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High-dose Chemotherapy and Autologous Bone Marrow Transplantation for Relapsed and Refractory Hodgkin's Disease

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The results of high-dose chemotherapy with melphalan or melphalan (carmustine) etoposide for 66 consecutive patients with relapsed or resistant Hodgkin's disease are described. 55 patients were evaluable for response and 22% of these achieved complete remission and 59% partial remission. The actuarial survival at 2 years was 45% and the principal factors determining survival were the sensitivity of the disease to therapy given before high-dose chemotherapy and the type of treatment received. Intensive chemotherapy with autologous bone marrow transplantation can produce long-term survivors among patients for whom long-term survival would otherwise be improbable. However, this treatment remains toxic with an uncertain place in management.
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INTRODUCTION

THE MAJORITY of patients with Hodgkin's disease whether localised or advanced can now be cured either by radiotherapy, combination chemotherapy or a combined use of both of these modalities [1]. Nevertheless, a proportion of patients, particularly those with advanced disease at presentation, still die as a result of failure to control their disease by any conventional therapy. Few patients whose disease is resistant to chemotherapy or who relapse within a year of treatment are cured by chemotherapy regimens given in conventional doses [2–4]. Salvage chemotherapy is more effective for late relapses [2, 5] and a minority of patients who relapse after chemotherapy do obtain durable remissions with radiotherapy, particularly if the disease is limited to lymph node areas [6, 7].

In an attempt to improve the results for patients who have primary drug resistant disease or early relapse, the doses of drugs used have been escalated together with autologous bone marrow transplantation to reduce the resulting mylosuppression. Early studies have used high doses of alkylating agents particularly cyclophosphamide or melphalan together with a range of other drugs in combination including nitrosoureas, etoposide and vinblastine [8–10].

In 1979, the use of high-dose melphalan with autologous bone marrow transplantation (ABMT) was introduced for the treatment of relapsed Hodgkin's disease by the late Tim McElwain at the Royal Marsden Hospital. The results of single-agent melphalan have been published [11] and a subsequent program in which carmustine and etoposide were added to melphalan has been the subject of a preliminary report [12]. Here we report the accumulative experience of high-dose treatment with autologous bone marrow transplantation at the Royal Marsden Hospital in the first 66 patients so treated and the series has been analysed to assess outcome and factors of prognostic significance.

PATIENTS AND METHODS

Between November 1979 and December 1988, 66 consecutive patients with relapsed or resistant Hodgkin's disease were treated with high-dose chemotherapy and autologous marrow rescue: 65 received a single intensive treatment and 1 patient had further high-dose therapy on relapse. Characteristics of these patients, summarised in Table 1, shows them to be a group of young (median age 29 years), relatively fit (median performance status 1) and heavily pretreated (median 3 regimens) patients. Inclusion criteria required the patients' informed consent, absence of clinical and radiological cardiac failure, glomerular filtration rate > 50 ml/min and no bone marrow infiltration seen on marrow trephine at the time of

Table 1. Patients' characteristics (n = 66)

Male : female	42 : 22	
Age (years)		
Median (range)	29(15–51)	
ECOG performance status		
Median (range)	1 (0–2)	
Prior treatment: (n = 67 courses)		
Chemotherapy regimen		
1	4	47%
2	27	
3	26	
4	6	53%
5	3	

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* Prof. McElwain died in Nov. 1991 and this paper is respectfully dedicated to his memory.
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harvest. However, 4 patients who had prior marrow Hodgkin's disease were treated when trephine samples were morphologically disease-free after conventional chemotherapy.

All but 4 patients had received ChlVPP/MOPP and ABVD/EVAP combinations, either sequentially or combined as first-line therapy in hybrid or alternating regimes. Those who had a single combination had primary resistant disease and progressed to high dose therapy immediately rather than the alternative regimen.

