Changing Practice of Gynecologic Oncology based on Current Evidence

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Evidence based medicine is the integration of the best medical research evidence with clinical expertise and patient values into daily practice. While the practice of evidence based medicine is desirable in all branches, it is even more important in oncology since oncological management is usually multidisciplinary, the benefits of adjuvant treatments are small and the therapeutic ratio of most treatments is generally low. Evidence is a moving object, with new evidence pouring in everyday and it is essential for us to review this and redefine our management guidelines based on the best available evidence.

The last few years has seen a plethora of new evidence in gynecological oncology being presented to us from the results of numerous prospective randomized trials, which have had a tremendous impact on the practice of this subspeciality - either in terms of improvement in survival or improvement in quality of life especially organ and fertility preservation. There is an urgent need for all practising gynecologic oncologists to redefine the practice guidelines based on this compelling new evidence.

The most striking impact of evidence from randomized trials has been in patients with locally advanced cervical cancer. Till recently, radical radiation therapy (external + brachytherapy) was the standard of care for these patients. In the past 4 years, data from 9 randomized controlled trials have been published, six of which showed benefit for concomitant cytotoxic chemotherapy with radiation therapy (chemoradiotherapy) compared to radiation therapy alone in patients with stage IB2-IVA cervical cancer [1-5]. All positive trials showed a 43-46% reduction in the risk of recurrence and death, translating into 16% absolute benefit in disease free survival and 12% absolute benefit in total survival. The magnitude of benefit was remarkably similar in all the trials. These trials also showed a reduction in the rate of distant metastases in the chemoradiation arm. These results were confirmed by two subsequent meta-

analyses [6-7]. In view of this, concurrent chemotherapy with single agent cisplatin given weekly in the dose of 30-50 mg/m² should now be considered the new standard of care of these patients with locally advanced cervical cancer.

Retrospective data from case control and non-randomized studies showed that stage IB/IIA cancer of the cervix can be treated equally well with radical surgery and radical radiation therapy. However, the evidence of equivalence of these two modalities was not forthcoming from randomized clinical trials. In 1997, Landoni[8] reported a randomized trial of 343 patients with stage IB/IIA carcinoma cervix, which showed that these two modalities were equally effective in controlling the disease judged by the disease free and total survival as well as by the relapse rates. This trial also conclusively showed that surgery has a survival advantage over radiation therapy for patients with adenocarcinoma cervix.

Recently published trials designed to look at the benefit of adjuvant therapy in early stage cervical cancer have redefined the standards of care in this area. Sedlis et al [9] reported the results of the GOG 92 trial - a randomized trial of pelvic radiation therapy versus no further therapy in stage IB patients with intermediate risk of relapse after radical hysterectomy and pelvic lymphadenectomy. Factors that indicated an intermediate risk of relapse were large tumour diameter, deep stromal invasion and capillary lymphatic space invasion (2 out of these 3 factors), in the absence of lymphnode metastases. Post-operative radiation therapy reduced the risk of recurrence by 47% (i.e. relative risk 0.53) and also improved survival (88% vs. 79%). Till now, adjuvant radiation therapy was commonly used for patients with lymph node metastases after surgical treatment of stage IB/IIA cervical cancer. However, the Intergroup 0107 trial [5] which randomized patients to concurrent chemotherapy (4 cycles of cisplatin and 5-fluorouracil) and pelvic radiation therapy compared with

pelvic radiation therapy alone as adjuvant therapy after radical surgery in high risk (pelvic lymphnode metastases, positive cut margins, parametrial spread) early stage carcinoma cervix showed an improved 4 year progression free survival for patients receiving chemoradiation as compared to radiation only. In the light of this new evidence, adjuvant radiation therapy for the intermediate risk group and adjuvant concurrent chemoradiation therapy for the high-risk group of patients with early stage cervical cancer after radical surgery should now be considered the new standards of care.

