Prognostic Factors for Carcinoma of the Uterine Cervix Treated with Concurrent-Chemoradiotherapy

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Abstract: Carcinoma of the uterine cervix is most commonly staged with the FIGO (Fédération Internationale de Gynécologie et d'Obstétrique) system, which is essentially based upon benevolent intentions of simplicity and accessibility. Locally advanced carcinoma of the cervix (LACC) is defined as disease belonging to stages which are not amenable to routine upfront surgery. Staging for any cancer can be expected to provide valuable information with regards to prognosis and in choosing the appropriate and optimal pathway of clinical management. Hence, it could be said that improper staging or inadequate staging can lead to improper management. Carcinoma of the cervix (CC) continues to be staged by the FIGO system, which continues to ignore proven prognostic factors such as lymph nodal involvement, volume of disease and various other factors. This review intends to acquaint the reader about the exhaustive list of prognostic variables which are of potential significance in predicting prognosis, in determining optimal treatment, in predicting outcomes of treatment and possibly suggesting a subset of patients who may benefit with modified or intensified treatment strategies.

Keywords: Locally advanced carcinoma of the cervix, uterine cervix, staging in ca cervix, lymph node in ca cervix, prognostic factors in cancer cervix, predictive factors in cancer cervix.

INTRODUCTION

LACC is one of the leading causes of cancer deaths throughout the world, and more-so in Asia. LACC by convention is treated with radiation based treatment, most often with concurrent-chemo-radiotherapy (CCRT). CC is staged world-wide with the use of the FIGO system, which though very convenient and widely applicable, is prone to various flaws which could arise from subjectivity as well as by the obvious fact that the FIGO system gives no value to established prognostic factors such as lymph-nodal involvement, disease volume, etc. Despite of a supposedly high radiosensitivity of LACC, the local control and survival rates remain dismal. In light of the prognostic value of the presence of involved lymph nodes, the 7th edition of the AJCC (American Joint Committee on Cancer) has recommended that patients with involved lymph nodes (LN) be staged 'IIIB". LN involvement and disease volume are best characterized and quantified by histopathology, which however is not feasible with LACC which is primarily treated with radiation based treatment, and this is a point in the favour of the FIGO staging system.

However, the recent decades have witnessed the rise of newer imaging techniques with higher predictive values. Additionally, the cervix is a rather easily accessible organ from which tumour samples can be obtained with ease for characterization by methods in the laboratory. Staging in any malignancy can be expected to be a constantly evolving technique, with timely incorporation of newly identified prognostic factors to augment the value that the staging system could offer for predicting prognosis, deciding optimal treatment and in detecting treatment outcomes. For example, since the AJCC discovered that histology is an independent prognostic factor for oesophageal carcinoma, the 7th edition did modify the 'TNM' system to include tumour histology as well, though originally the AJCC-TNM staging system was devised to assign a stage as per the status of the primary tumour, regional nodes and the presence or absence of metastases. Hence, the future holds for the integration of certain prognostic factors into staging systems, which would more accurately categorise carcinoma of the cervix with regards to prognosis and at the same time helping identify patients who could need more aggressive treatment strategies.

The current review is an attempt to elucidate the various patient-related and disease-related prognostic factors. In addition, newly identified factors based upon advanced laboratory (Table **1**) and imaging modalities

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Table 1: Prognostic Implications of Laboratory Based Histopathological and Serological Tests

TEST	Value	References
FROM TUMOUR BIOPSY		
Histopathology	Varying response and prognosis with SCC, adeno, adeno-squamous variants	[4, 53-59]
Grading	Nuclear and cytoplasmic grade of differentiation could be progonostic	[60,61]
EGFR	Cell-surface staining of EGFR and cytoplasmic staining of pEGFR are predictive of response and survival	[106-114]
COX-2	Expression may hold value in predicting response and disease-free survival	[99-105]
HPV/p-16	p16 (as a surrogate for HPV infection) or the detection of HPV DNA could be predictive of tumour behaviour, sensitivity and survival	[121-125]
MMP	MMP-2 & MMP-9 could be surrogates for tumour invasiveness and metastatic potential	[127,128]
EMMPRIN	Predictive of invasive and metastatic potential	[129]
Cathepsin-B	Predictive of invasiveness and nodal involvement	[132]
NF-kB	Predictive of loco-regional and distant failure	[134]
CXCR4/CCR7	Predictive of nodal involvement and survival	[135]
FROM SERUM		
SCC-Ag	Predictive of nodal involvement, response and relapse-free survival	[93-98]
CEA	May compliment SCC-Ag	[126]
CA-125	Potential value in adenocarcinoma in predicting LN involvement and survival.	[130,131]

are described. Lastly, an outline of the treatment related factors which have an un-ignorable impact on outcome are also elucidated.

PATIENT RELATED FACTORS

Age

Age has been for long considered as a prognostic factor in LACC, but its significance as an independent determinant of prognosis is unknown. Many studies have observed that patients younger than 35-years were likely to have lower OS (overall-survival) and higher recurrence rates when compared to patients older than 35-years, after matching for other possible prognostic factors [1,2]. It has also been noted that histologies with poorer prognosis such as adenocarcinomas and adenosquamous-carcinomas are commoner in younger patients [3,4].

