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Early Integration of Palliative Care in the Management of Patients with Carcinoma Cervix- Isn't it Time to Switch Gears to a Patient Centric Treatment Approach?

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Abstract

Carcinoma cervix is a common malignancy affecting a vast majority of women, especially in low- and middle-income nations. These women have a large magnitude of symptom burden right from diagnosis until completion of treatment and beyond. While oncological treatment modalities remain predominantly disease-centric, palliative care (PC) plays a multidimensional role involving communication, management of physical, psychological, social, spiritual issues and end-of-life care. In order to improve the patient's satisfaction, treatment compliance and quality of life, PC must be commenced early and integrated within the framework of multi-modality management of carcinoma cervix. Patients with advanced cervical cancer who become terminally ill require intensification of PC and a gradual transition into hospice care. Oncology teams must thus, work in tandem with palliative care teams to ensure holistic management of women suffering from cervical cancer.

Keywords

Palliative care; Carcinoma cervix; Early integration; Symptom burden

Introduction

Carcinoma of cervix (Ca.Cx) is the fourth most common malignancy among womenworldwide with respect to incidence and mortality [1]. Population based cytological screening has successfully diminished the rates of Ca.Cx in developed nations. However, the low- and middle-income nations are still facing the wrath of advanced stages of Ca.Cx, as a consequence of the dearth of effective screening activities across the population. It is the most frequently diagnosed cancer in sub-Saharan Africa and several central and south-east Asian nations [1], with China and India together accounting for more than a third of the global cervical cancer burden [2].

Oncology has always been a rapidly evolving specialty, with vast amounts of research efforts into disease centric treatment. Oncologists have been the front-line warriors and managed almost all aspects of cancer care. However, the patients, whose minds and bodies are the real battle fields, have multitude of issues during the course of treatment which remain under-addressed. Palliative care (PC) is the art and science which focuses on patient centric treatment approach. Unfortunately, PC is mistakenly assumed to be the care of terminally ill patients and has often been sought only at very advanced stages of cancer. This may largely be blamed on the seemingly incognizable meaning attributed by most people, including the medical fraternity to 'palliative care'. PC essentially means supportive care, comprehensively defined by World Health organization as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening or life limiting illness, through the prevention and relief of suffering by means of early identification and treatment of other problems, physical, psychosocial and spiritual" [3]. Early commencement of PC concurrently with other anticancer treatment modalities has demonstrated higher patient and caregiver satisfaction, lower costs and better patient reported quality of life (QoL) [4-6].

The current review article focuses on the spectrum of symptom burden in women with Ca.Cx and highlights the urgent need for an early integration of PC into the framework of the Oncological management.

Early Commencement of Palliative Care

A patient with Ca.Cx requires multimodality management. Early stage of Ca.Cx from FIGO IA to IB2 are commonly managed by surgery with or without adjuvant therapy; FIGO IB3 to IVA are managed by concurrent chemoradiation; patients with FIGO IVB disease are managed by chemotherapy (CT) and radiotherapy (RT) with a palliative intent [7]. Common consensus from several studies reflects that patients benefit from an early initiation as well as longitudinal integration of PC along with a tumor directed anticancer therapy [8]. PC must ideally commence right from the diagnosis through the entire course of disease management and beyond.

Breaking the Bad News

The diagnosis of Ca.Cx is often communicated abruptly and incompletely in busy clinics owing to lack of time to explore the woman's response and understanding of this life altering diagnosis. Breaking bad news is frequently assumed to be difficult, primarily due to the little importance given towards

development of communication skills during the training period [9]. The communication of diagnosis, goals of treatment, its complications and prognosis in an empathetic and genuine manner requires considerable expertise [10]. Oncologists struggle with complex scenarios like collusion, where families decide upon nondisclosure of diagnosis and prognosis of cancer to the patient, and force the oncologist to comply with the same. This creates an imbalance between the patient's understanding and expectation versus what her oncologist can deliver, thus jeopardizing the physician-patient relationship [11,12]. Integrating a PC team into outpatient care improves issues of communication by allowing the benefit of inter-disciplinary services [8].