Extent of disease, evaluated clinically and radiologically prior to myeloablative therapy is shown in Table 2. 10 patients had bulky stage IVB and 3 had bulky stage IIBE tumour, despite attempts to reduce tumour volume with prior conventional chemotherapy in 61 of 66 patients. 10 patients received treatment as consolidation of second (9 patients) or third (1 patient) complete remission, 4 were treated in first partial remission and 5 at relapse (first in 1 patient; second in 1 patient; third in 3 patients) without attempt at prior conventional salvage chemotherapy. Of the other treatments, 20 were given to patients with relapse who had responded to the chemotherapy given immediately prior to high-dose treatment (responding relapse), 14 patients had resistant relapse and 14 patients had disease resistant to all chemotherapy given previously (primary refractory disease). The median interval from original diagnosis to myeloablative therapy was 26 months.

High-dose therapy

This comprised melphalan alone (180–220 mg/m^2) in the initial 11 patients and 2 treated subsequently; 1 with pulmonary Hodgkin's disease and 1 with impaired lung function. All other patients received melphalan [80 mg/m^2 (n=1), 100 mg/m^2 (n=1), 140 mg/m^2 (n=52)] with carmustine [300 mg/m^2 (n=3), 400 mg/m^2 (n=10), 500 mg/m^2 (n=20), 600 mg/m^2(n=21)]: 42 also received etoposide [300 mg/m^2 (n=40), 1200 mg/m^2 (n=2)].

Melphalan was given with parenteral hydration and forced diuresis. Patients receiving melphalan alone had their bone marrow harvest on the day of treatment, and this was returned 12 h after melphalan administration without cryopreservation. Those patients treated with the combination received carmustine reconstituted in alcohol as a slow intravenous injection over 10 min with heavy sedation on day 5. Etoposide was given as a 1 h infusion on days 5, 4 and 3. Melphalan was administered on day 3 and cryopreserved bone marrow returned on day 0. The median number of nucleated cells harvested was 2.2 × 10^8/kg (range 0.95–6.0 × 10^8/kg).

Most patients were nursed in single rooms without laminar airflow, though 6 were treated in four-bedded units. Bowel decontamination was not attempted. All patients received oral antifungal prophylaxis and systemic antibiotic combinations during the period of severe leukopenia. Irradiated blood products were given to maintain a Hb > 8 g/dl and platelets were given to treat bleeding or to patients considered a risk of thrombocytopenic haemorrhage.

Table 2. Extent of disease at the time of high-dose therapy (n = 67)

Extranodal disease : Stage IIE	5	43%
Stage IV	24	
B symptoms	25	(37%)
Bulk (≥ 5 cm) disease	22	(33%)

Table 3. Relationship between disease status and response to high-dose therapy

	No.	Response (% of treated patients) CR	PR
Responding relapse	20		
Relapse untested	5	9 (31)	14 (48)
First PR	4		
Resistant relapse	14		
Primary refractory disease	14	3 (11)	18 (64)
	55	12 (22%)	32 (58%)

Response and survival

Complete remission (CR) was defined as regression of all clinical and radiological evidence of disease. Partial response (PR) was defined as reduction > 50% in measurable disease for at least 1 month. Progressive disease (PD) comprised an increase in tumour dimensions of 25% and no change (NC) included minor variation in tumour size insufficient to be categorised as either PR or PD. Response was evaluated clinically, including chest X-ray at 1 month: complete assessment with computed tomography was performed between 10 and 12 weeks following high-dose therapy.

All 66 patients are included in the survival analysis. Survival duration is taken from the day of bone marrow return (day 0) to most recent follow-up or death. For the single patient who underwent two high-dose therapies, response is evaluated separately for each treatment and survival is timed from day 0 of the procedure.

RESULTS

Response and survival

12 patients are not evaluable for response, 10 were treated in CR and 2 died prior to response assessment. 12 of 55 evaluable patients achieved CR (22%) and 32 achieved PR (58%). 11 patients (18%) failed to respond (9 no change, 2 progressive disease). Response was associated with disease status at the time of high dose therapy (Table 3) with fewer complete remissions in patients whose disease was resistant to conventional therapy.

7 of 10 patients receiving high-dose therapy in CR remained disease-free 7–35 months after treatment. The three deaths in this group were due to cardiac (n = 1) or pulmonary (n = 2) toxicity. 4 of 12 patients achieving CR have relapsed at 8, 12, 22 and 26 months. 1 patient died from late pulmonary toxicity, the median duration of CR exceeded 18 months. Overall survival is shown in Fig. 1 with progression-free survival in Fig. 2.