The significance of age as an independent prognostic factor is currently unknown, though in general there is a decreased survival with patients who are younger than 35 years and in those who are older than 70 years [5-8]. The poorer outcome in the very young could imply an unidentified cause of aggressive tumour biology, such as, early sexually-transmitted exposure to aggressive strains of HPV. The poorer survival in the very elderly can easily be attributed to the higher prevalence of life-limiting co-morbidities and the difficulties associated with completing ideal treatment due to low tolerance for toxicities.

Anemia

The correction of anaemia in the patient of LACC being planned for radiation therapy (RT) should be performed as early as possible, preferably before the initiation of RT to maximise the benefits. Routinely used photon-beam RT has high OER (oxygen enhancement ratio), hence, well-oxygenated tumours are more likely to be radiosensitive [9-11].

The optimal value of hemoglobin is undefined. In a retrospective analysis involving a large database of 2,800 patients of CC, it was found that a pre-treatment value < 12g/dL holds high significance as a poor prognostic-factor [12,13]. However, not all studies have found an unequivocal benefit with increasing hemoglobin to above 12g/dL [14,15]. Additionally, there are risks associated with blood transfusions, such as transfusion associated infections and adverse reactions. But given the rationale that low hemoglobin levels blunt radiosensitivity, it would be justifiable to maintain hemoglobin to at-least 10g/dL before the initiation of treatment.

Due impetus must also be placed on the value of hemoglobin across the course of CCRT. This is

important, given that patients of LACC may suffer a decrease in haemoglobin during CCRT due to bone-marrow toxicity. In addition to blood-transfusions, maintenance of haemoglobin during CCRT may be augmented by the supplementation of haematinics. Precautions should be in practise against bleeding, which could be spontaneous, or iatrogenic (such as during brachytherapy).

A fact which has not yet been adequately addressed in literature is regarding the qualitative aspects of hemoglobin levels. Transfused blood may lead to a quantitative increase in hemoglobin, but the functional ability of stored blood may not be equivalent to that of endogenously synthetized hemoglobin.

Increasing endogenous hemoglobin with the use of erythropoietin seemed to be unacceptable since a phase-3 trial (conducted to compare the benefit of maintenance of a hemoglobin level at or above 12g/dL with erythropoietin versus the maintenance of hemoglobin level at-least at 10 g/dL with transfusions) had to be prematurely closed due to an unexpected increase in thromboembolic events involving erythropoietin.

Tumour hypoxia can be due to anaemia, as well as a result of various other factors in the tumour micro-environment, such as necrosis & improper tumour vasculature [16,17]. Dellas *et al.* [16] observed significantly higher levels of hypoxia-inducible factor-1a (HIF-1*α*) among patients with Hb < 11g/dL. Tumour hypoxia as a prognostic factor will be discussed subsequently in this article.

Renal Status

In reality, all large scale trials utilize inclusion criteria which demand 'normal renal function'. Hence, the optimal treatment for subsets of patients with sub-optimal renal function is largely undefined.

LACC involves treatment with CCRT with cisplatin as the standard of care. However, the clinical dilemma involves the fact that cisplatin is nephrotoxic, and that a considerable proportion of LACC may present with compromised renal function as a result of obstructive nephropathy. The FIGO-system upstages patients with disease not extending to the lateral pelvic wall to 'stage-IIIB' provided there is hydronephrosis which is not attributable to other causes. This implies that the FIGO recognizes obstructive nephropathy as a poor-prognostic factor.

An incidental detection of deranged renal function tests should always prompt the search for non-obstructive causes of renal dysfunction, such as intrinsic or pre-renal causes, which often can be reversible.

Medical Co-Morbidities

Co-morbid life-limiting diseases such as severe diabetes, hypertension and cardiopulmonary afflictions may inflict higher risk of mortality often by themselves. This could be a cause for lower OS among series involving the very elderly patients. Uncontrolled medical conditions reduce performance status, and compromise the patient's likelihood of tolerating an aggressive course of CCRT.

Pulmonary conditions such as chronic-obstructive-pulmonary-disorders and bronchial-asthma should be corrected prior to initiation of RT, since obvious benefits exist with improved performance status and enhanced oxygenation.

Surgical Co-Morbidities

Prior surgery in the abdomino-pelvic area can induce adhesions limiting small bowel mobility which may increase the risk of small bowel toxicity, hence compromising successful completion of RT [18,19]. No specific studies could be found regarding the impact of abdomino-pelvic RT among patients with hernias. Theoretically, increased bowel toxicities can be expected among patients with hernias containing bowel loops, especially if they lie within the RT portals.

Human Immunodeficiency Virus (HIV)

HIV infection and its consequential immunosuppression allows for an unperturbed proliferation of the human-papilloma-virus (HPV). Patients with HIV may have rapidly progressive tumours, and have a higher risk of tumour recurrence after RT and also have a shorter duration of remission in comparison to HIV negative patients [20,21].

In addition, the use of chemotherapy in these patients may be associated with an increased risk of opportunistic infections since marrow suppression may further reduce the already diminished CD4 T-lymphocyte count. The role of highly-active-anti-retroviral-therapy (HAART) and its safety in conjunction with chemotherapy is a grey-area not backed by clear guidelines or definitions.

Psychological Factors

Some patients may be at higher risk for psychological issues- the very young, the very old, those with lack of social support, those with other stressful life events, those with prior history of psychiatric illnesses, those belonging to families with financial and marital difficulties.

Patients with psychological issues may present at advanced stages, may have unsatisfactory compliance to treatment, and hence may suffer an overall poor outcome. Patients with certain somatoform disorders may additionally suffer an exaggerated discomfort from the expected nausea and gastrointestinal upset during CCRT, and may force more treatment breaks upon their course of therapy.