The Four Dimensions of Palliative Care

PC caters to physical, psychological, social and spiritual dimensions of a patient's needs.

Physical Dimension

The primary symptom complexes experienced by patients with cervical cancer are pain, vaginal bleeding, vaginal discharge, gastrointestinal symptoms, genitourinary symptoms and limb oedema. PC plays a pivotal role in symptom management to improve patients' compliance to treatment. However, patients often get referred to PC services only at advanced stages of disease, after she has spiralled down to a poor performance status or has a symptom crisis. The median interval between registrations in the oncology wing to being referred to palliative care was as late as 120-190 days as demonstrated Atreya et al. [13] and Dalal et al. [14] respectively. This highlights the troubling fact that clinicians are hesitant to refer patients for symptom management during anticancer treatment, probably under the misconception of destroying patient's hopes.

Pain

Pain is one of the most dominant presenting symptoms in more than 70% of these patients [13]. Oncologists must be cognizant of the concept of 'total pain' described by Dame Cicely Saunders, which encompasses the physical, psychological, social and spiritual dimensions of a patient's suffering [15]. Physical pain may be classified broadly into tumor related causes and treatment related cause.

Tumour Related Pain

Locally advanced cervical lesions extending up to the pelvic side walls with direct involvement of pelvic and presacral muscles by the primary tumor stimulates nocciceptors triggering a somatic variant of nociceptive pain [16,17]. Involvement of smooth muscles of the uterine myometrium, rectum, bladder and other hollow viscus triggers off a visceral variant of nociceptive pain, which is often described as poorly localized, spasmodic or colicky pain. Impingement or direct involvement of the lumbo-sacral plexus results in a neuropathic variant of pain, which has a characteristic deep ache in the neuro-dermatomal distribution with a referred pattern. Metastatic foci in the bones result in a combination of nociceptive and neuropathic pain depending upon the size of the lesion. A large metastatic lesion in the liver causes diffuse visceral pain due to the stretch of Glisson's capsule. Tumor induced bowel obstruction sets off a classical intermittent colicky pain associated with bilious or feculent vomiting and constipation or obstipation [16,17].

Treatment Related Pain

Colicky abdominal pain is also a common symptom arising from other causes such as post-operative sub acute intestinal obstruction, radiotherapy or chemotherapy induced enteritis. RT for cervical lesions involving lower third of the vagina, often manifest with painful acute radiation induced dermatitis. Radiation induced acute cystitis and proctitis present with uncomfortable dysuria and tenesmus. These treatment related pain complexes will undoubtedly hamper the compliance of the patient to treatment, if not identified and managed effectively.

Pain and PC specialists play a crucial role in providing optimum relief in patients with cancer pain. The WHO analgesic ladder [18,19] is an excellent guide to titrate analgesics as shown in Figure 1. Adjuvants such as corticosteroids, antidepressants, anti-epileptics, antispasmodics, muscle relaxants, sedatives etc are useful drugs which can be combined at any step of the analgesic ladder. Readers are referred to the guidelines for detailed pharmacological management of cancer pain as elaborated by Ramanjulu R et al. [20].

