Original Article

Survival and Impact of Tumor Grade, Residual Disease and Age in Patients Suffering From Epithelial Ovarian Cancer

Sarah Saeed, Mohammad Akram, Sherjeel Sana and Zeba Aziz

Objective: To determine the overall survival and impact of histopathological grade, residual disease and age on survival of patients with epithelial ovarian cancer.

Study Design: Retrospective study.

Place and Duration of study: Department of Medical Oncology, Jinnah Hospital Lahore, from Jan 01, 2001 to Dec 31, 2002.

Patients & Methods: Patients with all stages of epithelial ovarian cancer with histological documentation of the disease were included in the study. Patients with malignant ascites consistent with adenocarcinoma with an ovarian mass were also included. Patients with germ cell or stromal tumors were excluded. Patients with ovarian metastases from any other malignancy were also excluded. Survival from the date of diagnosis was the end point. Overall survival was calculated from the date of diagnosis to the date of death or the date when the patient was last known to be alive. The impact of age of the patient (< 50 yrs vs ≥ 50 yrs.), tumor grade (low grade vs. intermediate and high grade) and residual disease (≤1.5 cm vs. >1.5 cm) on survival was evaluated. Information was collected from medical records and a thorough review was done. The data was analyzed by SPSS. Survival was evaluated by the Kaplan- Meier Survival plot.

Results: Seventy-five patients were accrued to the study. Median age of the patients was 47 years. Mean overall survival was 36 months (95% C.I, 26 to 47). Overall 5-year survival rate was 38%.Younger age at presentation, high tumor grade and bulky residual disease are poor prognostic factors, having an adverse affect on survival in epithelial ovarian cancer. Patients with well-differentiated tumors had a mean survival of 44 months as compared to just 17 months for patients with moderate to poorly differentiated tumors (p=.002). Patients with minimal residual disease after initial surgery had a mean survival of 52 months whereas those with bulky disease had a survival of 13 months only (p=.000). The overall survival of patients younger than 50 years was 29 months and those older than 50 years was 39 months.

Conclusion: Younger age at diagnosis, high histological grade and suboptimal debulking are associated with inferior survival in patients with epithelial ovarian cancer.

Key words: Ovarian cancer, survival, grade, prognostic factors.

Introduction

Ovarian cancer is one of the most common gynaecological cancer, comprising 23% of all gynaecologic tumors.[1] It is the leading cause of death from a gynaecologic cancer.[1] In the past two decades, there has been an annual increase in the incidence of ovarian cancer of approximately 0.1%. Although the number of deaths from this disease continues to increase, notable advances in chemotherapy and surgery have improved the overall 5-yr survival rate from 36% in the mid 1970's to 50% in the late 1980's to mid 90's.

Epithelial ovarian cancer is primarily a disease of post menopausal women, with the vast majority of cases occurring in women between 50 and 75 years of age with a median age of 63 years. Although etiology remains largely unknown, hormonal, environmental and genetic factors play an important role in the development of ovarian cancer. The vast majority of cases of ovarian cancer are sporadic in nature and only 5-10% of cases can be defined as hereditary ovarian cancer.[2]

The prognosis of epithelial ovarian cancer depends on a number of factors. Of primary importance is the disease stage, which when properly determined, is of strong prognostic significance. Survival in early stage disease is significantly better than in advanced disease. Other factors known to have an impact on survival include age of the patient, residual tumor at the conclusion of the initial operation, histopathological grade, histological type of the tumor and serum CA 125 levels. Most studies have found grade of the

tumor to have prognostic significance; the histologic cell type of the tumor is of less importance, although patients with clear-cell and possibly mucinous tumors may have a worse prognosis. For patients with advanced ovarian cancer, the amount of residual tumor after surgery is of major importance. Patients with stage III disease who have minimal or no residual tumor may have a 30%-50% chance of 5-year survival, whereas those with stage III disease with bulky tumor masses have a 5-year survival rate of only 10%.

