

## Persisting Challenges in Prevention, Management and Prediction of Prognosis in Cervical Cancer

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### Abstract

**Introduction:** It is possible to prevent mortality due to cervical cancer by appropriate and timely therapy. But it continues to be a major contributor of cancer related deaths globally because of failure in prevention, early detection and timely, appropriate therapy.

**Objectives:** Objective was to collect information about persisting challenges in management, prevention, prediction of prognosis of cervical cancer.

**Methodology:** A Simple review was done by using Up-to-date, ERMED CONSORTIUM, Cochrane Library, Delnet, MedIND to get information from available studies and reviews related to prevention, management, prediction of prognosis in cervical cancer and personal experiences were added.

**Results:** Usually, management of cervical cancer is as per age, parity, stage of cancer, associated disorders. It may be conservative or aggressive multimodality therapy. However after planned therapy outcome is not always as per expectations. Answers need research. Nearly 20% of women with cervical cancer die within the first year of diagnosis. Research continues about factors which affect outcome and recurrence after surgery, radiotherapy, chemoradiotherapy, and differences in efficacy of surgery, chemotherapy, radiotherapy. Despite significant developments in management, results seem to be far from optimal. Over years there has been no demonstrable reduction in the incidence of cervical cancer and deaths due to cervical cancer. More than 50% of women diagnosed with cervical cancer are younger than 50 years, so the quality of life is becoming a challenge. Sometimes extensive surgeries like complete or anterior or posterior exenteration might give satisfaction to treating surgeon but what matters is survival with quality. It is not possible to predict the prognosis and know the best therapy for recurrent disease. In developing countries lack of awareness about prevention, geographical, economic inaccessibility, poor quality services, lack of support from families are barriers to early diagnosis and also safe therapy. A lot of more research seems to be necessary for the best therapy.

**Conclusion:** In spite of being almost preventable cancer mortality due to cervical cancer continues to be high. At present, it is mostly not possible to predict prognosis. Appropriate management needs more research and a lot needs to be researched about prognosis too.

**Keywords** Cervical cancer; Chemosensitization; Chemoradiation; Metastasis

### Introduction

Although the overall incidence of cervical cancer has not changed significantly, it has become increasingly common in younger women in many countries, new challenge for management. Nearly 85% of cervical cancer deaths occur in developing countries and India reports about 122,000 new cases of cervical cancer annually and accounted for 25% of all cervical cancer deaths (67,500 deaths) [1]. Ferlay [2] reported that cervical cancer was the third most common cancer in women, and the seventh overall, with an estimated 529,000 new cases in 2008. A total of 1,658,3770 new cancer cases and 589,430 cancer deaths were projected to occur in the United States in 2015 [3]. In a rural institute analysis of cancer cases in women revealed that cervical cancer constituted 29% of all cancers in women, similar to other reports [4]. Unfortunately very few women complied to therapy. Follow up after completion of therapy has also been very low [5]. All

these challenges need more research, which too is a challenge in places where cervical cancer is most common.

Objectives were to share persisting challenges in the prevention and management of cervical cancer and dilemmas in prediction of the prognosis.

### Methodology

Simple review was done to get information about persisting problems in prevention, challenges in management and prediction of prognosis of cervical cancer.

### Results

Cervical cancer needs to be prevented, diagnosed at early stage, and removed or made to shrink, slow its growth and spread with minimum effects of therapy to surrounding tissues and organs, nearby and at distant places. But the modes of achieving this mission continue to be

elusive and research continues. In advanced cases it is essential that attempts are made to allay symptoms which affect everyday life of sufferer and family too. Smell of discharge in advanced cases and spread of cancer to nearby organs affecting urinary, bowel function causing fistulae due to disease or its therapy affect the family too. Quality life of survivors is also becoming an increasingly important challenge because more than 50% of women diagnosed with cervical cancer are younger than 50 years. For quality disease free survival (DFS), treatment is tailored to the extent of the disease, but outcome is not as per the expectations. So research continues.