5 of 32 patients achieving a PR received additional radiotherapy to sites of residual disease: 4 are progession free at 14–36 months and 1 relapsed at 11 months. 4 patients with PR died without evidence of disease clinically (n = 1) or at postmortem (n = 3) from pulmonary toxicity (n = 3) and late septicaemia (n = 1). Median duration of PR in the remaining 23 patients was 6 months: 5 are progression free more than 20 months from treatment. The median follow-up for patients currently alive is 28 months (range 12–71 months).

Factors of prognostic significance in univariate analysis are shown in Table 4. Other factor studied, which in this patient population had no influence on progression-free interval or survival, are listed in Table 5. Cox regression analysis revealed

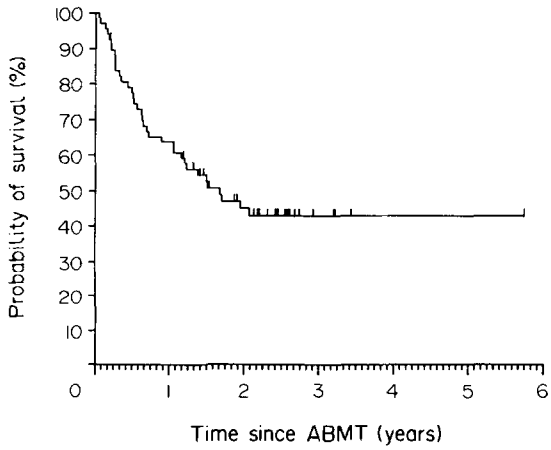

Fig. 1. Overall survival of 66 patients treated with high-dose chemotherapy and autologous bone marrow transplantation for Hodgkin's disease.

that disease status at high-dose therapy and type of treatment received were the only factors which independently predicted outcome. Treatment with melphalan alone was associated with significantly shortened progression-free interval ($P \leq 0.0001$) and reduced survival ($P = 0.038$). The adverse influence of demonstrable resistance to conventional therapy, including primary refractory disease and resistant relapse, was significant for both progression-free interval ($P \leq 0.0001$: Fig. 3) and survival ($P = 0.001$: Fig. 4). However, the advantage of treatment in CR on progression-free interval was not reflected in improved survival, owing to the three toxic deaths among these patients.

Toxicity

The duration of myelosuppression varied widely. Median time from ABMT to neutrophil count $> 0.5 \times 10^9$/l was 35 days (range 14–115) and to platelet count $> 50 \times 10^9$/l was 79 days (range 17–500). Marrow recovery was accelerated by an ABMT nucleated cell count $> 2.05 \times 10^8$/kg but was uninfluenced by bone marrow infiltration at presentation, number of previous chemotherapeutic regimes or prior extended field irradiation. There was no instance of fatal infection or life-

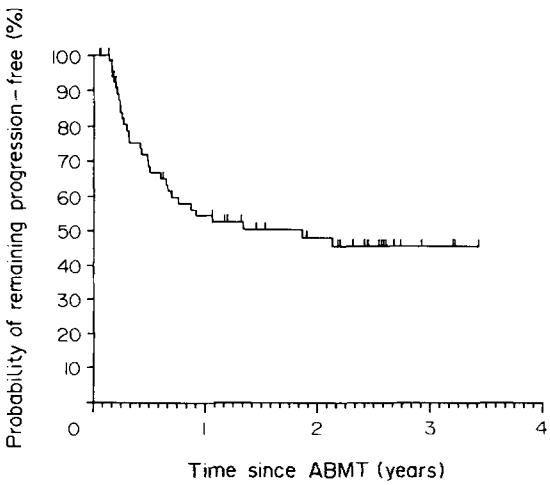

Fig. 2. Progression-free survival for 66 patients treated with high-dose chemotherapy and autologous bone marrow transplantation for Hodgkin's disease.