In recent years, a great deal of work has been done to identify molecular markers of prognosis in ovarian cancer. Studies of HER2, p53, ras, and other oncogenes and tumor-suppressor genes have had varying results relative to prognostic significance. Currently, the assessment of molecular markers of prognosis has no clinical utility, although much effort continues in this promising area.

In Pakistan, ovarian cancer ranks among the ten commonest cancers in women. The ranking varied from second to fifth in various Pakistani studies.[3-6] It is the most common cancer of gynaecologic origin in Pakistani women.[7,8] Despite being commonly encountered, information regarding the clinico-pathological features, biologic behaviour and survival rates is scarce in our country. The objective of this study was to determine the survival and prognostic factors in epithelial ovarian cancer in our patients.

Patients and Methods

The study was conducted at the Department of Medical Oncology, Jinnah Hospital Lahore, affiliated with Allama Iqbal Medical College. This study was a retrospective evaluation of all patients who were referred to our department between Jan 01 2001 to Dec 31 2002. Information was collected from the medical records and a thorough review was done. It was a descriptive type of study with emphasis on disease-free and overall survival and the impact of age of the patient, tumor grade and residual disease after initial surgery in ovarian cancer.

Seventy-five patients with epithelial ovarian cancer were accrued to the study. Patients with all stages of epithelial ovarian cancer with histological document-ation of the disease were included. Patients with malignant ascites consistent with adenocarcinoma on fluid cytology along with an ovarian mass were also included in the study. Patients with germ-cell or stromal tumors were excluded. Patients with ovarian metastases from any other malignancy were also excluded from the study.

Overall survival was calculated from the date of diagnosis to the date of death or the date when the patient was last known to be alive. Well-differentiated tumors were compared to moderate to poorly differentiated tumors for overall survival. Minimal residual disease after initial surgery was compared to bulky disease where minimal disease was taken as $\leq$ 1.5cm and bulky was >1.5cm. Patients who did not undergo surgery initially due to any reason were included in the group with bulky residual disease. The impact of age on survival was also taken into account. Younger patients (<50yrs) were compared to older patients ($\geq$ 50 yrs) for overall survival.

The data was analyzed by the SPSS. Survival was evaluated by the Kaplan-Meier Survival Plot.

Results

A total of seventy-five patients with epithelial ovarian cancer were accrued to the study. The median age of the patients was 47 years. About two-thirds (62.6%) of the patients were below the age of 50 years, indicating early onset of disease in our patients. 89.3% of the patients were pre-menopausal and only 10.7% were post-menopausal. Majority of the patients (74.6%) belonged to rural areas, were illiterate and of low socioeconomic status.

Most of the patients presented with advanced disease. Only 9 patients had stage I or II disease. Forty-five patients (60%) had stage III disease at the time of diagnosis and 21 patients (28%) presented with stage IV disease.

About 25.3% patients had well-differentiated tumors whereas 36% had moderately differentiated and 26% had poorly differentiated tumors. The grade was unknown in 12% patients.

Fifty-nine (78.6%) patients underwent surgery i.e. total abdominal hysterectomy and bilateral salpingo-oophorectomy. Approximately 18% (14) of the patients had residual disease after surgery. Sixteen patients did not undergo surgery. Sixty-nine (92%) patients received chemotherapy (cisplatin and endoxan).

Mean overall survival was 36 months (95% C.I, 26 to 47). The overall 5-year survival rate, as predicted by the survival curve, was 38%.

The impact of tumor grade, age of the patient and minimal versus bulky disease on survival was evaluated. The overall survival of patients with low grade tumors was 44 months in comparison to just 17 months for patients with high grade tumors.

Patients with minimal ($\leq$ 1.5cm) residual disease had an overall survival of 52 months whereas the overall survival of patients with bulky (> 1.5cm) disease was only 13 months.

The overall survival was also found to be superior in patients 50 years or older. It was 39 months as compared to 29 months for patients < 50 years of age.