Clinical staging is many times incorrect and modalities are still elusive. Some modalities are not accessible to those who need them the most. So treatment and response too get affected. A study revealed that clinical and intraoperative agreement in staging was in 72% cases and between clinical staging and final histopathologic staging 64% [6]. Also primary disease may be diagnosed while investigating and treating disorder caused by secondaries like fracture due to metastasis (Personal experience). Also sometimes local early disease could really be advanced with secondaries in the abdomen [7,8]. At present these surprises are difficult to understand and dilemmas continue. Though standard management is planned as per age, parity and stage, presence of other disorders also affect the selection of therapy. For individual patients outcome is not easy to predict. No consensus has emerged about factors, such as structure, differentiation, nuclear polymorphism, mitosis, extent and mode of invasion. Research continues about the factors which affected the outcome and the disease free survival. Lymphoplasmocytic cell response or vascular invasion has consistently been in use as reliable predictors of response to treatment and overall outcome. Those who should get aggressive multimodality regimens even with clinical early disease from the outset have not been defined. Preservation of reproductive health seems to be possible if the disease is diagnosed in very early stage; however whether it is truly early may not be possible to know. And future of such women is difficult to predict and so research is needed. It is being proposed that Sentinel Lymph Node (SLN) mapping and ultrastaging should become standard practice in the surgical management of early-stage cervical cancer [9]. Intraoperative detection of metastasis by SLN mapping with peritumor injection of radio isotope and blue dye with or without lymphoscintigraphy with a gamma probe has been proposed for identification of glands involvement in early stages. SLN can be subjected to extensive evaluation by immunohistochemistry to detect micrometastasis more accurately and minimize post-operative morbidity by avoiding unnecessary lymphadenectomy. However at present there is no evidence to suggest that by doing sentinel node removal. Rapid pathological examination for the detection of metastasis to the obturator lymph nodes and external iliac lymph nodes is considered helpful in indicating the risk of metastasis to other sites, making it possible to plan the extent of lymph node dissection. Pelvic lymphadenectomy can be avoided [10]. Where lymphadenectomy is done, the number of metastatic nodes might suggest prognosis in squamous cell cancer cases. Whether surgical treatment is superior to concomitant chemoradiation has also not been evaluated prospectively. Research is needed for creation of less toxic treatment schedules in low risk like therapy with preservation of fertility and / or sexual function in early invasive and also for management of recurrent disease. In a study of recurrences of cervical cancer 8% women had well differentiated, 54% moderately differentiated and 44% had poorly differentiated carcinoma. At recurrence there were more well differentiated cancers than primary disease.

Surgical techniques such as laparoscopically assisted radical vaginal hysterectomy or trachelectomy are being established but need to be evaluated for long- term safety, especially in regions where compliance is a big problem. In one study, with the mean follow up of 23 months there were no recurrences. The locally radical procedure for a highly selected group of women who wished to preserve their fertility, trachelectomy was believed to offer a safe alternative to radical hysterectomy [11]. Sert [12] reported that Robotic-assisted laparoscopic radical hysterectomy in early stage gave better results than total LRH. Kruijdenberg et al. [13] reported that results of Robot assisted total LRH were equally adequate and feasible. More research is needed. Author has seen cases with early disease managed laparoscopically at private centers reporting to medical institute with such advanced stage that nothing could be done.