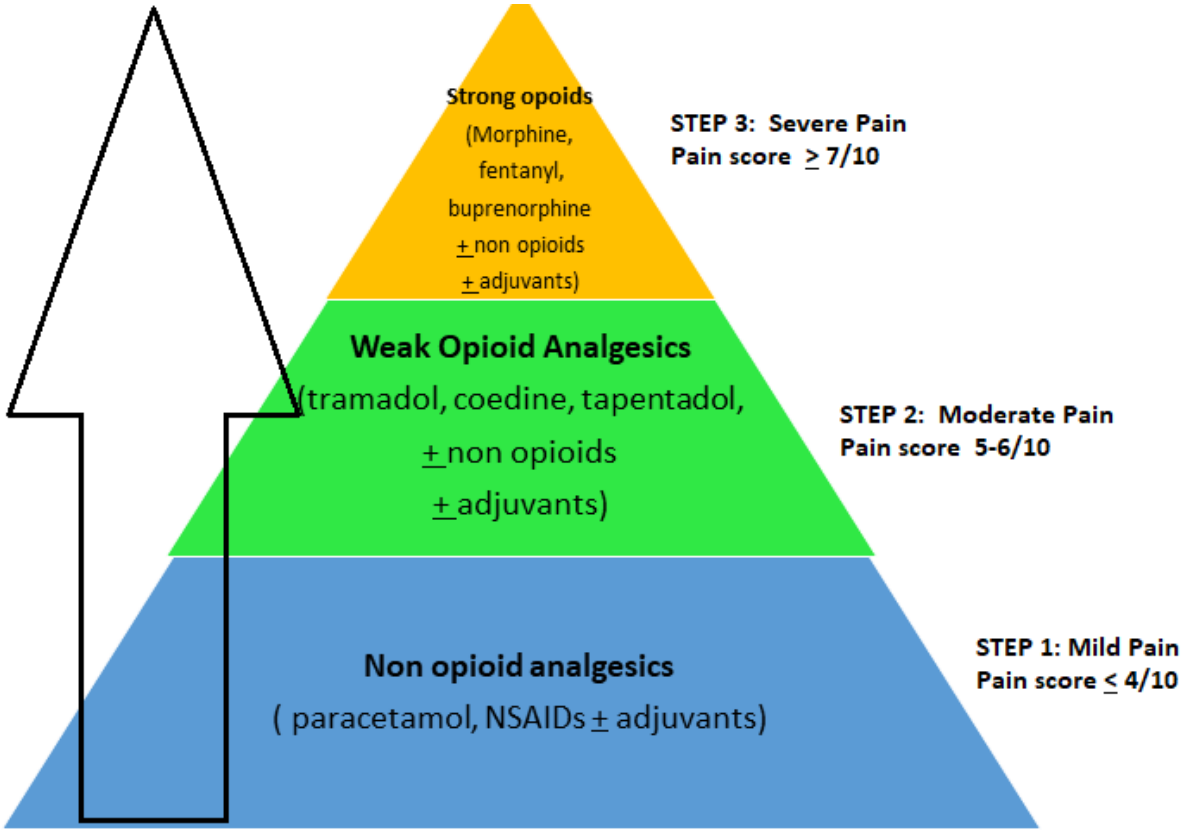

Figure 1: WHO analgesic ladder [17-19].

Bleeding

Bleeding is the presenting symptom in most patients with Ca.Cx. Large volumes of acute or chronic blood loss due to menorrhagia, metrorrhagia or post-coital bleeding often leaves these patients with moderate to severe anaemia at baseline. Pre-treatment baseline haemoglobin has been identified as an independent poor prognostic factor for both local control as well as overall survival in patients with Ca. Cervix [21-24]. A torrentially bleeding cervical tumor can be potentially life threatening and must be managed swiftly with adequate haemostatic vaginal packing, intravenous haemostatic agents such as tranexamic acid or hemocoagulasebotro phase and packed cell transfusion [25,26]. Other historically used vaginal hemostatic agents such as 4% formalin solution [27], Monsel's solution of 20% ferric sulphate [28,29] may be avoided as they have little evidence. Patients with recurrent and progressive disease also suffer chronic blood loss resulting in persistent fatigue and QoL. PC becomes essential in both the above scenarios which will allow multidisciplinary joint decision making as to which patient would benefit from an aggressive radical therapy and which patients may have limited benefit and would be served better by palliative measures alone.

Palliative hypo-fractionated RT is an excellent haemostatic option. It may however, not be available, affordable or accessible to patients in low-resource settings, where, the above-mentioned measures remain the mainstay to tide over the crisis [30]. A patient with a large bleeding tumor along with obstructive uropathy may neither tolerate nor benefit from radical chemo-radiotherapy. Local palliative RT with regimens such as 20-25Gy in 5 fractions [31] to 30 Gy in 10Gy/Fraction once every 4 weeks [32,33] may be more suitable with integration of other palliative measures. Choice of a larger dose per fraction depends on the expected survival of the patients as they may present with late gastrointestinal morbidity [34]. Radical measures such as uterine artery ligation or radio embolization must be attempted only for a patient with good performance status, to whom a reasonably good outcome can be offered with further curative therapy.