The management of stage IB2 cervical cancer has been a matter of great debate. The survival of these patients is relatively poor (approximately 60% five year survival) with the standard treatment of radical surgery or radiation therapy. Keys et al [1] have demonstrated that addition of concurrent cisplatin chemotherapy to radiation therapy improves survival compared to radiation therapy alone. On the other hand, Sardi et al [10] reported a statistically significant difference in survival using neoadjuvant chemotherapy prior to radical surgery versus radical surgery alone in these patients (80% vs. 61%). However, there has never been a direct comparison of concurrent chemoradiation therapy and neoadjuvant chemotherapy + surgery. Two such trials - one conducted by EORTC and one at the Tata Memorial Hospital, Mumbai, are currently under way.

There have been significant advances in radiation therapy for cervical cancer in recent times. Recent reports indicate that there is better pelvic control and improved survival when doses above 85 Gy were delivered to point A as demonstrated by the total radiation dose response curves [11]. This suggests that the optimum dose for point A in the treatment of cervical cancer should be in the range of 85-90 Gy [12]. Recent evidence also suggests that high dose rate brachytherapy is an established alternative to low dose rate therapy in terms of local control, five year survival as well as morbidity [13]. The Gynecologic Oncology Group has now accepted HDR as an alternative to LDR brachytherapy in the current GOG 165 protocol for advanced cervical cancer, with the fractionation schedule of 30 Gy in 5 HDR fractions in combination with 45 Gy to the whole pelvis.

An estimated 10-15% of cervical cancer cases are presently diagnosed in young women in the child bearing years, in whom removal of uterus will deprive them of an opportunity of having babies (Van der Vange et al 1995). Radical trachelectomy, which allows preservation of the body of the uterus, thereby preserving reproductive function seems to be a significant advance in the management of these young women with cervical cancer

who have suitable disease characteristics i.e. stage IB1 or less squamous carcinoma, without vascular space invasion and less than 2cm in size [14,15]. Trachelectomy is usually preceded by a laparoscopic pelvic node dissection. The overall recurrence rate in the 4 published series is 3.1% (4 of 130 patients), which is similar to that reported after radical hysterectomy. The obstetric outcome in the reported data has also been encouraging. This procedure is still experimental and needs to be tested in a prospective randomized trial with a larger number of patients in order to define its exact role.

In ovarian cancer also, new evidence has had a significant bearing on practice. Recent evidence has indicated that spillage during surgery for stage I epithelial ovarian cancer is harmful and should be avoided at all costs [16]. In this study, rupture before surgery (hazard ratio 2.65) and rupture during surgery (hazard ratio 1.64) were found to be important independent prognostic parameters affecting outcome. This information is extremely important in today's era of laparoscopic surgery where spillage during laparoscopic surgery should be strongly condemned.

The last decade has been marked by two significant developments in the chemotherapeutic management of advanced ovarian cancer through controlled randomized clinical trials. The optimum treatment for patients with early stage ovarian cancer with unfavourable prognostic factors (stage IC, grade III or unfavourable histologic subtype) has been better defined. Recently published randomized trials like ICON 1 [17] and ACTION [18] as well as the combined analysis of these trials [19] have shown a significant improvement in disease free and overall survival in the adjuvant chemotherapy arm, making it a new standard of care. The choice of chemotherapy at present appears to be a platinum compound (cisplatin or carboplatin). In advanced stage ovarian cancer, 2 landmark studies (GOG 111 and OVO 10) established the superiority of paclitaxel and cisplatin combination over cyclophosphamide + cisplatin regimen [20, 21]. With the equivalence of cisplatin and carboplatin demonstrated in randomized trials, paclitaxel + carboplatin was considered the gold standard in late 1990s. However, 2 large randomized trials (GOG 132 and ICON 3) published subsequently indicated that single agent therapy with either carboplatin or cisplatin was as effective as its combination with paclitaxel [22, 23], a conclusion which was corroborated by a recent meta-analysis [24]. In view of this, it appears that optimally dosed single agent carboplatin is a safe, effective and optimum first line treatment for women with advanced ovarian cancer.