Table 4. Prognostic factors for progression-free interval and survival (univariate analysis)

	n	Progression-free at 18 months (%)	*P*	Survival at 18 months (%)	*P*
Disease status					
CR, responsive relapse, relapse untested	39	74	<0.0001	69	0.0008
Primary refractory disease, resistant relapse	28	16		28	
Performance status					
0	20	55		65	0.068
1 or 2	36	35	0.037	39	
B Symptoms					
No	31	49	0.056	60	0.072
Yes	25	33		33	
Bulk disease					
No	45	64	0.002	60	NS
Yes	22	23		44	
Extranodal disease					
No	38	63	0.036	60	NS
Yes	29	35		44	
Treatment					
Melphalan	13	8		23	*
MB	12	88	<0.0000167		NS
MBE	42	55		58	

Table 5. Factors not shown to influence progression-free interval or survival

	n	% progression free at 18 months	% survival at 18 months
Gender			
Male	41	44	50
Female	26	61	58
Age			
<30	36	52	56
>30	31	49	49
Number of prior chemotherapy regimens			
<3	55	55	56
>3	12	31	34
Interval diagnosis to ABMR			
<26 months	33	40	46
>26 months	34	60	60
Relapse in prior radiotherapy field			
Yes	18	44	55
No	21	57	59
No prior XRT	28	48	46

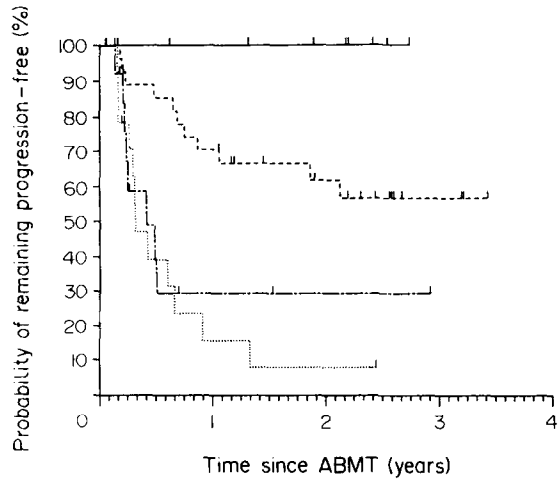

Fig. 3. Progression-free interval by disease status at the time of high-dose chemotherapy (complete remission 10, first partial remission and responding or untested relapse 29, primary refractory disease 14, resistant relapse 14).

threatening haemorrhage during the period of myelosuppression.

There were nine treatment related deaths. 1 patient died on day 26 from biventricular failure and acute renal failure; chemotherapy was believed to have been contributory to the former as she was 33 years old with no prior cardiac history or irradiation, the previous anthracycline cumulative dose had been 150 mg/m^2.

Pulmonary toxicity was responsible for eight deaths: these comprised of five instances of acute respiratory failure between 19 and 103 days with death from pneumonitis despite ventilatory support. There were three late deaths at 7, 9 and 18 months from pulmonary fibrosis, including one patient who had survived initial acute pneumonitis. A further patient had an ECOG performance status of 2 due to pulmonary fibrosis but died 21 months later from a combination of Hodgkin's disease and infection. 8 additional patients experienced transient shortness of breath with non-specific radiological changes between 3 and 6 months post-treatment and were assumed to have lesser degrees of pneumonitis: in 2 of these patients with prior supradiaphragmatic irradiation, quite marked concurrent changes compatible with pulmonary fibrosis occurred on the computed tomography scan in the irradiation field.

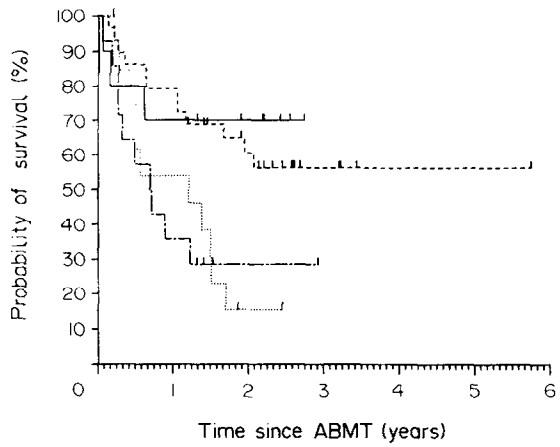

Fig. 4. Survival by disease status at the time of high-dose chemotherapy.