Discussion

Epithelial ovarian cancer is the most common cause of death among all gynaecologic malignancies. Unlike several other Asian countries, ovarian cancer is the most common gynaecologic cancer among Pakistani women but data on epidemiology, survival and prognostic factors is scarce. The aim of this study was to determine the survival and the impact of age, tumor grade and residual disease on survival in our patients with epithelial ovarian cancer.

In this study, the mean age at diagnosis was 47 years. This is more than 10 years less than the mean age of 61 years reported in Western literature in patients with epithelial ovarian cancer.[9] Several local studies have reported younger age at time of presentation in our patients.[10,11] The early onset of ovarian cancer in Pakistani women is similar to Japanese, Chinese, Indian and Israeli women of Afro-Asian origin. Median age at onset is significantly lower than the Caucasian women in Europe or North America and Ashkenazi Jewish women in Israel.

Women with epithelial ovarian cancer have poor overall survival rates, largely because the disease is so often diagnosed at an advanced, less curable stage. Eighty-eight percent of our patients presented with stage III or IV disease. Though most of the patients with epithelial ovarian cancer are diagnosed in advanced stages of the disease because of vague symptoms and signs initially, this percentage is quite high. In one of the local studies, 78% of the patients had stage III or IV disease at time of diagnosis.[10] This reflects lack of health education and disease awareness in our patients. Poverty is the other reason leading to neglect and delay in diagnosis as most of the patients lack financial means to seek medical attention early in the course of disease.

In this study, mean overall survival was 36 months as compared to 44 months reported by a study from USA.[12] One reason for the relatively inferior survival in our patients could be advanced disease at time of diagnosis. About 88% of our patients presented with stage III and IV disease. However if we look at our predicted 5-year survival rate (38%), it is comparable with the survivals of stage III and IV patients as reported by Cmelak et al and Averette et al i.e. 40% and 30% for stage III and 15% and 19% for stage IV disease, respectively.[13,14]

Several clinicopathological prognostic variables have been identified in epithelial ovarian cancer. Stage at presentation is the main determinant of prognosis in epithelial ovarian cancer.[15] The International Federation of Obstetrics and Gynaecology (FIGO) staging system is based on a careful examination of the extent of the malignancy at initial laparotomy. The five-year survival rates vary in different stages: stage I 76%-93%, stage II 35%-79%, stage III 11%-50% and stage IV 4%-17%.[16] The large differences in the reported survival rates of the patients within the same FIGO stage suggests that under-staging is common, although evolving treatment methods also affect survival rates.[17] In many studies the patients are divided into two groups: early (stage I and II) and advanced stage (stage III and IV), because survival in early stage is significantly better than that in the advanced disease. The factors which have been found to correlate with poor prognosis in early stage disease are histopathologic type (serous vs. non serous), grade of differentiation, the presence of dense adhesions, large volume ascites and spontaneous rupture of a cyst.[18] For advanced stage disease, the amount of residual tumor after primary cytoreductive surgery, performance status, type of chemotherapy, stage, age of the patient, grade and histological type have been reported as prognostic factors.[18,19]

In this study, survival of the patients was evaluated according to age of the patient, histologic grade of the tumor and minimal versus bulky disease, so as to determine prognostic factors in our patients.

Patients with well differentiated tumors were compared to those with moderate to poorly differentiated tumors. There were 15 patients with well-differentiated tumors and 40 patients with moderate to poorly differentiated tumors. The mean overall survival of patients with well-differentiated tumors was 44 months while that of patients with moderate to poorly differentiated tumors was 17 months. This correlates with what has been reported in the literature. According to most studies, the histopathological grade correlates with prognosis. Some authors suggest that tumor grade is of good prognostic value in early stage ovarian cancer, but its value decreases in patients with advanced stage disease. The estimated 5 year survival for all stages with grade I tumors is 73-82% and with grade II and III, 41-43% and 20-21%, respectively.[20] In a recent study, the five-year survival rates for stage I disease of grade I, II and III were 94%, 81% and 61%, respectively.[18]

The other prognostic factor affecting survival was residual disease. Minimal ($\leq$1.5 cm) disease was compared to bulky disease (>1.5 cm) and significant

The overall survival was also found to be superior in patients 50 years or older. It was 39 months as compared to 29 months for patients < 50 years of age.