Attempts at counselling to indicate the need for adherence to treatment, and prior honest disclosures of the expected toxicities during treatment may reduce distress which may otherwise arise during the course of treatment [22].

Socio-Economical, Racial and Regional Factors

Patients with lower socioeconomic status may present at more advanced stages, and may often not be able to afford the 'standard of care' Though some studies have highlighted a difference in prognosis with regards to race, it could be that confounding socio-economic factors, comorbidities and regional factors may have played a role. As an illustrative example, a patient in a country with no RT facility with a stage-IIB cancer of the cervix will have a dismal prognosis in comparison to a patient with a higher stage disease, living in a country with abundant resources with regards to therapy and supportive services [23-25].

DISEASE CHARACTERISTICS AS PROGNOSTIC FACTORS

FIGO Stage

The FIGO system has many shortcomings (Table **2**). Most notably, the system is oblivious to the lymph-nodal status. In addition, subjective inaccuracies very commonly affect the interpretation of stage. An analysis of 290 patients reported errors ranging from 24% for Stage-IB, increasing to 67% for Stage-IVA [26]. In-spite of various shortcomings, the FIGO stage is indeed prognostic, increasing stage portending decreasing survival (Table **3**).

While the FIGO system stands by its principle of being applicable even by the lowest resource settings, the AJCC staging in its latest edition of the TNM staging has recommended that patients be staged-IIIB in the event of LN involvement [27]. The risk of LN involvement as per FIGO-stage is illustrated in Table **4**.

Table 2: Shortcomings of the FIGO Staging System for Carcinoma of the Cervix

SHORTCOMING:
Does not consider tumour volume in any way beyond Stage-IIA onwards, though volume of disease can influence local control, survival and may correlate with risk of extra-pelvic metastasis [28,29].
Does not regard lymph nodal involvement even though lymph-nodal involvement drastically decreases survival [30-36].
Does not regard uterine corpus extension even though uterine corpus extension may be predictive of lymph-nodal involvement and poorer outcome [66-71].
Does not take histology into consideration, though non-squamous histologies are associated with poorer response and survival [4,58,59].
Large intra-stage variations can occur, extent of parametrial involvement may be minimal to massive, but still stage remains un-altered.
Overlooking prognostic factors beyond FIGO stage may lead to under-treatment.

Table 3: Approximate 5-Year Overall-Survival with Regards to FIGO Stage

FIGO stage	Prior to CCRT era [55,61,66,143]	Current CCRT era [55,66,178-180]
IB	85%	95%
IIA-IIB	70%	77%
IIIA-IIIB	40%	43%
IVA	15%	18%

Table 4: Risk of Lymph-Nodal Involvement as Per FIGO-Stage [37,38,48-50,55,66]

FIGO stage	Pelvic LN+ (%)	Para-aortic LN+ (%)
I	10-15%	0-7%
IIA	20-25%	10-15%
IIB	35-45%	15-20%
IIIA	50-55%	25-30%
IIIB	70-80%	30-40%
IVA	85-95%	45-50%

Tumour Volume: 'Intra-Stage' Variations

The FIGO system does not completely ignore 'bulk', as elucidated by the recent division of Stage-IIA into IIA_1 and IIA_2 based on diameter, however with higher stages the system ignores bulk/volume, and relies instead upon disease extent.

Increasing bulk increases complexity of treatment. For an illustrating example, a patient of Stage-IIB carcinoma with minimal parametrial involvement could be amenable for integration of intracavitary brachytherapy (ICBT) early in the treatment; on the other hand, a patient with bilateral bulky parametrial involvement just short of the lateral pelvic wall would still be assigned Stage-IIB, and this patient may or may not attain a suitable configuration for application of ICBT even after EBRT. Increasing tumour volume is associated with higher probability of LN involvement, distant-metastasis, pelvic-recurrence and poorer survival, even within patients grouped into the same FIGO-stage [28,29].

Nodal Status

As per the results of various multivariate analyses, LN involvement has emerged as the single most important determinant of adverse prognosis, even more than FIGO stage [30-35]. The importance of LN status is starkly illustrated by the observation that even among Stage-IB patients, while the 5y OS was 88% among node-negative patients; it reduced to 40% among node positive patients. Among stages IIB-IVA, 5-year OS was observed to be 57%, 34% and 12% among patients with node-negative, pelvic-node positive and paraaortic node positive statuses respectively (Table **5**) [36].

The presence of LN involvement increases in probability with increasing FIGO-stage. The presence of LN disease is amenable to be detected upon imaging; however, all currently available modalities such as computed-tomography (CT), magnetic-resonance-imaging (MRI) and positron-emission-tomography (PET) have been associated with various issues pertaining to sensitivity, specificity, cost and availability (Table **6**) [37-41].

Table 5: Impact of Lymph-Nodal Involvement on 3-Year Disease Free Survival [36]

	Node negative	Node positive
Stage IB-IIA	100 %	67 %
Stage IIB-IVA	56 %	24 %

Table 6: Performance of CT, MRI and PET/CT for Detection of Lymph-Nodal Involvement [37-41,55,139,154]

Modality	Method	Sensitivity	Specificity
CT	*Cut-off short axis 1cm*	35-40%	80-90%
	Cut-off short axis 0.5cm	43-50%	40-50%
MRI	*Cut-off short axis 1cm*	30-40%	80-86%
	Cut-off short axis 0.5cm	50-60%	50-60%
PET/CT	*Fusion imaging*	75-88%	80-90%

Attempts at surgical nodal staging have been unfortunately associated with increasing morbidity and mortality after subsequent RT [48-50]. Various groups in the 1990s suggested laparoscopic nodal staging prior to definitive treatment. However, no statistically significant benefit was observed with this approach [51-52].