Pulmonary toxicity was only seen in patients receiving carmustine and was more common at the highest carmustine dose of 600 mg/m^2, particularly in association with bleomycin doses > 150 mg. There was no correlation between pulmonary toxicity and pulmonary Hodgkin's disease or prior mediastinal or mantle irradiation.

Alopecia and neutropenic fever were universal. Acute nausea and vomiting were commonly associated with melphalan administration prior to the introduction of ondansetron in 1988.

DISCUSSION

The conclusions that can be drawn from any uncontrolled study of this kind must be limited. It is clear that a proportion of patients with relapsed or refractory Hodgkin's disease achieve long-term survival after melphalan-based high-dose chemotherapy with autologous bone marrow rescue. This seems to be in the order of 40% at 2 years in our experience. Our results are similar to those reported by others using different regimens [13–17]. Treatment-related mortality in this study was high because of carmustine and melphalan toxicity to the lung [12].

In this study the most important predictor of outcome was the presence of chemosensitivity to conventional salvage therapy prior to the high-dose treatment. Although other features of the disease predicted for a poor outcome on univariate analysis (performance status, B symptoms, extra nodal or bulky lymphoma) almost all of these patients had chemoresistant disease and these factors were not significant on multivariate analysis. Other reports have indicated this finding [15, 14].

The difference in this study between the patients treated with melphalan or those treated with the melphalan-based combination is significant even on multivariate analysis. However, the patient selection criteria changed so much over time that we feel that this observation must be interpreted with great caution, and no non-randomised study can prove treatment superiority.

Is it is possible to make recommendations about the place of high-dose therapy with ABMT in Hodgkin's disease? Some tentative recommendations are possible. The treatment is ineffective for the majority of patients whose disease is absolutely resistant to chemotherapy and the existing high-dose regimens probably should not be used. The groups who seem to be candidates for this treatment are patients entering partial remission after first or subsequent chemotherapy, who have wide spread disease that cannot be encompassed by radiotherapy fields, and those who enter complete remission after salvage chemotherapy if their first remissions were less than 1 year. At the present time it is difficult to identify any group of patients who should receive this therapy as part of their primary management.

Further studies of the place of high-dose chemotherapy should now include randomised prospective trials. We probably cannot learn a great deal more from small, isolated, uncontrolled series using minor variations of high-dose regimens. New salvage strategies need to be explored for patients with drug resistant disease.

1. Selby PJ, McElwain TJ. *Hodgkin's Disease*. Oxford, Blackwell Scientific Publications, 1987.
2. Fisher R, de Vita V, Hubbard SP, *et al.* Prolonged disease free survival in Hodgkin's disease with MOPP reinduction after first relapse. *Ann Intern Med* 1979, **90**, 761–763.