Discussion

Epithelial ovarian cancer is the most common cause of death among all gynaecologic malignancies. Unlike several other Asian countries, ovarian cancer is the most common gynaecologic cancer among Pakistani women but data on epidemiology, survival and prognostic factors is scarce. The aim of this study was to determine the survival and the impact of age, tumor grade and residual disease on survival in our patients with epithelial ovarian cancer.

In this study, the mean age at diagnosis was 47 years. This is more than 10 years less than the mean age of 61 years reported in Western literature in patients with epithelial ovarian cancer.[9] Several local studies have reported younger age at time of presentation in our patients.[10,11] The early onset of ovarian cancer in Pakistani women is similar to Japanese, Chinese, Indian and Israeli women of Afro-Asian origin. Median age at onset is significantly lower than the Caucasian women in Europe or North America and Ashkenazi Jewish women in Israel.

Women with epithelial ovarian cancer have poor overall survival rates, largely because the disease is so often diagnosed at an advanced, less curable stage. Eighty-eight percent of our patients presented with stage III or IV disease. Though most of the patients with epithelial ovarian cancer are diagnosed in advanced stages of the disease because of vague symptoms and signs initially, this percentage is quite high. In one of the local studies, 78% of the patients had stage III or IV disease at time of diagnosis.[10] This reflects lack of health education and disease awareness in our patients. Poverty is the other reason leading to neglect and delay in diagnosis as most of the patients lack financial means to seek medical attention early in the course of disease.

In this study, mean overall survival was 36 months as compared to 44 months reported by a study from USA.[12] One reason for the relatively inferior survival in our patients could be advanced disease at time of diagnosis. About 88% of our patients presented with stage III and IV disease. However if we look at our predicted 5-year survival rate (38%), it is comparable with the survivals of stage III and IV patients as reported by Cmelak et al and Averette et al i.e. 40% and 30% for stage III and 15% and 19% for stage IV disease, respectively.[13,14]

Several clinicopathological prognostic variables have been identified in epithelial ovarian cancer. Stage at presentation is the main determinant of prognosis in epithelial ovarian cancer.[15] The International Federation of Obstetrics and Gynaecology (FIGO) staging system is based on a careful examination of the extent of the malignancy at initial laparotomy. The five-year survival rates vary in different stages: stage I 76%-93%, stage II 35%-79%, stage III 11%-50% and stage IV 4%-17%.[16] The large differences in the reported survival rates of the patients within the same FIGO stage suggests that under-staging is common, although evolving treatment methods also affect survival rates.[17] In many studies the patients are divided into two groups: early (stage I and II) and advanced stage (stage III and IV), because survival in early stage is significantly better than that in the advanced disease. The factors which have been found to correlate with poor prognosis in early stage disease are histopathologic type (serous vs. non serous), grade of differentiation, the presence of dense adhesions, large volume ascites and spontaneous rupture of a cyst.[18] For advanced stage disease, the amount of residual tumor after primary cytoreductive surgery, performance status, type of chemotherapy, stage, age of the patient, grade and histological type have been reported as prognostic factors.[18,19]

In this study, survival of the patients was evaluated according to age of the patient, histologic grade of the tumor and minimal versus bulky disease, so as to determine prognostic factors in our patients.