Histology

While squamous cell carcinoma (SCC) is the predominant histology in CC, the second most common variety is the adenocarcinoma which makes up 8-20% of CC [53-55]. Various studies have indicated lower response to therapy and poorer overall prognosis for adenocarcinoma, especially for non-early stages, i.e. LACC [56-59].

Adenosquamous carcinoma contains glandular stuctures along with clearly recognizable squamous elements [53]. Adenosquamous carcinomas supposedly have an even more worse prognosis than adenocarcinomas [4].

Grade of Differentiation

Stendahl *et al.* proposed a 'malignancy grading system' for CC which utilized 8 parameters (cell-differentiaion, nuclear-pleomorphism, mitosis, mode of invasion, stage of invasion, vascular invasion & host cellular response). Each parameter could be scored 1 to 3 points, and hence a 'total malignancy grade score' could vary from 8 to 24. Stendahl *et al.* claimed that their malignancy grading system was of greater prognostic significance than staging [60,61].

The significance of tumour-grade however remains controversial [62-63]. Crissman *et al.* did not observe correlation between grade and survival [62]. But a very large recent study demonstrated that keratinizing SCC may be less radiosensitive and associated with poorer survival in comparison to non-keratinizing SCC [64].

Uterine Corpus Extension

Extension to the uterine corpus is quite common due to the interconnected lymphatics between the lower-uterus and the cervix-uteri [65]. The FIGO-system explicitly ignores the uterine-extension of CC. However, various studies have demonstrated reduction in survival and an increase in distant metastases [66-67].

Narayan *et al.* observed an increasing probability of uterine corpus involvement with increasing FIGO stage (58%, 73%, 88% & 100% with stages I, II, III & IV respectively). With the presence of uterine corpus involvement, the probability of node positivity on FDG-PET (^{18}F-fluoro-deoxy-glucose positron-emission-tomography) was significantly higher, and on their multivariate analysis, uterine involvement emerged an independent risk factor for nodal involvement [68-71].

Hypoxia & its Markers

Hypoxia may decrease radiosensitivity, especially with routinely used high-OER photon beams. In addition, hypoxia may also increase tumour aggressiveness and metastatic potential by the induction of mediators of 'angiogenic-response' [72]. Since measurement of hypoxia within tumours would require the invasive insertion of probes, surrogate markers of hypoxia have been sought and investigated. But to be clinically useful, further clarity is needed in the method and timing of testing for surrogates of hypoxia.

Hypoxia-inducible-factor (HIF)-1*α* can serve as an intrinsic marker of hypoxia in CC. HIF-1*α* activates the expression of various hypoxia-response mediators such as *VEGF* (to promote angiogenesis), *GLUT-1* (for enhanced glucose transport), *LDH* (involved in anaerobic glycolysis) and nitric oxide synthase (which too promotes angiogenesis and vasodilatation) [73-76]. Carbonic-anhydrase-IX (CA-IX) expression is also controlled by HIF-1*α*. Studies have associated increased CA-IX to be a predictor of LN involvement [77-79].

Intrinsic Radiosensitivity

'Survival-fraction after 2-Gray' (SF_2) is a measure of intrinsic-radiosensitivity [80-81]. SF_2 involves the measurement of the fraction of cells that survive after 2Gy irradiation. In a multivariate analysis, West *et al.* demonstrated that SF_2 was an independent prognostic-factor for CC treated with RT. Their study observed that the 5-year survival with SF_2 values above and below the median were 51% and 81% respectively [82].

Huang *et al.* [83] proposed a predictive-model for CC treated with RT. The model importantly incorporated 'repopulation' also as a predictive factor. Given that SF_2 is an indicator of radiosensitivity, ultimate 'radio-curability' would require more than just 'sensitivity', since repopulation after good response would offset the advantages of 'good sensitivity' [83,84].

Recently, markers predictive of radio-resistance have emerged. Vidyasagar *et al.* [85] observed that serum glutathione levels performed as early as in the first week of CCRT can be a very early predictor of radioresistance. In addition, galectin-1, which is associated with poor prognosis in head & neck and prostate cancers, is also likely to be a radio-resistance marker for CC [86-88].

Interstitial Hypertension

It has been observed that the interstitial pressure within tumours reduce across the course of fractionated RT. Roh *et al.* hypothesized that such lowering of interstitial pressure could enhance delivery of chemotherapy. Additionally, tumour oxygenation may improve, leading to improved radiosensitivity since a lowering of interstitial hypertension may lead to the opening up of occluded microvasculature [89-90].

HISTOPATHOLOGICAL AND BIOCHEMICAL MARKERS

SCC Ag

Squamous cell carcinoma antigen (SCCAg) is a serologic marker which has the prospects of prognostic

value in LACC, much akin to PSA in prostate carcinoma [91,92]. Pre-treatment SCCAg has shown value as a predictor of LN involvement [93,94] and treatment outcome [95,96]. Post-treatment measurements are predictive of relapse free survival [97].

