FIGO Stage 1B2 Cervical Carcinoma – The KK Women's and Children's Hospital Experience

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Abstract

Introduction**: The objectives of this review were to document the surgicopathological characteristics of surgically resected FIGO stage 1B2 cervical carcinoma and to review our overall experience with this disease. **Materials and Methods**: This is a retrospective review of 35 patients diagnosed and treated from September 1990 to November 2001. **Results**: The median age was 42 years and the mean tumour diameter was 5.1 cm. Majority were squamous cell carcinomas (65.7%), 28.6% were adenocarcinomas and 5.7% were adeno-squamous carcinomas. The primary treatment comprised radical surgery in 77.1%, radiotherapy in 20% and neoadjuvant chemotherapy followed by radical surgery and adjuvant radiotherapy in 2.9%. Significant surgicopathological features noted were deep stromal invasion (66.7%), lymphovascular space invasion (55.6%), parametrial involvement (22.2%), positive margins (3.7%) and pelvic node metastases (33.3%). Postoperative radiation was given to 92.6% of the patients who underwent primary surgery, of whom 29% received concurrent chemotherapy. Radiation toxicity was mild with no grade 3 or 4 toxicity documented. For the patients who had surgery, the recurrence rate was 14.8% (11.1% pelvic and 3.7% distant) and the survival rate was 88.9%. For those who had primary radiation, the rate of persistent disease was 28.6%, the distant recurrence rate was 28.6% and the survival rate was 57.1%. **Conclusion**: FIGO stage 1B2 cervical carcinomas are associated with significant rates of adverse surgicopathological features. The ideal primary treatment is yet to be established and should be determined by prospective randomised trials.

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Introduction

Important prognostic factors in stage 1B cervical carcinoma include primary tumour diameter, nodal metastases, depth of stromal invasion, lymph-vascular invasion, microscopic parametrial extension and status of surgical margins.[1] In 1994 FIGO addressed the significance of tumour diameter by designating stage 1B into 1B1 (clinical lesions no greater than 4.0 cm in size) and 1B2 (clinical lesions >4 cm in size) in an attempt to delineate the spectrum of disease so that the best treatment modality may be determined.[2] Large tumours are known to be associated with deep stromal invasion and increased frequency of nodal metastases. This leads to increased local, regional and distant relapses, regardless of primary treatment modality. Compared to the treatment of small volume disease, the optimal primary treatment for stage 1B2 disease remains controversial.

This is a retrospective review of FIGO stage 1B2 primary cervical carcinoma treated at the Gynaecological Oncology Unit, KK Women's and Children's Hospital. The objectives of this review were to document the surgicopathological characteristics of the patients who underwent primary surgical resection and to review our overall experience in the management of this challenging condition.

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Materials and Methods

The study period was from September 1990 to November 2001. Patients with histologically-proven primary cervical carcinoma FIGO stage 1B2 were included in the study. Patients staged before the 1994 FIGO modification were included if the clinical tumour diameter at initial assessment was greater than 4 cm. Unusual histological subtypes, e.g., mixed Mullerian tumours and small cell neuro-endocrine tumours, were excluded.

All patients were managed by a multidisciplinary team. Pretreatment evaluation included a cervical biopsy to confirm the histological diagnosis, a chest X-ray and computed tomography (CT) of the pelvis and abdomen to look for retroperitoneal nodal disease, obstructive uropathy or other metastases. All patients underwent a formal examination under anaesthesia with cystoscopy to determine the FIGO staging. Decision to treat with either primary surgery or primary radiotherapy was made according to the patient's age, performance status, co-morbidities and on radiological evidence of extra-pelvic disease. Postoperative adjuvant pelvic radiotherapy was given based on surgicopathological findings. Patients in whom there was deep stromal invasion and/or lymphovascular space invasion received adjuvant whole pelvic radiation to increase local pelvic control. This was given via the 4-field 'box' technique receiving the dose of 45 to 50.4 Gray over 5 weeks followed by 2 applications of high dose rate intravaginal vault brachytherapy of 10 Gray in 2 fractions at 5 cm depth of mucosa using cylindrical applicators.