Patients with well differentiated tumors were compared to those with moderate to poorly differentiated tumors. There were 15 patients with well-differentiated tumors and 40 patients with moderate to poorly differentiated tumors. The mean overall survival of patients with well-differentiated tumors was 44 months while that of patients with moderate to poorly differentiated tumors was 17 months. This correlates with what has been reported in the literature. According to most studies, the histopathological grade correlates with prognosis. Some authors suggest that tumor grade is of good prognostic value in early stage ovarian cancer, but its value decreases in patients with advanced stage disease. The estimated 5 year survival for all stages with grade I tumors is 73-82% and with grade II and III, 41-43% and 20-21%, respectively.[20] In a recent study, the five-year survival rates for stage I disease of grade I, II and III were 94%, 81% and 61%, respectively.[18]

The other prognostic factor affecting survival was residual disease. Minimal ($\leq$1.5 cm) disease was compared to bulky disease (>1.5 cm) and significant

difference in survival was found between the groups. The mean overall survival of patients with minimal residual disease after surgery was 52 months whereas the mean overall survival of patients with bulky residual disease was just 13 months. Several studies have shown improved survival of patients with residual tumors less than 1-2 cm in diameter after primary surgery as compared to patients with larger lesions.[19,21]

Table-1: Clinicopathological feature .

| Variables	No.	Percent
Age (Median 47 years) <50 years	35	46.6
> 50 years	40	53.4
Positive family history	14	18.7
Menopausal status		
Premenopausal	67	89.3
Postmenopausal	8	10.7
Stage I	3	4.0
II	6	8.0
III	45	60.0
IV	21	28.0
Grade Well differentiated	15	20.2
Moderately differentiated	23	30.6
Poorly differentiated	17	22.6
Histopathology Serous	40	53.3
Others	13	17.3
CA-125 Abnormal	49	65.3
Normal	7	9.3
Unknown	19	25.3
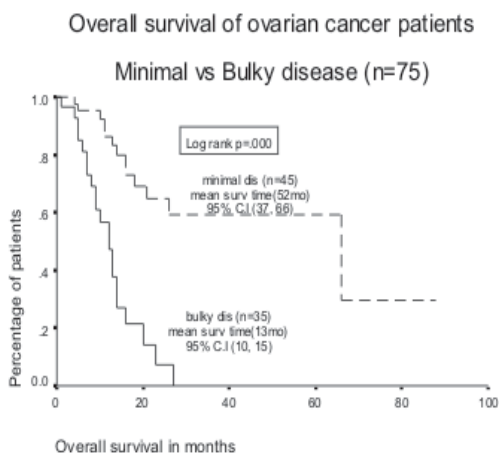
Fig.1 Survival minimal vs bulky disease
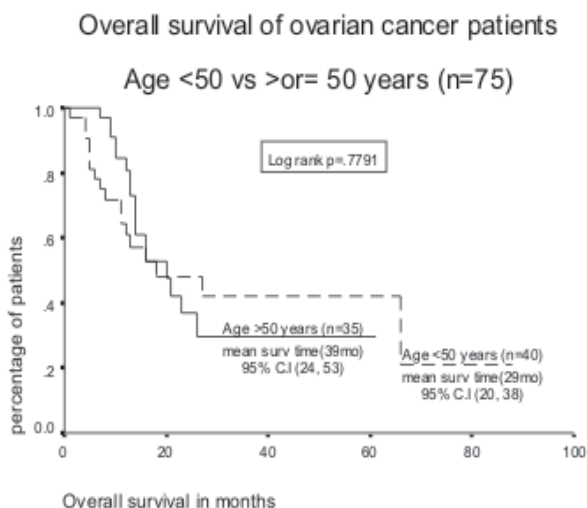
Fig 2. Survival - Age <50 vs ≥50
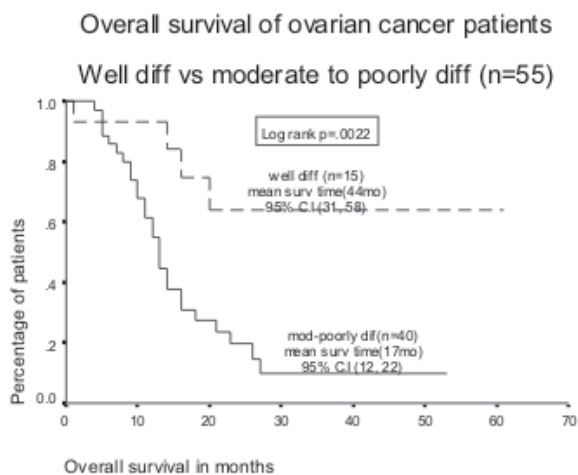
Fig 3. Survival - on the basis of histologic staging
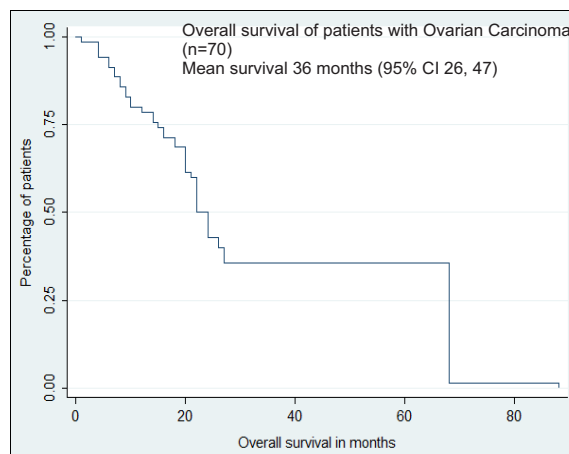
Fig 4. Survival - Mean survival