Oesen *et al.* [98] assessed the prognostic utility of SCCAg by correlation with pre- & post-treatment FDG-PET. Observations were that SCCAg > 30ng/mL at diagnosis was significant LN involvement. The most significant of their finding was that the progression free survival (PFS) was dramatically better in patients having normalization of SCCAg levels after CCRT in comparison to those in whom SCCAg levels failed to normalize (2 year PFS : 62% vs. 0%, p=0.0004).

COX-2

Cyclooxygenase-2 (COX-2) overexpression has been linked to tumor angiogenesis, progression and inhibition of apoptotic response after cytotoxic therapies. Various studies have indicated aggressive behaviour and an unfavorable prognosis for COX-2 overexpressing CC [99,100]. It has been estimated that the prevalence of COX-2 overexpression is around 30%, with adenocarcinomas displaying a higher frequency of COX-2 overexpression [101].

Though COX-2 expression has not been associated with decreased local response, there seems to be a trend towards delayed tumour-regression [102,103]. Higher risk of rapid relapse after regression has been observed with COX-2 overexpressing tumours [100,102].

COX-2 is amenable to be targeted by the readily available agents such as celecoxib. However, there have been no studies to define the optimum dose and schedule of COX-2 inhibitors in CC. Gaffney *et al.* [104,105] reported the RTOG-0128, a phase-2 trial which intended to evaluate the acute toxicities of celecoxib at a dose of 400mg *b.d.* with cisplatin & 5-FU CCRT. They noted significant toxicities- haematological in particular. However, it could be argued that the use of two drugs (cisplatin & 5-FU) for CCRT could in itself have caused the toxicities, and hence further studies are needed to prove or refute the likelihood of benefit with COX-2 inhibition.

EGFR

EGFR (epidermal growth-factor receptor) is overexpressed in 50-70% of cervical SCC, with lower expression among adeno- & adenosquamous carcinomas [106]. Experimentally, it has been shown that the blockade of EGFR in CC induces increased pro-apoptotic gene expression and reduces metastatic potential [107-109].

Perez-Regadera *et al.* observed that overexpression of EGFR membrane staining was associated with an increase in radioresistance. Noordhuis *et al.* found the membrane staining of EGFR, and the cytoplasmic staining of phosphorylated-EGFR (the activated form) are both independent factors predictive of poor response to CCRT [110-113].

Initiation of RT is associated with an increase in cancer cell migration, secondary to EGFR up-regulation. Hence, blocking of EGFR concurrently during RT may be theoretically beneficial irrespective of the level of EGFR expression [114]. Definitive trials are needed before advocating concurrent anti-EGFR therapy with RT.

HPV

HPV gene products may induce many cellular changes- promotes resistance to apoptosis, confers abilities of immune evasion and angiogenesis. HPV also enables bypass of cellular differentiation signals [115-117]. HPV also interferes with the tumor cells' hypoxic response, since they were shown to be capable of enhancing HIF-1*α* levels [72]. HPV may also increase radioresistance in CC by preventing EGFR degradation [106].

Schwarz *et al.* evaluated the prevalence and significance of p16 (an indirect marker of HPV-positivity [118-120]) in a study of 126-patients staged Ib_1-IVb. They observed a significant difference in the mean age at diagnosis- with p16-negative patients being older than p16-positive patients (65 years vs. 52 years; p=0.01). They also noted a trend for poorer response to CCRT in patients with p16-negative tumours. This important study draws one to draw a parallel with head/neck cancers, where cancers in younger patients are known to be HPV/P16 associated, while HPV/p16-negative tumours are commoner in the elderly with chronic exposure to non-viral carcinogens such as smoking and alcohol [121-123].

The detection of HPV in histopathologically negative LNs signifies a higher risk of subsequent recurrence [124,125].

CEA

Before the discovery of SCCAg, the carcinoembryonic-antigen (CEA) was the most

commonly measured tumor marker in CC [3]. Pre-treatment CEA≥10ng/mL is a risk factor for relapse following CCRT [126]. Huang *et al.* observed that elevated levels of both CEA and SCCAg were independent factors predictive of relapse in paraaortic nodes [126]. Thus pre-treatment CEA could possibly be complementary to SCCAg in the design of future predictive nomograms.

MMP

Matrix-metalloproteinases (MMP) are known for their ability for degradation of extracellular matrix, hence promoting dissemination of cancerous cells. The presence of MMP-2 (gelatinase-A) and MMP-9 (gelatinase-B) has been correlated with greater invasiveness and distant-metastases [127]. Ling *et al.* [128] found that the expression of MMP-2 gradually increased with increasing grade of lesion (ranging from 10% in LSIL to 81% in invasive carcinoma; and 91% among LN-positive cases).

EMMPRIN

Tumour cell-surface overexpression of extracellular matrix metalloproteinase inducer (EMMPRIN) is linked to growth, survival, invasive and metastatic capacities. Xu *et al.* [129] observed that pre-treatment EMMPRIN expression was associated significantly with increased risk of pelvic LN metastases. Post-treatment reduction in values of EMMPRIN was prognostic for tumour-specific survival.

CA-125

Elevated pre-treatment serum CA-125 is raised in 20-75% of cases of cervical adenocarcinomas, and this is associated with increased risk of LN-metastasis and an overall poor outcome [130]. Rising CA-125 post-treatment could possibly indicate recurrence of cervical adenocarcinoma [131].