A recent report [14] revealed that radiation therapy for cervical cancer increased risk for colorectal cancers. These are new challenges. Evidence revealed that prostaglandins (PG) may be implicated in the cytotoxic/cytoprotective response of tumor cells to ionizing radiation (IR). Resveratrol, a polyphenol isolated from the skins of grapes has been shown to significantly alter the cellular physiology of tumor cells, as well as block the process of initiation and progression. At least one mechanism for the intracellular actions of Resveratrol involved the suppression of PG biosynthesis, altered both cell cycle progression and the cytotoxic response to IR in two cervical tumor cell lines [15]. Some reports revealed that intra-arterial (IA) chemotherapy (CTX) used as neoadjuvant therapy for advanced cervical adenocarcinoma was superior to that achieved by intravenous therapy by improving the prognosis without increasing the complications [16-19]. This aspect needed further research [20]. Horn et al. [21] reported 27.5% recurrence in poorly differentiated cancers and 15% in well differentiated primary cancers though significant difference, but was not always possible to know which ones recurred. This aspect needs further studies. In a study it was revealed that nearly 20% of women with cervical cancer died within the first year of diagnosis and the 5-year survival was 50% [22]. There is evidence that hypoxia and subsequent reoxygenation affected the response to radiation and disease progression [23]. Gamboa et al [24] reported that 30-40% of patients with similar prognostic factors did not respond equally to a comparable standard treatment. Therefore, the study and identification of prognostic biomarkers which indicated the probable course of the disease in an untreated individual and predictive biomarkers, which allowed identification of subpopulations of patients, most likely to respond to a given therapy would be extremely useful in the selection of patients for the development of innovative and effective therapies for locally advanced, metastatic and refractory cervical cancers. In 513 patients with metastatic advanced disease or recurrent disease, it was revealed that the cisplatin/topotecan, cisplatin/gemcitabine, and cisplatin/viorelbine were not superior to cisplatin/paclitaxel. No significant differences in overall survival were seen. The trends for response rate, progression free survival, and overall survival suggested that cisplatin, paclitaxel were superior to the other regimens [25,26]. So, more research is essential. The level of EGF-R is believed to be indicative of the biological aggressiveness [27]. Researchers [28,29] have reported an increase in the c-myc product, p 62 associated with a decrease in survival rate and an increase in metastatic disease, difficult to use in everyday life. Over expression of genes seems to predict the prognosis, investigations which go beyond the reach of those who suffer from cervical cancer. Blood flow change assessed by ultrasound may be of limited use for the efficacy of chemotherapy. The relationship between DNA content in nuclei and prognosis remains

uncertain at present and requires more studies. So far studies of the correlation between HPV infection and prognosis have failed to produce consistent results [30]. Whether advances in diagnostic tools and therapeutic methods all improve the overall prognosis and decrease recurrence continue to be a research agenda but with appropriate treatment in early stages, cure rates are believed to go up to 90-100%. However some women with early disease do badly with conventional approaches for reasons not very well understood. Factors which affect the final outcome and survival continue to be dilemmas. Further cancer cervix is staged clinically and this has inherent limitations in identifying the nodal status and the real stage. The main reasons for the poor outcome are the delay in institution of definitive treatment, triggering accelerated repopulation of surviving oncogenes and cross resistance to further radiotherapy. Despite significant achievements in the use of chemo radiation and radical surgery, therapeutic results have been far from optimal. It is not possible to know best efficacy. Also compliance problems during and after therapy continue and need to be researched. Sometimes well done extensive surgeries like complete exenteration or anterior and/or posterior exenteration might give satisfaction to the treating surgeon, but finally what matters is the quality of life. More prospective studies are needed which are difficult too. In most of the cases the women are dependent on husbands or other family members to accompany them to health facility and compliance to needs during external beam radiotherapy (EBRT), which is not always possible. In addition, patient's fear and mistrust of the health system make situations more complex. In a study it was revealed that patient once told that the disease was advanced, though there were treatment options, just disappeared from outpatient or after biopsy or at initiation of the therapy [6]. Sometimes cancer diagnosis is taken as death any day. There are identified psychological challenges, fear of recurrence, negative social attitude and psychological distress Yan et al. [31] reported that the clinical outcomes were improved by case management in terms of timely diagnosis, timely initiation of cancer treatment. Case management, a cumulative process utilizing available resources to satisfy individual health needs to attain cost-effective outcomes, has been applied in management of cervical cancer. Study by Yang et al. [32] revealed that case management improved clinical outcomes at specified time points. Age, literacy and severity of abnormality affected the ability to adherence to follow-up and treatment. In view of heterogeneity in the components of intervention and outcome measures across the included trials, more rigorously-designed studies are needed to explore cost effective protocols of case management maximising adherence to follow-up and treatment, Relevant barriers also needed to be investigated further .

## Prevention

It is known that cervical cancer is mostly preventable, except for some aggressive cases reported in young women. Why the world is failing in prevention continues to be a problem. Answers are similar to the problems of maternal mortality, multi-layered. Ways and means are available but problems persist. Failure seems to be because of various visible and invisible reasons. The look sometimes is deceptive as seen in our own institutional and community experiences of invasive disease and dysplasia. In developed countries, cervical cancer prevention programmes have been shown to be effective in reducing the incidence and mortality from cervical cancer, while in developing countries, in some the programmes have not been properly implemented due to various reasons, including resources and where implemented limited centres for therapy have failed the mission