In the management of advanced epithelial ovarian cancer, optimal primary cytoreduction can be achieved

only in about 70% of patients. In those patients who cannot be optimally cytoreduced upfront, adding another surgical cytoreductive effort after 3 cycles of chemotherapy has been shown to impart a survival benefit (33% reduction in the risk of dying at 2 years) [25]. It is rather tempting to extrapolate these results to the group of patients without cytoreductive surgery i.e. those with clinically unresectable disease. This approach of neoadjuvant chemotherapy followed by interval surgery is likely to increase the rate of optimal cytoreduction, improve survival, reduce the morbidity of surgical debulking, improve the quality of life and be more cost-effective. This approach though yet unproven in randomized clinical trials holds promise in developing countries like India. These two approaches of primary debulking surgery and interval debulking surgery in patients with stage III C/IV epithelial ovarian cancer are presently being compared in a randomized EORTC trial.

The role and extent of retroperitoneal (pelvic and para-aortic) lymphadenectomy in patients with advanced epithelial ovarian cancer has been a matter of great debate. It was not clear whether the survival benefit seen in some of the retrospective studies was due to selection of patients with better tumour biology. An early report of a recent randomized trial comparing systematic pelvic and para-aortic lymphadenectomy versus resection of bulky nodes only, in optimally cytoreduced stage III/IV patients showed a statistically significant improvement in survival in the former group [26]. In view of this, it is recommended that systematic pelvic and para-aortic lymphadenectomy should be performed as a part of optimal cytoreduction.

Some interesting publications have shown that the survival of patients with epithelial ovarian cancer is linked to the subspecialty training of the operating surgeon, this effect being most pronounced for patients with stage III ovarian cancer [27], with a 25% and 32% reduction in the risk of death compared with surgery performed by a general gynecologist or a general surgeon. Optimal surgical staging as well as optimal cytoreductive surgery has been found to be performed more frequently by a specialist gynecologic oncologist [28].

Although lymphadenectomy in patients with endometrial cancer has the ability to determine prognosis and guide treatment, whether it also has a therapeutic role is not clear. However, recent studies have shown that a formal lymphadenectomy may directly impact both recurrence rates and overall survival [29-31], with the effect being most pronounced in patients with stage IAG3, IBG2-3, IC, vascular space invasion, adnexal involvement and high risk cell types. In view of this, it appears logical to add pelvic lymphadenectomy and para-

aortic lymph node sampling to the surgical chores in patients with endometrial cancer. There have been conflicting reports about the role of post-operative radiation therapy in stage I endometrial cancer. The GOG 99 randomized study demonstrated significant improvement in progression free and overall survival as well as reduction in the locoregional relapses, while Creutzberg et al showed that post-operative radiation therapy reduces local recurrences but has no impact on survival. Considering this, the current consensus is that all patients with stage I disease should have comprehensive surgical staging followed by adjuvant radiation therapy in the high-risk group, with the primary aim of reduction of pelvic relapses and with the hope of better survivals.

Sentinel node biopsy in gynecological malignancies - an approach aimed at avoiding or downscaling the morbid lymphadenectomy in those who do not need it, is under active investigation at present. It is of particular interest in vulvar cancer, since the ilioinguinal lymphadenectomy practised for this cancer is one of the most morbid surgical procedures due to poor wound healing and it is important to perform it only in patients who absolutely need it. Levenback et al (1995) and DeCesare et al (1997) using isosulfan blue dye and lymphoscintigraphy (technetium 99-m labelled sulfur colloid), respectively demonstrated the feasibility of mapping and identification of the sentinel node in patients with invasive stage I vulvar cancer. De Hullu et al (2000) using a combination of these 2 methods concluded that accurate identification of the sentinel node was feasible in all patients and even after step sectioning and immunohistochemistry staining for cytokeratin, only 4 of the 102 negative sentinel nodes were found to be metastatic. Similar findings have been reported in patients with invasive cervical cancer by several investigators - either at open surgery or laparoscopically. Results from prospective randomized trials should provide interesting data in the near future, which will guide us regarding incorporation of this procedure in routine clinical practice.

The treatment results of gynecological cancers, with the exception of ovarian cancer have improved considerably with more effective primary and adjuvant therapy of treatment. This has prompted the practising physician to devise treatment protocols with more emphasis on preservation of quality of life. With more and more women in the childbearing age being diagnosed with gynecological cancers, fertility preservation has become an important issue in young women afflicted with these cancers and has resulted in redefining the treatment of these cancers. Although the conservative approach appears to be justified in well-selected patients, it remains to be seen how much these indications for

conservative surgery can be expanded without jeopardizing the survival of these patients. While the western world is busy with advanced molecular, biological and genetic approaches to improve the end results of gynecological cancers, the emphasis in our country should be to ensure that all the unfortunate women afflicted with gynecological cancers should have the benefit of early diagnosis, optimum staging and state-of-the-art treatment in order to improve their outcome.