Miscellaneous Markers

Cathepsin-B expression was found to be associated with LN-involvement and greater local invasiveness [132]. Plasma levels of gelsolin was found to be significantly upregulated in 78% of patients of CC, with a 2.2 fold increase in comparison to healthy controls. Higher levels of gelsolin was linked to greater cell migration and proliferation [133]. NF-kB nuclear staining was correlated with increased risk of loco-regional and distant-failure [134]. CXCR4 is a chemokine which regulates lymphocyte homing to inflammatory tissues. It is involved in the metastatic processes of various neoplasms and mediates proliferation, invasion and angiogenesis. Expression of chemokine-receptors CXCR4 & CCR7 can indicate poorer prognosis [135-137].

PROGNOSTIC IMPLICATIONS OF ADVANCES IN IMAGING

Advances in imaging technology have revolutionized various aspects of health care in general. Oncology has gained immense benefits from these advances with regards to diagnosis, staging, treatment-planning, response-assessment and follow-up. Obvious benefits exist with regards to the advances in CT and ultrasonography, however this section reviews the potential prognostic significance associated with recent advances in imaging techniques involving MRI and PET (Table **7**).

Sequential-MRI Detected Tumour Volume Regression

The rate of tumour-shrinkage after initiation of RT has long been held as a surrogate for intrinsic-sensitivity. Volume estimates from diametric orthogonal measurements with the ellipsoidal formula though easy, would be blind to the irregularities that exist in tumour shape and volume. A more accurate, albeit labour intensive method, would be volumetric imaging after contouring of disease.

Mayr *et al.* [138] used a '4-dimensional' assessment of tumour-regression in their prospective study in which 115-patients of stages IB2-IVA underwent serial-MRI (before RT initiation, at 20-22Gy and at 45-50Gy) for 3-D volumetric measurements of tumour. The 4^{th} dimension would be the 'regression across time' parameter. They noted significant correlation of residual tumour volume, slope and area under the regression curve with local control and survival. The most important of their observations was that patients with ≥20% residual volume at 45-50Gy have a risk of local failure and death so high that it could be used in the future to justify tailored aggressive approaches to such patients. These findings were also supported by the work of Nam *et al.* [139], who suggested that mid-RT tumour volume-regression rate at 36-45Gy was a predictor of local-control in patients treated with RT and CCRT.

Nam *et al.* [139] also suggested that MRI performed mid-RT would also provide an indication of 'dead-cell clearance', which would in-turn be related to other

Table 7: Prospects of Newer Imaging Modalities as Predictors of Prognosis

Modality	Prospect	Remarks	Refs.
CE-MRI	Enhancing fraction detection using Gd-DTPA contrast	Predictive of areas of hypoxia. Predictive of response	[149]
T2-FS MRI	Serial measurement for changes in T2-FS signal intensity during RT	Can be predictive of response, irrespective of tumour volume regression	[143-144]
Serial MRI	For volumetric measurements on serial scans before and during RT.	Rate of regression and volume of residual are predictive of local control and survival	[138-139]
MRS	May be used to detect specific metabolites in the tumor-environment	Metabolites such as lactate may be indirect surrogate for hypoxia	[158-159]
^{18}F-FDG-PET/CT	Nodal staging, Treatment planning, Response evaluation, Follow-up	Can help personalize treatment. Can guide dose-escalation with newer RT techniques. Also, pre-treatment SUV_{max} is predictive of nodal involvement and recurrence.	[153-154]
^{18}F-Miso PET	Hypoxia detection within tumors	Extrapolation from head-neck cancers	[155]
^{60}Cu-ATSM PET	Hypoxia detection within tumors	Experimental phase	[155]

prognostic factors such as microcirculation and interstitial pressure. This is of significance, since after initiation of RT, as high as 99% of tumour cells are typically killed during the first two-weeks, and morphological shrinkage in tumour size would depend on dead-cell apoptosis and clearance [139-141].

Tumour residual detected on imaging near or after completion of RT could likely be indicative of a volume of cells with large potential for accelerated repopulation, and hence will likely be predictive of local control [139-140].

It must however be remembered that the prognostic value of tumour regression value will be diminished in the presence of LN metastases [138-139].

Sequential MRI for Changes in T2 Signal Intensity

Hyperintensity on T2-weighted MRI is representative of tumour permeability and surrounding inflammation [142]. Yuh *et al.* [143] observed that longitudinal changes in T2-Fat-suppression sequences during RT can be correlated with response and survival. Daniel *et al.* [144] compared pre- & mid-treatment T2-FS intensities in CC patients undergoing CCRT. They noted that high tumour T2-FS intensities persisting at mid-treatment scan was correlated with a high risk of treatment failure. One additional advantage with this technique is that it is less time consuming and is much less technically complicated when compared to contrast-enhanced MRI, diffusion-weighted MRI & MRI-spectroscopy.

DCE-MRI for Intratumoral Heterogeneity

Differential enhancement on contrast-enhanced imaging, either CT or MRI, has long been known to representative of differential vascularity. 'Enhancing-fraction' can be said to be the proportion of tumour-volume that enhances after contrast. While some studies have demonstrated a poorer survival with highly enhancing tumours (reasoning brisk angiogenesis), some studies have demonstrated better response and outcome with highly enhancing tumours (citing better oxygenation and enhanced radiosensitivity thereof) [145-148].

Mayr *et al.* [149] concluded that DCE-MRI and serial volumetric imaging could be two independent MRI based parameters that could quantify heterogenous tumour perfusion and predict response and survival. They reported feasibility of an 'ultra-early' assay for predicting treatment-failure at an early time when therapy adjustments could still be feasible.