For patients with positive nodes, positive surgical margins or parametrial involvement, besides adjuvant whole pelvic radiation, they also received, since 1999, concurrent chemotherapy with cisplatin 70 mg/m^2 and 5-fluorouracil 4 g/m^2 every 3 weeks for 4 cycles.[3] Patients on primary pelvic radiation therapy were mainly treated to receive 50 Gray in 25 fractions over 5 weeks via standard external beam portals encompassing the whole pelvis followed by high-dose rate intracavitary brachytherapy of 18 to 20 Gray via 3 to 4 applications. Patients treated with primary radiation therapy after 1999 also received concurrent weekly cisplatin chemotherapy 40 mg/m^2 for 6 cycles.[4,5]

All pathology was reviewed by an experienced gynaecological pathologist. Data from this retrospective study were obtained from the clinical records of the KK Women's and Children's Hospital, Singapore General Hospital, the National Cancer Centre and the KK Gynaecological Cancer Centre Tumour Registry. Telephone interviews were carried out for cases where patients had defaulted follow-up, to verify if the patient was still alive. Treatment complications were recorded where documented in the clinical records, in particular those requiring hospital admission, surgery or invasive procedures, affecting the performance status of the patient or fatal complications. Grading of radiation toxicity was based on Radiation Therapy Oncology Group (RTOG) toxicity criteria.

Results

There was a total of 1405 cases of primary cervical carcinoma registered for treatment during the study period. Of these, 484 (34.4%) were FIGO stage 1B; 35 of these patients (7.2%) were FIGO stage 1B2 or had a clinical primary tumour diameter of greater than 4 cm.

The age range was from 31 to 67 years, with a median age of 42 years. Only 5 patients were 50 years or older. All the patients presented with abnormal bleeding at the time of referral. Only one patient was asymptomatic and was referred for an abnormal Pap smear.

The clinical tumour diameter ranged from 4.7 to 7.0 cm, with a mean tumour diameter of 5.1 cm. Histological cell types included 23 squamous cell carcinomas (65.7%), 10 adenocarcinomas (28.6%) and 2 adenosquamous carcinomas (5.7%). Eight patients (22.9%) had grade 1 tumours, 16 patients (45.7%) had grade 2 tumours and 11 patients (31.4%) had grade 3 tumours. Pretreatment CT scan of the abdomen and pelvis showed evidence of parametrial spread in 9/35 patients (25.7%); 4 patients (11.4%) had evidence of enlarged pelvic lymph nodes and only 1 patient (2.9%) had evidence of enlarged para-aortic nodes. The final histology report correlated closely to the preoperative CT findings. Of the 4 patients with enlarged pelvic nodes, all had positive histological findings. Of the 9 patients with parametrial spread, 2 underwent primary radiation therapy, thus no histological correlation was possible, while 3 of the 6 patients operated on had confirmatory parametrial involvement.

Of the 35 patients, 27 (77.1%) were treated with primary radical surgery and 7 patients (20%) were treated with primary radiation therapy, including concurrent chemoradiation. Only 1 patient (2.9%) had neoadjuvant chemotherapy.

All 27 patients underwent type III radical hysterectomy[6] and pelvic lymphadenectomy. Only 1 patient underwent dissection of macroscopic para-aortic lymph nodes, which were found to be negative for malignancy. The primary tumour diameter ranged from 4.7 to 6.0 cm, with a mean of 5.0 cm. Significant surgicopathological features are listed in Table I. All macroscopically involved nodes were resected. There were 9 patients with positive lymph nodes (of which only 4 were identified on CT scan), 6 with parametrial spread (of which only 3 were detected on CT scan), 15 with lymph-vascular space invasion, 1 positive surgical margin and 18 with deep stromal invasion. Twenty-five patients (92.6%) received postoperative adjuvant radiotherapy in view of the presence of high-risk

TABLE I: SURGICOPATHOLOGICAL CHARACTERISTICS (n = 27)

Tumour characteristics	No.	%
Deep stromal invasion	18	66.7
Lymphovascular space invasion	15	55.6
Parametrial involvement	6	22.2
Positive surgical margin	1	3.7
Positive lymph nodes	9	33.3
Macroscopic pelvic nodes	3	11.1
Microscopic pelvic nodes	6	22.2
Macroscopic para-aortic nodes	0	0
Microscopic para-aortic nodes	0	0

surgicopathological characteristics. Of these 25 patients, 7 (25.9%) received standard pelvic field radiation with concurrent chemotherapy. Fifteen received standard field pelvic radiation alone, 2 received extended-field para-aortic radiation and 1 received modified small field pelvic radiation. Two patients (7.4%) had no adjuvant therapy after radical surgery.

Seven patients were treated with primary radiotherapy. Two of these received concurrent chemotherapy. Both of these patients are well. One patient had adjuvant hysterectomy 6 weeks after completing radiotherapy.