because of logistical, financial and socio behavioural problems, lack of awareness, lack of familiarity with the concept of prevention, the geographical and economic inaccessibility of care, the poor quality of services. Lack of support from husbands and families are also barriers to the success of prevention. Since cervical cancer is mostly preceded by a long phase of precursor lesions, cellular atypia, various grades of cervical intraepithelial neoplasm (CIN) before progression to invasive cancer, prevention is possible even with limited resources. Presently there are no available means to differentiate, CIN lesions that will progress to cancer from those that will not progress, though attempts are being made to identify factors which will help in prediction. Based on the existing knowledge, UICC supported by multiple partners is spreading the Cervical Cancer Initiative (CCI) to significantly reduce the incidence and mortality of women dying from cervical cancer through targeted and resourced interventions [33].

With the advent of highly effective HPV vaccines, earlier against HPV 16 and 18, and now against additional high-risk types of over a relatively short period, more than 80 countries or territories have introduced HPV vaccination into their national immunization programs, and 33 of these are from LMICs, with many more implementing pilot projects [34]. There are 2 vaccines, Gardasil and Cervarix available for protection against the 2 types of HPV implicated in 70% cervical cancer cases Thompson [35] reported that new research suggested that a single dose of HPV vaccine was enough. However controversies about its use, because of various reasons continue. Cervical cancer occurs in poor women who cannot afford the vaccine and those who are being advised the vaccine rarely get cervical cancer. HPV free cervical cancer is also known [36]. Research is also needed regarding duration of protection induced by vaccines, need for boosters, effect on prevalence and incidence of HPV types after the vaccine. Further details on different HPV types vaccines for different populations, general safety and pregnancy outcomes, safety and immunogenicity of simultaneous administration with other vaccines needed to be looked into [37]. American College of Paediatricians have opined that vaccines may be associated with premature ovarian failure (POF). Post-menarcheal adolescent girls developed laboratory documented POF within weeks to several years of receiving Gardasil, a four-strain human papillomavirus vaccine (HPV4) [38,39]. The overwhelming majority (76%) of Vaccine Adverse Event Reporting System (VAERS) reported that ovarian failure was associated solely with Gardasil. A Vaccine Safety Data link POF study has been planned to address an association between these vaccines and POF, but it may be years before results will be determined. Also POF within a few years of vaccination could be the tip of the iceberg since ovarian dysfunction manifested by months of amenorrhea may later progress to POF and other problems [40]. The challenges faced by low resource countries are many and include affordable point-of-care HPV detection test, minimizing over-treatment and installing an effective information system to ensure high compliance to treatment and follow-up [39].

The relationship of diet has only been in relation to progression and improving overall outcome. The protective effects of Carotene, Folic acid and vitamins need to be studied. Studies have revealed that folate deficiency affected cervical carcinoma [41,42]. Bax, protein proliferative markers, presence of *bel-2*, *p21* and *p53*, have a role in determining resistance.

In economically less developed countries, the major barrier to widespread use was thought to be the high cost of the vaccine. So attempts continue to help women with low resources. However it is not

only the cost. There are various other reasons. Also it is extremely important that all women, even those who have been vaccinated, need to continue with screening, because HPV vaccines do not protect against established infections, nor do they protect against all the types of HPV that cause cervical cancer and there may be cervical cancer without HPV.

## Conclusion

Key goals in cervical cancer management are quality life, if needed with preservation of fertility; limit the number of visits to health facilities and to ensure high compliance with treatment. This is most relevant in low-resource settings, where women must overcome huge social and economic barriers for treatment. One of the major barriers to the success of cervical cancer prevention is the failure of screen-positive women to complete diagnosis and treatment. This problem is common in LMICs, as women cannot afford to travel to health facilities multiple times because of social and economic constraints. Effective tracking of patients is not feasible owing to poor health information systems. Non-availability of comprehensive coordinated approach, pain, emotional and spiritual support, as per the need are the big challenges. The facilities for therapy, patients stay homes around the place of therapy are limited in countries where the disease is more common. Most importantly, it is essential to understand the outcome with the treatment being offered, need of emotional support and counselling. Many factors come in the way of quality survival. It is essential to ensure that the treatment offered does not do more harm to the body than the cancer itself. A combination of social support, transport and the cost of treatment are other challenges.

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