Further work in refinement and standardization of the techniques and associated algorithms are needed before widespread use [150-151]. However, without doubt, there is no doubt in the fact that DCE-MR images contain critical information, which when utilized in mathematical modelling holds immense potential in predicting outcomes of treatment [152].

FDG-PET for Predicting Response and Survival

FDG-PET has a proven performance in staging and LN detection. As earlier elucidated, FDG-PET detected LN involvement is in itself a predictor of relapse and survival. However, recent data has suggested that additional data obtained from FDG-PET scans can provide extra prognostic information. Grigsby *et al.* [153] reported that the pre-treatment SUV_{max} of primary tumour had its own prognostic significance, in that high values were predictive of non-response as well as recurrence.

Post-therapy scans showing complete-metabolic-response (CMR) are associated with excellent survival, and incomplete response is associated with poorer outcomes. New areas of metabolic-activity on post-treatment scans were associated with very poor survival [153].

FDG-PET for Metabolic Heterogeneity

Intra-tumoral metabolic heterogeneity as detected on the basis of differential FDG-uptake within tumours could be an independent prognostic factor. Kidd *et al.* [154] observed that FDG-PET detected intra-tumor heterogeneity in the cervical primary tumour was significantly relatable to LN involvement, incomplete response and recurrence.

Other Technical Advances of Potential Significance

Recently imaging of intra-tumoral hypoxia with ^{18}F-MISO-PET and ^{60}Cu-ATSM-PET are in active research for cervical, lung and head-neck malignancies [155].

USPIO (ultra-small super-paramagnetic iron oxide) enhanced MRI has been investigated for the detection of involved LN. However, inspite of the good specificity, the modality suffers from rather low sensitivity. Research is in progress to improve the sensitivity associated with this technique [156-157].

Magnetic resonance spectroscopy (MRS) has the potential for characterization of the tumour content, especially with regards to metabolites such as 'lactate' which could be indirect markers of hypoxia [158-159].

Additional prospects may be unlocked with MR-PET fusion, which utilized fusion of MRI and PET.

TREATMENT RELATED PROGNOSTIC FACTORS:

In a single statement, 'correct' treatment will lead to favourable results. But deciding 'what is correct' in each patient is often challenging. An optimized treatment for one patient may be under-treatment for the second patient, and over-treatment for the third patient.

In-spite of the traditionally held belief that CC is radiosensitive, the treatment outcomes have not been very encouraging. Since the advent of CCRT as an accepted standard of care, no additional breakthroughs of remarkable significance have occurred over the last decade. As a matter of fact, various studies indeed have even challenged the rationale for CCRT as the uniform standard of care for LACC.

The advent of advanced techniques such as IMRT (intensity-modulated RT) and IGABT (image-guided adaptive brachytherapy) have offered prospects of toxicity limitation, customized dose distribution and dose escalation. However, though promising results have been observed in studies performed by pioneers, it must be acknowledged that newer techniques could be less effective, if applied without meticulous attention to detail with regards to correct delineation of target volumes and in execution of the treatment.

An overview of the treatment related impact on prognosis can be had from Table **8**. This section briefly mentions the potential impact on treatment outcomes with regards to treatment technique and related parameters.

Brachytherapy and its Importance on Prognosis

Intracavitary brachytherapy (ICBT) in the past has often been considered as the main treatment for CC, and that the role of external beam RT (EBRT) is mainly to 'facilitate a successful ICBT application'. However, such a claim can now be confidently disputed, in this era given the newly identified significance of nodal involvement, which if present cannot be adequately dosed by the use of ICBT alone.

Though studies have shown that successful completion of ICBT is an independent factor for successful outcomes, many factors often preclude the use of ICBT- such as the presence of disease configuration that cannot be covered by the classical 'pear-shaped' dose distribution. Indeed, medical contraindications and patient refusal can also be grounds for non-completion of ICBT.

The latest development has been the emergence of MRI-based-brachytherapy. This approach favours dose prescription to CTVs stratified as high-risk (HRCTV, for gross-residual disease), intermediate-risk (IRCTV for areas which previously contained disease) and low-risk (LRCTV for areas of potential microscopic spread). A dose of $\geq$87Gy (in EQD2: dose equivalent as delivered in 2Gy fractions) to the high-risk CTV by the use of IGABT can be expected to achieve >95% local control rate in LACC. Potter *et al.* postulated that a 10-20% gain in survival can be expected for LACC if MRI based brachytherapy is utilized. Schmid *et al.* [160] in a study analysed the local recurrences occurring after IGABT, and observed that 85% of local recurrences were arising from regions which received <87Gy, even though originally included within the HRCTV contour. Their conclusion was that low dose regions could be

