moderately well differentiated tumours. No patient had cirrhosis of the liver.

FOLLOW UP

Follow up varied from six months to almost six years (table III). All seven patients with fibrolamellar hepatoma survived with a mean follow up of 18 months (range 8-41 months). One of these was operated on for removal of a recurrent tumour two years after the initial operation and was followed up for 17 months after the second operation. Of the remaining six patients, two died at two and 35 months and the four others survived with a mean follow up of 23 months (range 6-70 months).

Recurrence of tumour developed in the patient in whom a palliative resection was performed and in one other patient. The nine other surviving patients remained free of disease and returned to school or work. Liver function tests yielded entirely normal results except in one patient (case 12), in whom persistently raised alkaline phosphatase activity was related to narrowing of the bile duct after an extended left lobectomy.

Discussion

We do not suggest that this highly selected group of patients who underwent resection for primary hepatocellular cancer are representative of Western patients generally. Nevertheless, the rate of resectability indicates that we have adopted an aggressive policy over the surgical treatment of primary hepatocellular cancer. The patients were selected in that most were young, none had cirrhotic livers, and metabolically they were good candidates for surgery as shown by biochemical variables. On the other hand, most had huge liver tumours, most of which were regarded as inoperable by the referring institutions. Some were referred after unsuccessful chemotherapy or for primary devascularisation (embolisation) as palliative treatment.

Several factors should be remembered in cases of huge primary liver tumours. Firstly, the clinical course of hepatocellular cancer shows that it remains confined to the liver for a long period and that metastases occur late.[5 8] Secondly, detailed and elegant anatomical studies have defined the anatomy of the liver and thus provided surgeons with a framework for safe operations. Thirdly, the liver has enormous potential to regenerate after resection.[26] We agree with Foster[27] and Starzl *et al*[25] that in the non-cirrhotic liver concern about the size of the remnant should rarely compromise a decision to proceed with resection. The neoplastic tissue is non-functioning parenchyma, indicating that a large tumour in a patient who is metabolically fit and does not have underlying cirrhosis can almost certainly be safely resected. Hepatic failure after resection in the non-cirrhotic liver is always related to compromised circulation of the remaining liver tissue.[9] Fourthly, the size of the liver tumour per se seems not to be a prognostic indicator.[28] In particular, a clear cut tumour margin indicates a lesion growing and compressing adjacent structures with displacement should encourage the surgeon.

Thus, obviously, precise criteria of resectability are of paramount importance. Two basic aspects require discussion—namely, the size and location of the tumour, and vascular and extrahepatic invasion. It is clear that distant metastases preclude surgical treatment, and it is also generally accepted that major resection in a cirrhotic liver is not justified. On the other hand, large size on its own is not a criterion for irresectability.[9 25] Several authors state that invasion of both main liver lobes is a contraindication to resection.[2 12 29] We cannot agree with such categorical statements. Indeed, if we had adopted such criteria most of our patients would have been deemed to have irresectable tumours as computed tomography showed that the tumours crossed Cantlie's line. Thus, instead of confining resectability to the main hepatic lobes, we should like to introduce the term "resectable area." This term is clearly correlated to detailed knowledge of the segmental and vascular anatomy of the liver.

We would agree with Lee *et al*[1] that resection should not be precluded by the finding of multiple tumour nodules so long as these are located within a resectable area or if it can be combined with segmental wedge resection of apparently isolated lesions, as was done in one of our patients.

Several authors have stated that invasion of inflow and outflow vessels constitutes the most important criterion for irresectability.[2 29] The definition of invasion, however, is difficult and not without hazards. It is evident from this study that if one main portal branch is affected, whether by severe compression, obstruction, or direct invasion, this can be safely dealt with if it is within the area to be resected. The second point is that presumed invasion of the main trunk of the portal vein or of the inferior vena cava as shown by preoperative radiology proved to be fallacious in several cases. Thus a tumour should not be deemed irresectable on angiographic or phlebographic criteria alone. Indeed, operative techniques are now available to deal with invasion of the portal vein and inferior vena cava.[30 31] Tsuzuki *et al* recently reported removal of tumour thrombi in five of 41 patients who underwent resection,[8] and we described excision of a portal venous segment with reconstruction.[32] Even segments of the retrohepatic inferior vena cava can be excised without replacement,[33] and direct invasion of adjacent organs should not preclude resection.[8] Such statements do not negate the great value of preoperative angiographic studies but simply indicate that improvement in technique and the interpretation of such studies is needed.