3. Santoro A, Bonfante V, Bonadonna G. Salvage chemotherapy with ABVD in MOPP resistant Hodgkin's disease. *Ann Intern Med* 1982, **96**, 139–143.
4. Perren TJ, Selby PJ, MilS, *et al.* Etoposide and adriamycin containing combination chemotherapy (HOPE-Bleo) for relapsed Hodgkin's disease. *Br J Cancer* 1990, **61**, 919–923.
5. Viviani S, Santoro A, Negretti E, *et al.* Salvage chemotherapy in Hodgkin's disease: results in patients relapsing more than twelve months after first complete remission. *Ann Oncol* 1990, **1**, 123–127.
6. Fox KA, Lippman SM, Cassidy JR, *et al.* Radiation therapy salvage of Hodgkin's disease following chemotherapy failure. *J Clin Oncol* 1987, **5**, 38–45.
7. Roach M, Kapp DS, Rosenberg SA, Hoppe RT. Radiotherapy with curative intent: an option in selected patients relapsing after chemotherapy for advanced Hodgkin's disease. *J Clin Oncol* 1987, **5**, 550–555.
8. Carella AM, Santini G, Santoro A, *et al.* Massive chemotherapy with non-forzen autologous bone marrow transplantation in 13 cases of refractory Hodgkin's disease. *Eur J Cancer Clin Oncol* 1985, **21**, 607–612.
9. Philip T, Dumont J, Teillet F, *et al.* High dose chemotherapy and autologous bone marrow transplantation in refractory Hodgkin's disease. *Br J Cancer* 1986, **53**, 737–742.
10. Canellos G, Selby PJ, McElwain TJ. Chemotherapy for Hodgkin's disease. In: Selby PJ, McElwain TJ, eds. *Hodgkin's Disease*. Oxford, Blackwell Scientific Publications, 1987.
11. Russell JA, Selby PJ, Ruether BA, *et al.* Treatment of advanced Hodgkin's disease with high dose melphalan and autologous bone marrow transplantation. *Bone Marrow Transplantation* 1989, **4**, 425–429.
12. Zulian GB, Selby P, Milan S, *et al.* High dose melphalan, BCNU and etoposide with autologous bone marrow transplantation for Hodgkin's disease. *Br J Cancer* 1989, **59**, 631–635.
13. Carella AM, Congiu AM, Gaozza E, *et al.* High dose chemotherapy with autologous bone marrow transplantation in 50 advanced resistant Hodgkin's disease patients: an Italian study group report. *J Clin Oncol* 1988, **6**, 1411–1416.
14. Jaganneth S, Armitage JO, Dicke KA, *et al.* Prognostic factors for response and survival after high-dose cyclophosphamide, carmustine and etoposide with autologous bone marrow transplantation for relapsed Hodgkin's disease. *J Clin Oncol* 1989, **7**, 179–185.
15. Gribben JG, Linch DC, Singer CRJ, *et al.* Successful treatment of refractory Hodgkin's disease by high-dose combination chemotherapy and autologous bone marrow transplantation. *Blood* 1989, **73**, 340–344.
16. Jones RJ, Piantadosi S, Mann RB, *et al.* High-dose cytotoxic therapy and bone marrow transplantation for relapsed Hodgkin's disease. *J Clin Oncol* 1990, **8**, 527–537.
17. Wheeler C, Antin JH, Churchill WH, *et al.* Cyclophosphamide, carmustine and etoposide with autologous bone marrow transplantation in refractory Hodgkin's disease and non-Hodgkin's lymphoma: a dose-finding study. *J Clin Oncol* 1990, **8**, 648–656.

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Adrenal Masses in Lung Cancer: Sonographic Diagnosis and Follow-up

Christian Goerg, Wolf B. Schwerk, Martin Wolf and Klaus Havemann

Ultrasound has become an important diagnostic modality in the staging of patients with lung cancer. Between 1980 and 1990, 410 patients with histologically proved lung cancer were evaluated. In 44 patients (11%) an adrenal mass was discovered on ultrasound; in 13 patients it was isolated, and in 31 further evidence of abdominal disease was shown. Sonographic follow-up examinations of adrenal masses showed changes of size in all but 2 patients, and were therefore found to be adrenal metastases. In the 2 patients with isolated and stable adrenal disease, fine-needle biopsy revealed adenomas. Adrenal masses in patients with lung cancer are more likely to be metastatic than benign. The existence of neoplastic adrenal disease can be retrospectively confirmed by changes of size during sonographic follow-up examinations in almost all patients. Histologically verification would only appear necessary in stable adrenal disease and in cases with isolated adrenal disease in which prompt diagnosis affects treatment decision.
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INTRODUCTION

THE ADRENAL glands are the most common site of extranodal spread from primary lung cancer. Lung tumour metastases may involve adrenal glands when other metastases are absent. Autopsy series have shown common occurrence of metastases to the adrenal gland in patient with bronchogenic carcinoma, ranging from 35–38% [1, 2]. However, these patients had late or disseminated disease.

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With the increasing use of ultrasound and computed tomography for staging of bronchogenic carcinoma, many adrenal masses are now being detected. Benign clinically apparent adenomas of the adrenal are quite common with a prevalence from autopsy series ranging from 1.4–8.7% [3, 4].

When an adrenal mass is found in the staging of patients with bronchogenic carcinoma, the question arises whether it is an adrenal metastasis or a benign adenoma. This study has two goals: the first was to define the incidence of adrenal masses found by sonographic staging examination in patients with lung cancer, and the second to evaluate the utility of sonographic follow-up examinations and percutaneous ultrasound-guided fine-needle biopsy in diagnosing diseases in adrenal tissue.