Profuse foul-smelling vaginal discharge stigmatizes the patient within their own family and society. This could occur due to the co-existent anaerobic bacterial or fungal infection within large necrotic tumors. Advanced or recurrent cervical lesions may present with rectovaginal or vesico-vaginal fistula. Chronic dribbling of urine and stools through the fistula is another ethology of vaginal discharge, which leaves the patient thoroughly debilitated. The offensive smell is further responsible for inducing nausea, vomiting and anorexia. Untreated vaginal discharge also creates moist desquamation of the vulval and perineal skin with severe burning type of somatic pain. Poorly managed unhygienic patients with long standing large cervical growth may also present with maggot infestation.

Patients presenting with advanced local disease in resource limited oncology centres often get lost in the long waiting lists and invariably end up with debilitating fistulae [35,36]. Such patients need care extending beyond palliative RT alone. George R et al. [37] have presented an excellent description of the real-life scenario which highlights the pressing need of appropriate and timely referral to PC physicians. Training the patient to maintain genital hygiene and use clean homemade sanitary napkins is of utmost importance. Periodic vaginal douching with twice a day using metronidazole (5-10 tablets of sugar free metronidazole 200mg crushed into 500 ml of boiled water) alone or in combination with vinegar (one part in four parts of water) and sodium bicarbonate (one tablespoon in 500ml warm water) has proven

useful to control the infection and smell [38].

Based on their 10-year retrospective cohort, George et al[39] have proposed long term low dose oral metronidazole, based on a clinical grading criterion called Smell-Nil, Faint, Foul, or Forbidding (SNIFFF) ladder. They have used oral metronidazole at 400mg three times a day for one week followed by maintenance dose of 200 mg once a day. Breakthrough smell has been treated with 400mg three times a day for 1-2 weeks. The rates of fistulae have been successfully lower (22.4% vs 41.7%; p =0.005) with longer fistula free survival of (42.9 months vs 14.1 months; p< 0.001) in their series. This is worth exploring in a prospective manner, especially to suit the needs of resource limited facilities as it is easily accessible, applicable and cost effective.

Women with large necrotic cervical lesions with foul smelling discharge, when neglected, pave way for maggot infestation, known a myiasis. Warm tropical climate, poor hygiene and exposed dead host tissue make it conducive for the Musca domestica to lay their eggs. Genital maggot infestation requires sensitive management by palliative care teams [40]. Using turpentine oil on the lesion will allow the larvae to crawl out. Without shining light, these larvae must be carefully handpicked using forceps, keeping the patient under good analgesic and anti-inflammatory support. The malignant wound must be debrided, dressed with metronidazole and kept covered at all times to avoid any further infestation. Patel et al. [41] recommend a Triple therapy with oral Ivermectin 12 mg per day for 3 days, Albendazole 400 mg two times a day for 3 days and Clindamycin 300 mg thrice a day for 5 days, supplemented with turpentine oil dressing to treat maggot infestations. They report patients to have a significant improvement in the pain, odour, exudation, itching, bleeding, oedema, number of maggots as well as the distress scores (p<0.05).

Gastro-Intestinal Issues

Nausea and vomiting are crippling symptoms in patients with Ca.Cx due to radiotherapy, chemotherapy, intestinal obstruction due to tumor/surgery/radiotherapy, liver metastasis or hypercalcemia. According to the European Society of Medical Oncology (ESMO) and the Multinational Association of Supportive Care in Cancer (MASCC)[42], pelvic RT is considered to have low emetic risk (30-60%) whereas, extended field RT to cover para-aortic nodes poses moderate emetogenic risk (60-90%). Cisplatin, the most commonly used platinum CT agent in Ca.Cx management is a highly emetogenic drug with a >90% emetogenic potential. It has an acute (within 24 hours of CT administration), delayed (beyond 24 hours of CT administration) as well as an anticipatory emetogenic pattern. Symptom management in PC relies on addressing the pathophysiology as elaborated in Table 1.0. Dopamine antagonists like metoclopramide and domperidone may be avoided in Radiation induced nausea and vomiting (RINV) in view of their prokinetic properties which will increase the radiation induced hyper-peristalsis [43]. The extrapyramidal adverse neurological effects also make dopamine antagonists a poor choice of antiemetic.