References

1. Keys HM, Bundy BN, Stehman FB et al. Cisplatin, radiation and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med* 1999;340:1154.
2. Morris M, Eifel PJ, Lu J et al. Pelvic radiation with concomitant chemotherapy compared with pelvic and para-aortic radiation in high-risk cervical cancer. *N Engl J Med* 1999;340:1137.
3. Rose PG, Bundy BN, Watkins EB et al. Concurrent cisplatin based chemotherapy and radiotherapy for locally advanced cervical cancer. *N Engl J Med* 1999;340:1144.
4. Whitney CW, Sause W, Bundy BN et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyureas as an adjunct to radiation therapy in stage II B-IV A carcinoma of the cervix with negative para-aortic nodes. A Gynecologic Oncology Group and Southwest Oncology Group Study. *J Clin Oncol* 1999;17:1339.
5. Peters WA, Liu PY, Barrett RJ 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 carcinoma of the cervix. *J Clin Oncol* 2000;18:1606.
6. Green JA, Kirwan JM, Tierney JF et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet* 2001;358:781.
7. Lukka H, Hirte H, Fyles A et al. Concurrent cisplatin based chemotherapy plus radiotherapy for cervical cancer: a meta-analysis. *Clin Oncol* 2002;14:203.
8. Landoni P, Maneo A, Colombo A et al. Randomized study of radical surgery versus radiotherapy for stage IB-IIA cervical cancer. *Lancet* 1997;350:535.
9. Sedlis A, Bundy BN, Rotman MZ et al. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients of stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. *Gynecol Oncol* 1999;73:177.
10. Sardi JE, Giaroli A, Sananes C et al. Long term follow up of the first randomized trial using neoadjuvant chemotherapy in stage IB squamous carcinoma of the cervix: the final results. *Gynecol Oncol* 1997;67:61.
11. Choi D, Wong L, Sham J et al. Dose tumour response for carcinoma of cervix: Analysis of 594 patients treated by radiotherapy. *Gynecol Oncol* 1993;49:311.
12. Eifel P, Thomas W, Smith T et al. The relationship between brachytherapy dose and outcome in patients with bulky endocervical tumours treated with radiation alone. *Int J Radiat Oncol Biol Phys* 1994;28:113.
13. Petereit D, Schink J, Potter D et al. High dose rate brachytherapy is equivalent to low dose rate brachytherapy in the treatment of stage IB and II cervical cancer. *Gynecol Oncol* 1998;68:103.
14. Dargent D, Martin X, Sacchetoni A et al. Laparoscopic vaginal radical trachelectomy: A treatment to preserve the fertility of cervical carcinoma patients. *Cancer* 2000;88:1877.
15. Plante M, Roy M. Pregnancies following radical trachelectomy for the treatment of early-stage cervical cancer. In : Pecorelli S, Atlante A, Beneditti Panici P et al. editors 7th Biennial meeting of the International Gynecological Cancer Society. Bologna Monduzzi 1999;449
16. Vergote I, DeBrabanter J, Fyles A et al. Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma. *Lancet* 2001;357:176.
17. Colombo N, Guthrie D, Chiari S et al. International Collaborative Ovarian Neoplasm (ICON) collaborators: International Collaborators Ovarian Neoplasm Trial I: A randomized trial of adjuvant chemotherapy I women with early stage ovarian cancer. *J Natl Cancer Inst* 2003;95(2):125.
18. Trimbos JB, Vergote I, Bolis G et al. For the EORTC-ACTION collaborators: Impact of adjuvant chemotherapy and surgical staging in early stage ovarian carcinoma: European Organization for Research and Treatment of Cancer -Adjuvant chemotherapy in ovarian neoplasm trial. *J Natl Cancer Inst* 2003;95(2):113.
19. Trimbos JB, Parmar M, Vergote I et al. International Collaborative Ovarian Neoplasm I, European Organization for Research & Treatment of Cancer Collaborators - Adjuvant chemotherapy for Ovarian Neoplasm: International Collaborative Ovarian Neoplasm Trial I and Adjuvant Chemotherapy for Ovarian Neoplasm Trial:two parallel randomized phase III trials of adjuvant chemotherapy in patients with early stage ovarian carcinoma. *J Natl Cancer Inst* 2003;95(2):105.
20. McGuire WP, Hoskins WJ, Brady MF et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and IV ovarian cancer. *N Engl J Med* 1996;334:1.
21. Piccart MJ, Bertelson K, James K et al. Randomized Intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three year results. *J Natl Cancer Inst* 2000;92:699.
22. Muggia FM, Braly PS, Brady MF et al. Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer. *J Clin Oncol* 2000;18:106.
23. The International Collaborative Ovarian Neoplasm (ICON) Group. Paclitaxel plus carboplatin versus standard chemotherapy with either single agent carboplatin or cyclophosphamide, doxorubicin, cisplatin in women with ovarian cancer. The ICON 3 randomized trial. *Lancet* 2002;360:505.
24. Sandercock J, Parmar MKB, Torri V et al. First line treatment for advanced ovarian cancer:paclitaxel, platinum and the evidence. *Br J Cancer* 2002;87:815.
25. Vander Bergh ME, van Lent M, Buyse et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. *N Engl J Med* 1995;332:629.
26. Beneditti-Panici P, Landoni F, Scarabeili C et al. Systematic aortic and pelvic lymphadenectomy (SAPL) versus resection