21

Even in stage IV disease with or without hepatic metastasis, optimal cytoreduction is associated with a more favorable survival (25-40 months), compared with 10-18 months for those to whom only exploratory laparotomy was performed.[19] Optimal cytoreduction can only be achieved in 15-45% of cases with advanced disease.

The effect of age on survival was also evaluated. Patients 50 years or more were compared to those less than 50 years of age. The mean overall survival was superior for older patients (39 months). In comparison, the survival of patients <50 years of age was 29 months. The reasons for inferior survival in younger patients could be due to higher grade tumors. 75% of patients <50 yrs of age had a high histopathological grade, and unfavourable histology was seen in 37% of younger patients. This finding is in contrast with what has been reported in the western studies, where favourable outcome was seen in younger patients. In one of the studies, younger women (<30 years) had a better prognosis than older women (5-year survival 71% vs. 47%), which is due to a higher rate of early stage (44% vs. 35%) and low grade tumors (68% vs. 37%).[22] The survival advantage among younger women is seen even after correction for stage and death from other causes, reflecting different tumor character, co-morbidity, less aggressive treatment methods in older women and possibly a lower immunologic defense capability. With ten years increase in age, there is a 1.6 times greater risk of death. One age-related reason for an increased risk of cancer may be an accumulation of somatic cell mutations. The overall five-year survival for different age categories has been as follows: 66% for 14-44 years, 39% for 45-59 years, 24% for 60-74 years, and 20% for women 75 years or older.[20]

Conclusion

We found that stage, grade and age are important determinants of survival. Majority of our patients presented with advanced disease and optimal debulking was not possible. This reflects lack of health education and disease awareness in our patients and primary health care workers. We also observed that younger age at presentation is a striking feature of Pakistani women with epithelial ovarian cancer. About one-third of our patients had poorly differentiated cancer; both these features contribute to poor survival rate in our patients. The need for optimal debulking and proper staging cannot be over emphasized. Health education programmes are needed for the awareness of the masses about the disease and medical facilities should be accessible to all across the country.