Etiology	Patho-physiology	Management of Choice [44,45,46)

Radiation induced nausea and vomiting (RINV)	Release of serotonin or 5 hydroxytryptamine (5HT) by the enterochromaffin cells, damaged by radiation induced gastro-intestinal mucositis	5 hydroxytryptamine-3 ($5HT_3$) receptor antagonists: ondansetron, granisetron, palonosetron
Chemotherapy Induced Nausea and Vomiting (CINV)	Stimulation of chemoreceptor trigger zone (CTZ)	Triple drug regimen of neurokinin 1 (NK1) receptor antagonist- Aprepitant, $5HT_3$ antagonist with dexamethasone.
Intestinal Obstruction	• Physical obstruction leading to accumulation of secretions and reverse peristalsis • Functional obstruction due to hypokalaemia induced paralytic ileus	• Medicalmanagement: decompression with nasogastric tube; iv fluids • For those passing flatus: trial of prokinetics and enema (if constipation is the aetiology) • For those with obstipation: Prokinetics are contraindicated • Antisecretory agents: 5HT3 antagonists, Hyoscine butyl bromide and Octreotide. • Trial of Steroids to reduced oedema • Surgical correction as clinically indicated • Correction of hypokalaemia
Liver Metastasis	Stretch of Glisson's capsule causing visceral pain and vomiting	Corticosteroids-Dexamethasone
Hypercalcemia	Autonomic dysfunction, smooth muscle hypotonicity and increased residual gastric volume	Intravenous Hydration, forced diuresis with loop diuretics; Bisphosphonates; Calcitonin
Chronic Constipation	Obstructive aetiology	Appropriate Laxative and high fibre diet, Digital evacuation and enema when clinically indicated

Table 1: Etiopathology and Management options for vomiting as a symptom in patients' with Ca.Cx.

Constipation may be caused by organic causes, functional or treatment related causes. In a patient with carcinoma cervix, anorexia, dehydration, poor intake of food, lack of exercise, use of opioid medication, hypercalcemia and tumor related obstruction are a few important ones amongst the plethora of aetiologies [47]. 'One size fits all' approach of laxative usage cannot be applied to treat constipation in Oncology [48,49]. Patients with advanced Ca.Cx on morphine for pain relief may end up with repeated and severe constipation, if not educated about the importance of taking the prescribed laxative. Stimulant laxative such as bisacodyl is the drug of choice to treat opioid related constipation, both prophylactically and therapeutically, along with stool softeners such as docussate. Bulk forming laxatives

like isphagula husk and osmotic laxatives such as lactulose can be counter-productive when prescribed to treat opioid induced constipation.

Often patients may be prescribed laxatives without appropriate per rectal examination in busy clinics. A patient with impacted stools will not benefit from any laxative and manual digital evacuation is mandatory to offer symptom relief. Patients with chronic constipation might have hard stools in the high rectum or sigmoid colon which may be above the reach of a routine low rectal sodium phosphate enema. Instillation of a high rectal sodium phosphate enema requires trained nursing personnel. Such advanced symptom management would not be possible without seeking PC references at the appropriate time intervals.