Is extensive surgical intervention justified? Morbidity and mortality figures would seem to furnish adequate grounds for such an approach. Although the morbidity was high, most of the complications were minor and easily managed. When only the serious complications of infection and bleeding were considered the incidence of complications was 23%, which is comparable with that found by other authors,[1 8 29] although comparison is often difficult owing to differing patient populations. Biliary fistula is a risk of extended left hepatic lobectomy,[25] and indeed four of our patients undergoing this operation had biliary fistulisation.

No patient died in the postoperative period (30 days), indicating that major resection may be undertaken without undue risk. Secondly, the follow up data seemed to justify aggressive surgical efforts. This is in keeping with other published data with median survival exceeding two years and a five year survival of roughly 25%.[8 9 12 28] The third point is the recognition of the fibrolamellar variety of hepatocellular carcinoma.[13 14] This tumour has a favourable prognosis[34] and should be suspected in young patients with large liver tumours, a normal α fetoprotein concentration, and non-cirrhotic livers. Seven of our patients mean age 22, range 16-32) had tumours of this variety. In this group of patients even removal of recurrences can be successful, as shown in one of our cases.

The results after resection are better than those after liver transplantation. One of the great difficulties in selecting patients for transplantation is that resectability for such large lesions is usually determined only at the time of laparotomy, although all our patients in whom resection was planned preoperatively did undergo resection. Nevertheless, patients submitted for laparotomy and extensive dissection and then found to have irresectable tumours and subsequently referred for transplantation would present the transplant surgeon with a more difficult problem. On the other hand, should transplantation be decided on preoperatively, a donor liver procured, and the abdomen opened, transplantation rather than resection will probably be proceeded with. Taking into account the fact that in our experience carefully selected candidates submitted for laparotomy all underwent resection, we believe that patients

with large, apparently solitary primary liver cell tumours in non-cirrhotic livers should be considered firstly for resection and only secondarily for liver transplantation.

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Effectiveness of treatment with antihypertensive drugs and trends in mortality from stroke in the community

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Abstract

A study was made of the changes in the treatment of hypertension, in the effectiveness of that treatment, and in mortality from cerebrovascular stroke in men and women in two counties in Finland. One of these counties was North Karelia, where a comprehensive cardiovascular programme based in the community had been launched in 1972. Cross sectional surveys in large representative samples of the middle aged populations were carried out in 1972, 1977, and 1982. Average annual mortality from stroke adjusted for age was calculated for the two year periods 1971-2, 1977-8, and 1980-1.

The proportion of hypertensive men being effectively treated for their hypertension increased in both areas from 1972 to 1977 and further from 1977 to 1982. Mortality from stroke in middle aged men decreased in both areas during both observation periods. The proportion of hypertensive women being effectively treated greatly increased in both areas from 1972 to 1977. This was associated with a large decline in mortality from stroke. In North Karelia the proportion of women being effectively treated was remarkably high but decreased somewhat between 1977 and 1982; this decrease was associated with an increase in mortality from stroke in the women aged 35-64.

These results support the idea that effective antihypertensive treatment in the community is a major determinant of mortality from stroke in both men and women.

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Introduction

The fact that high blood pressure is the most important risk factor in cerebrovascular stroke has been well documented both in Finland[1 2] and elsewhere.[3-7] Several clinical trials have shown that the risk of stroke can be reduced by lowering blood pressure in hypertensive patients by treatment with antihypertensive drugs.[8-14] Reducing the risk of stroke has been a major argument for recommending and implementing large scale,