In the patients who underwent primary surgery, the mean operating time was 241 minutes, the mean blood loss was 1163 ml and 18 patients (66.7%) required blood transfusion. Operative complications included 1 ureteric injury which was repaired intraoperatively, 2 cases of deep venous thrombosis treated with anti-coagulation and 1 upper abdominal abscess, which resolved with antibiotics. Postoperative bladder dysfunction was transient and the duration of dysfunction ranged from 10 to 52 days postoperatively with a median of 15 days. In the 25 patients who underwent adjuvant postoperative radiotherapy, one patient had mild radiation proctitis which was controlled with medications and there was no grade 3 or 4 radiation toxicity observed. All postoperative adjuvant radiation commenced within 6 weeks of surgery except for 1 patient who delayed radiation until 8 weeks after surgery due to social reasons. There were no significant treatment delays among those undergoing adjuvant radiation.

In the group of patients treated with primary radiation therapy with and without concurrent chemotherapy, all cases completed the treatment without significant delays. In these patients there was also no grade 3 or 4 radiation toxicity observed.

Among the 35 patients treated, there was only 1 case of symptomatic lymphoedema which resolved with lymphatic massage and compression stockings.

The mean follow-up duration was 46.8 months. Two patients (5.7%) were lost to follow-up. There were in total 2 cases of persistent disease, 6 recurrences and 5 deaths from the disease. The overall survival rate was 85.7%. Of the 27 patients who underwent surgery, there were 4 recurrences (14.8%) – 3 in the pelvis (11.1%) and 1 distant recurrence (3.7%). One patient with pelvic recurrence was alive with disease at the end of this review while the other 3 (11.1%) died of disease despite salvage chemotherapy. On surgicopathological review of these 4 patients, all 4 had deep stromal invasion, 2 had lymphovascular space invasion, 1 had microscopic parametrial invasion and 1 had microscopic pelvic node metastasis. The overall survival among patients who underwent primary surgery was 88.9%.

Among the 7 patients undergoing primary radiation therapy, 2 (28.6%) patients had histologically-proven persistent cervical disease at 3 months post-radiation. One patient was cured with total pelvic exenteration while the other died despite salvage chemotherapy. Of the remaining 5 patients who responded to radiation, 2 (28.6%) subsequently developed distant metastases and both died despite salvage chemotherapy. The overall survival rate for patients who underwent primary radiotherapy was 57.1%.

Discussion

In small volume stage 1B cervical carcinomas the 5-year survival rates are about 90% to 95%[7] regardless of primary treatment modality. Bulky stage 1B tumours, on the other hand, are associated with deep stromal invasion and lymph node metastases.[8] A prospective surgical-pathological study of stage 1B squamous cell carcinoma of the cervix by the Gynecological Oncology Group in 1990[9] identified clinical tumour size, together with depth of stromal invasion and status of capillary-lymphatic spaces as independent prognostic variables for disease-free interval (DFI). For patients with occult tumours, the DFI at 3 years was 94.6% while primary tumours 3 cm or greater were associated with a DFI of 68.4%. FIGO in 1994 subdivided stage 1B into 1B1 (lesions no >4 cm) and 1B2 (lesions >4 cm in size) to delineate the spectrum of disease and to determine the best primary treatment modality.[2] To date, however, the ideal primary treatment for stage 1B2 cervical carcinoma is still controversial as the risks of both local and distant relapses remain high regardless of the choice of treatment modality.

The major limitation of this study is its retrospective nature. As attention is focussed on a subset of bulky tumours comprising only 7.2% of all stage 1B disease treated at a single centre, the numbers reviewed are also too small for any firm conclusions to be drawn. Similarly, the incidence of treatment toxicities, e.g., lymphoedema or other mild symptoms, were likely to be underestimated as there was no prospective recording or if this was not documented in the case records.

TABLE II: SURGICOPATHOLOGICAL CHARACTERISTICS OF DIFFERENT STUDIES

	Present study	Finan[8]	Bloss[10]	Boronow[11]	Alvarez[12]	Rettenmaier[13]
n	27	48	84	21 (diameter > 6 cm)	48 (stage 1B/2A)	92
Deep invasion	66.7%	77.1	41.7%	–	68.8%	55.4%
Lymphovascular space invasion	55.6%	—	–	–	56.3%	–
Parametrial involvement	22.2%	29.2%	7.1%	42.9%	6.3%	–
Positive surgical margin	3.7%	12.8%	1.2%	–	8.3%	–
Positive nodes	33.3%	43.8%	29.8%	61%	29.2%	26.1%