Diarrhoea

Pelvic RT and CT produce gastrointestinal mucositis resulting in hyperperistalsis and hypersecretory diarrhoea. Uncomplicated diarrhoea is best managed by antimotility agents such as loperamide at a standard dose of 4mg to begin with, followed by 2 mg every 4 hours or after each unformed stool (maximum dose of 16mg/day); continued for 12 hours following resolution of diarrhea [50,51]. Octreotide is a somatostatin analogue with anti-secretory properties. It has been evaluated in the prospective setting to treat acute radiation enteritis with conflicting outcomes. Subcutaneous short acting octreotide injections at 100 micrograms three times a day have been shown to resolve acute radiation enteritis within 3 days in comparison with diphenoxylate (61% vs 14%; $p < 0.002$) by Yavuz et al. [52]. However, Zachariah et al. [53] report no benefit when long acting Octreotide preparations have been used. Routine application of octreotide has, thus been limited by the paucity of evidence for its use, its injectable route of administration and high cost.

Complicated diarrhea with abdominal cramps, mucus or bloody discharge per rectum and fever can progress to sepsis and must be worked up for *Clostridium difficile*, *Escherichia coli*, *Salmonella typhi* and other infectious agents. Antimotility agents are contraindicated; aggressive management with appropriate antibiotics and supportive care must be commenced at earliest [51].

Genito-Urinary Issues

Urinary urgency and dysuria are common acute toxicities associated with RT, which are managed by the primary team using adequate hydration, urinary alkalization and antispasmodic medication such as flavoxate. Late radiation induced haemorrhagic cystitis is difficult to treat, where cold saline bladder wash and irrigation with 1% potash alum are the commonly used methods.

Obstructive uropathy is a common presentation in patients with locally advanced Ca.Cx, especially owing to the delay in seeking medical care by patients, coupled upon by long waiting periods for treatment. A judicious decision making requires a multidisciplinary team involving radiation oncologist, gynaecologic oncologist, urologist and the palliative care specialists for such patients. National cancer grid consensus guidelines for management of Ca.Cx recommend palliative RT for patients presenting with obstructive uropathy with serum creatinine>3mg/dl [7]. Urinary diversion with percutaneous

nephrostomy followed by radical CT-RT are of limited benefit to such patients, as they perform poorly with a survival of less than 8 months [54,55].

Lower Limb Oedema

Varying degrees of lower limb oedema in patients with Ca.Cx can be attributed to lymphedema, deep venous thrombosis (DVT), hypo albuminemia and chronic renal failure. Lymphedema may be an outcome of advanced malignancy blocking the lymphatic channels or disruption of the lymphatics by surgery and pelvic radiotherapy. Most oncologists have little help to offer with lymphedema, which is in reality, can be very debilitating. Palliative care specialists play an irreplaceable role in long term management of lymphoedema [56,57]. Skin care of the affected limb is the first step to avoid any trauma that may precipitate cellulitis. Patients and caregivers must be trained to pay attention to details such as trimming nails with clippers, avoiding razors, wearing protective footwear, moisturizing the skin and prompt antiseptic application of any small wounds or insect bites. Use of exercises, limb elevation and graded compression garments along with manual lymphatic drainage by trained palliative care personnel is a part of this multipronged management of lymphedema.

Psychological Aspects

Clinicians often underestimate the psychological distress experienced by patients with Ca.Cx. Women remain silent as they lack opportunity to express their distress. Srivastava et al. [58] have identified nearly 55% of patients with Ca.Cx suffer from various psychologic morbidity; with 26% having major depressive disorder, 17% with anxiety disorder and 8% with adjustment disorder. Feelings of humiliation, anger, hopelessness and helplessness often remain unvoiced until probed by keen and patient physicians. Urbaniec et al. [59] have elaborated the several unmet needs of survivors of gynaecologic malignancies among which the fear of recurrence of the disease post treatment and the lack of free communication with the treating team seem to be the major concerns. Age> 65 years and those with pre-existing comorbidities are major risk factors for depression among these patients [60]. Insomnia is another crucial factor, which determines a patient's perception and tolerance to pain [61].
External beam RT followed by brachytherapy is the mainstay of management of Ca.Cx with excellent local control rates. The improvement of overall survival has now made post treatment QoL an important aspect of oncological care. Pelvic RT does lead to inevitable long-term toxicities such as vaginal dryness, varying degrees of vaginal fragility and fibrosis which cripple the patients' sexual lives. Jensen et al [62] have reported as large as 85% of women to have low or no sexual interest, 35% with lack of lubrication, 55% with pain during coitus and 50% with reduced vaginal dimensions. Patients treated by conventional two field technique on tele cobalt develop painful subcutaneous fibrosis of the anterior abdominal wall. Sexual and body image concerns are often the root cause of abandonment of the women by their spouse, which further complicates their psychological morbidity.