of bulky nodes (RBN) only for optimally debulked advanced ovarian cancer (AOC): preliminary report from an international randomized trial (abstract). *Int J Gynecol Cancer* 1999;9(suppl 1):44.

27. Junor EJ, Hole DJ, McNutty L et al. Specialist gynecologists and survival outcome in ovarian cancer; A Scottish national study of 1866 patients. *Br J Obstet Gynecol* 1999;106:1130.
28. Eisenkop SM, Friedman RL, Wang HJ. Complete cytoreductive surgery is feasible and maximizes survival in patients with advanced epithelial ovarian cancer. A prospective

study. *Gynecol Oncol* 1998;69:108.

29. Podratz K, Mariani A, Webb M. Editorial: staging and therapeutic value of lymphadenectomy in endometrial cancer. *Gynecol Oncol* 1998;10:163.
30. Orr JW Jr., Roland PY, Leichter D et al. Endometrial Cancer: Is surgical staging necessary. *Curr Opin Oncol* 2001;13:408.
31. Barnes MN & Kilgore LC. Complete surgical staging of early endometrial adenocarcinoma: optimizing patient outcomes. *Semin Radiol Oncol* 2000;10:3.

Distinguished Award To Armed Forces Medical Officer

Lt Gen Bijoy Nandan Shahi (Retd), PVSM, AVSM, VSM, after graduating from Darbhanga Medical College, with Honours and distinction in 1964, joined the Army Medical Corps on 15 Aug 1964. He acquired his M.D. (Gen Medicine) from AFMC, in 1973 and Post Doctoral DM degree in Cardiology from PGIMER Chandigarh, in 1981. He was the first Cardiologist to be posted at IMTRAT. He held various prestigious appointments during his career of almost 40 years; like Commandant Armed Forces Clinic, New Delhi, DGHS (Armed Forces), DGMS (Army) and the highest post of DGAFMS. He taught and guided several officers in Medicine and Cardiology and has been examiner of DM Cardiology, Pune University and National Board of Examination to DNB (Cardiology). The General Officer, known and acclaimed nationally and internationally for his professional excellence, has been solely responsible for bringing the Cardiac Sciences in the Armed Forces to the forefront of the National arena. For his exceptional professional contribution as an eminent cardiologist, he was awarded Padma Bhushan. Acknowledging the contribution and professional attributes of the highest level, the Government has bestowed upon him the prestigious appointment of "Emeritus Medical Scientist (Cardiology)" for a period of two years from the date of his retirement on 31 Jan 2004. We wish him success in all his future endeavours.