Department of Medical Oncology
Jinnah Hospital, Lahore
theesculapio@hotmail.com
www.sims.edu.pk/esculapio.html

References

1. Merino MJ, Jaffe G. Age contrasts in ovarian pathology. Cancer (Suppl) 1993; 71: 537-44.
2. Chang J, Fryatt I, Ponder B. A matched control study of familial epithelial ovarian cancer: patient characteristics, response to chemotherapy and outcome. Ann Oncol 1995; 6:80-82.
3. Malik I, Khan W, Khan Z. Pattern of malignant tumors observed in a University hospital: a retrospective analysis. J Pak Med Assoc 1998; 48:120-22.
4. Bhurgi Y, Bhurgi A, Hassan SH. Cancer incidence in Karachi, Pakistan: first results from Karachi Cancer Registry. Int J Cancer 2000; 85:325-29.
5. Khan SM, Gillani J, Nasreen S. Cancer in North West Pakistan and Afghan refugees. J Pak Med Assoc 1997; 47:122-24.
6. Ahmed M, Khan AH, Mansoor A. The pattern of malignant tumors in Northern Pakistan. J Pak Med Assoc 1991; 41: 270-73.
7. Ahmed J, Hashmi MA, Naveed IA. Spectrum of malignancies in Faisalabad; 1986-90. Pak J Pathol 1992; 3: 103-10.
8. Jaffery NA, Zaidi SHM. Cancer in Pakistan. J Pak Med Assoc 1987;37:178-83.
9. Miller BA, Ries LAG, Hamlley BF. SEER Cancer statistics review, 1973-1990. Bethesda, MD; National Cancer Institute, 1993.
10. Malik IA. A prospective study of clinicopathological features of epithelial ovarian cancer in Pakistan. J Pak Med Assoc 2002; 52:155-60.
11. Ahmed Z, Kayani N, Hasan S, Muzaffar S. The morphological pattern of benign and malignant ovarian neoplasms. J Pak Med Assoc 2000; 50: 416-18.
12. Gershenson DM. Prognosis of surgically determined complete responders in advanced ovarian cancer. Cancer 1985; 55:1129-35.
13. Cmelak AJ, Daniel SK. Long-term survival with whole abdominopelvic irradiation in platinum-refractory, persistent or recurrent ovarian cancer. Gynecol Oncol 1997; 65:453-60.
14. Averette HE, Janicek MF, Menck HR. The National Cancer Darabase reports on ovarian cancer. Cancer 1995; 76:1096-99.

15. Brun JL, Feyler A, Chene G. Long-term results and prognostic factors in patients with epithelial ovarian cancer. Gynecol Oncol 2000; 78:21-7.

16. Holschneider CH, Berek JS. Ovarian cancer: Epidemiology, biology and prognostic factors. Sem surg Oncol 2000; 19(1):3-10.

17. Friedlander ML. Prognostic factors in ovarian cancer. Sem Oncol 1998; 25: 305-14.

18. Vergote I, Fyles A, Einhorn N. Prognostic importane of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma. Lancet 2001; 357:176-82.

19. Akahirs JI, Yoshikawa H, Shimuzi Y. Prognostic factors of stage IV epithelial ovarian cancer: a multi center retrospective study. Gynecol Oncol 2001; 81: 205-12.

20. Baker TR, Piver MS. Long-term survival by cytoreductive surgery to less than 1 cm, induction weekly cisplatin and monthly cisplatin, doxorubicin & cyclophospha-mide therapy in advanced ovarian adenocarcinoma. Cancer 1994; 74: 656-63.

21. Makar AP, Baekelandt M, Trope CG. The prognostic significance of residual disease, FIGO substage, tumor histology and grade in patients with FIGO stage lll ovarian cancer. Gynecol Oncol 1995; 56: 175-80.

22. Massi D, Susini T, Saveno L. Epithelial ovarian tumors in the reproductive age group: age is not an independent prognostic factor. Cancer 1996; 77:1131-36.

Picture Quiz

These are the X-rays of hands and lumbosacral spine from a patient who has been on haemodialysis for the last 5 years

1.   What are findings on these x-rays?
2.   What is the diagnosis?

Clinical History:
Hand and low back pain in a patient on dialysis.

See Answer on Page No. 38