Unless clinicians have a keen eye to identify and support these psychologic issues in a patient, compliance to treatment as well as post treatment QoL will be severely impaired. Supportive psycho-oncologic evaluation and therapy must be mandatorily integrated in all Oncology setups. Patients must receive the benefit of cognitive behavior therapy, coping mechanisms, appropriate counseling and

specialist medical management when clinically indicated [63].

Social and Spiritual Aspects

Owing to the social stigma attached to this diagnosis, patients fail to come forward early in the course of their symptoms. As a consequence, advanced loco regional disease and distant metastasis is a common presentation, especially among patients hailing from rural and low socio-economic background. With issues of accessibility and affordability, long term care becomes an ordeal and they are often considered a financial burden by their family.

While cancer treatment has been made more accessible and affordable through various financial schemes, social support systems must be created to ease the care giver burden which may reduce abandonment issues. Public health awareness programmes are the need of the hour to educate the masses regarding increasing rates of Ca.Cx. This will allow screening programmes to become more acceptable in the society.

Patients often face spiritual crisis such as 'Why me?' and search for meaning within their suffering and existential concerns [64,65]. Patients with progressive Ca.Cx and terminal cancers confront issues of death and dying. It is imperative for oncologists to understand their limitations in addressing such spiritual concerns. These complex issues require psychotherapeutic counseling and interventions by trained psycho-oncology professionals [66]. Identifying this requirement and enabling the patient and their caregivers to obtain the same is the responsibility of every Oncologist in order to achieve the goal of holistic care of a cancer patient.

Patients with Progressive Malignancy and End of Life Issues

Advanced Ca.Cx with progressive disease or recurrence may not be amenable to curative therapy. At this juncture, stopping further aggressive CT must not be deemed a failure because, truth be told, it yields minimum benefit at a heavy cost of impaired QoL [67]. It would be rather prudent for Oncologists to avoid overtreatment and refer patients for intensification of advanced PC. The need for advance care planning and transparent communication is mandatory to educate patients and care-givers to anticipate and deal with difficult symptoms. This avoids futile admissions of terminally ill patients to intensive care units, which can be both financially and emotionally draining to the patient and care givers.

Hospice Care

A gradual transition to hospice care must be executed to cater to the needs of terminally ill patients. Inaccessibility, under-availability and underutilization of hospice care remains a pressing issue in Oncology [67,68]. Communicating poor prognosis accurately and having delicate end-of life conversations require skilled PC teams; which will eventually allow the patients and families to plan their life events ahead, resolve conflicts and cater to any unfinished business which has a deep familial significance after bereavement [69]. Issues pertaining to advanced directives, extent of resuscitation and palliative sedation are important domains of advanced PC for dying patients [70].

Palliative Sedation

Metastatic cervical cancers within tractable symptoms such as dyspnoea or delirium can be a terrifying ordeal for both the patient and family members. Palliative sedation is defined as "the monitored use of medications intended to induce a state of decreased or absent awareness in order to relieve the burden of otherwise intractable suffering in a manner that is ethically acceptable to the patient, family and health-care providers" by European Association for Palliative Care (EAPC) [71]. Well trained PC teams play a vital role in initiating and maintaining palliative sedation. It is important for oncologists to be aware of the unequivocal differences that exist between palliative sedation and euthanasia and appropriately refer patients in agony to be cared for and managed by palliative care teams [72,73].

Conclusion

Patients with Ca.Cx experience a vast magnitude of symptoms which remain inadequately addressed, in the currently existing disease-centric treatment approach. Early integration of PC in tandem with radical anti-cancer therapies will allow a holistic patient-centric cancer management.

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