The surgicopathological features of stage 1B2 cervical carcinoma in our small series of 27 patients who underwent primary surgical resection are comparable with the data in other similar series (Table II). The general low rate of positive surgical margins demonstrates that complete surgical resection of such tumours is not a major problem. Authors who advocate a primary surgical approach for stage 1B2 and large 2A cervical carcinomas cite the advantage of surgical staging to accurately delineate the extent of the disease.[10] As large tumours are more often associated with nodal metastases, occult parametrial extension and extrapelvic disease, the outcome of any primary treatment without first defining the extent of the may be confounded by the presence of such unknown variables. Accurate surgical staging allows for adjuvant radiation fields to be tailored according to the extent of disease. A second advantage cited is that primary surgical staging also allows for the resection of bulky lymph nodes, improving the prognosis significantly.[14,15] Thirdly, surgery also allows the removal of the primary tumour, avoiding the subsequent difficulty in determining whether there is residual disease after radiation. Fourthly, it allows for ovarian preservation in the pre-menopausal patient.[14] Finally, it also avoids a situation where adjuvant post-radiation hysterectomy is performed and viable lymphadenopathy is found. There is no further therapeutic option for such patients.[11]

Combined surgery and adjuvant radiation however is generally accepted as being associated with higher morbidity.[16] For this reason, primary radiation therapy has been generally advocated for stage 1B2 cervical carcinomas. A randomised trial of adjuvant pelvic radiation versus no further treatment after radical hysterectomy and pelvic lymphadenectomy in selected stage 1B2 carcinoma of the cervix by Sedlis et al[17] showed that adjuvant radiotherapy reduces the recurrence rate at the cost of 6% grade 3-4 adverse events versus 2.1% in the control arm. In a randomised study of radical surgery versus radiotherapy for stage 1B to 2A cervical cancer by Landoni et al in 1997,[18] surgery and adjuvant radiotherapy was associated with 25% rate of grade 2 to 3 morbidity compared with 11% in the radiotherapy alone group for the subset of patients with tumours larger than 4 cm. The overall relapse rates in this subset were 37% for surgery plus radiotherapy compared with 42% in the radiotherapy only group, although not statistically significant. In our retrospective review, although there was no grade 3 or 4 toxicity noted in the patients who underwent surgery and adjuvant radiation, the numbers are too small for any firm conclusions to be made.

In our unit, the current treatment approaches for stage 1B2 and 2A (>4 cm) cervical carcinoma consist of either: primary radical hysterectomy and bilateral pelvic lymphadenectomy – cases with deep stromal invasion or lymphovascular space invasion receive adjuvant pelvic radiotherapy to increase local pelvic control[17] and cases with positive lymph nodes, parametrium or resection margins receive adjuvant pelvic radiotherapy with concurrent cisplatin and 5-fluorouracil[3] – or, radical pelvic radiotherapy and brachytherapy with concurrent weekly cisplatin chemotherapy.[4,5]

The role of neoadjuvant chemotherapy in stage 1B2 cervical carcinoma should also be explored. In 1993, Sardi et al[19] reported the results of a controlled randomised trial of neoadjuvant chemotherapy in patients with bulky stage 1B carcinoma of the cervix. The control arm was radical hysterectomy with pelvic radiation therapy, while patients on the study arm received preoperative neoadjuvant chemotherapy comprising cisplatin, vinblastine and bleomycin (PVB) for 3 cycles. Operability was improved, with a decreased incidence of parametrial extension, lymph node metastases, lymphovascular space involvement, tumour-cervix quotients, and tumour volume for cases in which the cervical tumour volume was greater than 60 cc. Increases in survival and disease-free interval were mainly due to decreased incidence of locoregional failures (24.3 versus 7.6%). The distant recurrence rate was 5.1% and the 4-year survival rate was 88% in the neoadjuvant arm. There was only one patient in our study who was treated with neoadjuvant chemotherapy followed by radical surgery and adjuvant pelvic radiotherapy, and she has been recurrence-free for 10 years.

Conclusion

FIGO stage 1B2 cervical carcinoma remains a challenging condition to treat. It would appear that the management of these tumours and probably bulky FIGO stage 2A

carcinomas of the cervix might necessitate a combination of treatment modalities. From our experience, primary radical surgery in such cases is not technically difficult and may provide accurate surgicopathological data, allowing for adjuvant therapy to be tailored according to the area determined to be at greatest risk of recurrence. Treatment efficacy could be further improved with neoadjuvant chemotherapy. Primary radiotherapy is another option for primary treatment and should be administered with concurrent chemotherapy by experienced centres. The question of whether both options are equal would be best answered by a multicentre prospective randomised trial to compare the efficacy and morbidities of primary chemoradiation versus neoadjuvant chemotherapy followed by radical surgery and tailored adjuvant radiotherapy.

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REFERENCES

1. Delgado G, Bundy B N, Fowler W C, Stehman F B, Sevin B, Creasman W T, et al. A prospective surgical pathological study of stage IB squamous carcinoma of the cervix, 1988. A Gynecologic Oncology Group Study. Gynecol Oncol 1989; 35:314-20.
2. FIGO Committee on Gynecologic Oncology. Modifications in the staging for stage I vulvar and stage I cervical cancer. Int J Gynaecol Obstet 1995; 50:215-6.
3. Peters W A 3rd, Liu P Y, Barrett R J 2nd, Stock R J, Monk B J, Berek J S, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000; 18:1606-13.
4. Morris M, Eifel P J, Lu J, Grigsby P W, Levenback C, Stevens R E, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high risk cervical cancer. N Engl J Med 1999; 340:1137-43.
5. Keys H M, Bundy B, Stehman F B, Muderspach L I, Chafe W E, Suggs C L III. Cisplatin, radiation and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage Ib cervical carcinoma. N Engl J Med 1999; 340:1154-61.
6. Piver M S, Rutledge F, Smith J P. Five classes of extended hysterectomy for women with cervical cancer. Obstet Gynecol 1974; 44:265-72.
7. Benedet J L, Odicino F, Maisonneuve P, Beller U, Creasman W T, Heintz A P, et al. Carcinoma of the cervix uteri. J Epidemiol Biostat 2001; 6:5-44.
8. Finan M A, DeCesare S, Fiorica J V, Chambers R, Hoffman M S, Kline R C, et al. Radical hysterectomy for stage 1b1 versus 1b2 carcinoma of the cervix: does the new staging system predict morbidity and survival? Gynecol Oncol 1996; 62:139-47.
9. Delgado G, Bundy B, Zaino R, Sevin B, Creasman W T, Major F. Prospective surgical–pathological study of disease-free interval in patients with stage Ib squamous cell carcinoma of the cervix: a Gynaecologic Oncology Group study. Gynecol Oncol 1990; 38:352-7.
10. Bloss J D, Berman M L, Mukherjee J, Manetta A, Emma D, Ramasanghani N S, et al. Bulky stage 1B cervical carcinoma managed by primary radical hysterectomy followed by tailored radiotherapy. Gynecol Oncol 1992; 47:21-7.
11. Boronow R C. The bulky 6-cm barrel-shaped lesion of the cervix: primary surgery and postoperative chemoradiation. Gynecol Oncol 2000; 78:313-7.
12. Alvarez R D, Gelder M S, Gore H, Soong S J, Partridge E E. Radical hysterectomy in the treatment of patients with bulky early stage carcinoma of the uterine cervix. Surg Gynaecol Obstet 1993; 176:539-42.
13. Rettenmaier M A, Casanova D M, Micha J P, Moran M F, Ramsanghani N S, Syed N A. Radical hysterectomy and tailored postoperative radiation therapy in the management of bulky stage 1b cervical cancer. Cancer 1989; 63:2220-3.
14. Hacker N F, Wain G V, Nicklin J L. Resection of bulky positive lymph nodes in patients with cervical carcinoma. Int J Gynecol Cancer 1995; 5:250-6.
15. Potish R A, Downey G O, Adcock L L, Prem K A, Twiggs L B. The role of debulking in the cancer of the uterine cervix. Int J Rad Biol Phys 1989; 17:979-84.
16. Grigsby P W. Should the new FIGO staging system define therapy? [Editorial]. Gynecol Oncol 1996; 62:135-6.
17. Sedlis A, Bundy B N, Rotman M Z, Lentz S S, Muderspach L I, Zaino R J. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage Ib carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group study. Gynecol Oncol 1999; 73:177-83.
18. Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, et al. Randomised study of radical surgery versus radiotherapy for stage IB-IIA cervical cancer. Lancet 1997; 350:535-40.
19. Sardi J, Sananes C, Giaroli A, Bayo J, Rueda N G, Vighi S, et al. Results of a prospective randomized trial with neoadjuvant chemotherapy in stage 1b, bulky, squamous cell carcinoma of the cervix. Gynecol Oncol 1993; 49:156-65.