Table 8: Treatment-Related Factors Impacting Prognosis

Parameter	Remarks
Overall treatment time	Keep overall time <7-8 weeks
	Avoid breaks as far as possible.
	Avoid practices that may cause undue toxicities to cause treatment breaks
	Strong psychological support
	Use of aggressive supportive therapy
	Integrate brachytherapy as early as feasible
Target volume delineation	Either with conventional RT or IMRT, success depends upon adequate coverage of all disease
	Do not inadvertently overlook nodal disease
	Cover the entire sacral-hollow on the lateral portals if using traditional 4-field-box technique
	Never ignore risk organ constraints
	Consider IMRT whenever para-aortic irradiation, nodal dose escalation or when parametrial boosting is needed
Dose	Point A dose to be atleast 85-90Gy in 2Gy/fraction equivalents
	Consider EBRT boost to involved nodes, and to parametria not covered by the fixed shape dose distribution of intracavitary brachytherapy
	IMRT or conformal sterotactic techniques, or proton beam RT may be of special benefit in patients unable to undergo brachytherapy.
	If dose escalation not feasible with residual disease after full course of therapy, adjuvant hysterectomy may be an option
Hemoglobin	Adequate notice should be placed on maintenance of haemoglobin across the duration of RT.
	Hematinic support should be balanced against their benefits versus their risk of adding to gastrointestinal discomfort
	Consider marrow-sparing IMRT whenever feasible, especially in the setting of concurrent use of chemotherapy
Concurrent chemotherapy	Currently the standard of care. However, issues remain unresolved- regarding the exact dose and timing of cisplatin.
	Chemotherapy should not be given at the cost of compromising the patient's overall treatment time, or in those with known renal disorders, or in the very old
Neo-adjuvant chemotherapy	To be avoided, since it may worsen outcome
Adjuvant chemotherapy	Investigational, may be beneficial in subsets of patients with partial response or with high risk of local recurrence and distant failure

expected within the HRCTV even if a D90 > 87Gy was imposed.

Though the completion of brachytherapy is often considered as a strong prognostic factor, some argue that its non-completion is often due to other significant factors which could be more prognostic in themselves. A patient who is unfit for ICBT due to low or no response to EBRT may have an inherently radioresistant disease, which would fail with or without ICBT [161].

When ICBT is not feasible due to any reason, alternatives may include image-guided-interstitial brachytherapy (ISBT) [162-165], stereotactic irradiation and adjuvant hysterectomy when feasible [166]. It must be remembered that even the tempting new technologies of stereotactic irradiation can never be able to achieve the high-dose (>100-200Gy) delivered by ICBT to the endocervix and paracervical areas medial to point A.

Dose of Radiation as a Prognostic Factor

It has been widely considered that a Point-A (defined as the point 2cm superior from the mucus membrane of the lateral fornix and 2 cm lateral from the central uterine canal, in a plane perpendicular to the long axis of the central tandem) dose of 85-90Gy (in EqD2) is necessary for acceptable local control. While dose to the primary-tumour is often attainable with ICRT and ISBT, the presence of LN involvement poses serious challenges. Given that the FIGO staging does not compulsorily rule out LN disease, it is not

unreasonable to question the validity of all data before the era of imaging obtained from studies not using nodal status as a stratifying factor.

Techniques such as ISBT or IGABT do not deliver adequate 'curative' doses to involved nodes. At the same-time, the maximum dose deliverable through EBRT is limited, even with IMRT. Hence, inadequate ability to dose the involved nodes could be another reason for the poor survival with node-positive disease.

One important point to note would be that the use of sub-lethal dose of radiation may not only be ineffective in cure, but may also be detrimental in increasing cell migration and enhancing metastatic potential. Su *et al.* have analysed radioresistant cell lines from CC after a suboptimal radiation dose and observed increased metastatic potential *via* K-Ras/c-Raf/p38 signalling pathways [167]. We believe this to be of special significance in LACC where often, in the absence of dose verification, it is likely that foci of parametrial or nodal disease could be underdosed inspite of adequate 'point A' dose.

Concurrent Use of Chemotherapy

CCRT with cisplatin is widely considered to be the standard of care for LACC. There seems to be survival benefit with CCRT over RT alone (Table **3**). However, investigators have not found an unequivocal benefit with this approach [168-170]. Furthermore, the NCI alert of 1999 which recommended the use of cisplatin CCRT was primarily based on five trials which were heterogeneous with regards to study design, and had serious non-uniformity in the control arm [171-176].

Dutta *et al.* [169] observe a high rate of failure with the use of CCRT and stated various reasons for the same. They state that the use of cisplatin in patients with stages IIIB-IVA could be associated with the risk of aggravating renal toxicities. The use of CCRT in the elderly could cause more intense marrow suppression. Given that marrow in the adults is largely situated in the pelvis and the lower spine, irradiation of these very areas along with the use of chemotherapy could lead to serious toxicity which could be detrimental in terms of inducing treatment breaks (increasing OTT) as well as causing direct mortality. Induction of early accelerated repopulation with the concurrent use of chemotherapy was another point against CCRT [177].

The recent Cochrane metaanalysis declared a benefit in absolute survival (6%) and also a benefit in 5 year DFS (8%). The results of the recent Cochrane metaanalysis can be considered to be more valid since it has been an individual patient data (IPD) metaanalysis (earlier metaanalysis by Green *et al.* [178] and Lukka *et al.* [179] were plagued by inconsistency in the definition of outcomes between trials, and were complicated by the fact that different treatments were used in the control arms of the studies). The benefit CCRT appeared consistent across patient subgroups defined by age, histology, grade, or pelvic nodal involvement. But there seemed to be a decreasing relative benefit with increasing stage [180]. While the absolute 5year OS benefit for early stages (IA-IIA) was 10%, the benefit for IIB was 7% and it reduced to 3% for Stages III-IVA.

Hong *et al.* in their review questioned the very use of indiscriminate use of CCRT for all patients of CC. They observed 27%, 30% and 33% distant relapse rates among patients with pre-treatment SCCAg >10, stages III/IVA and pelvic node positive cases respectively. They have argued that the use of 'single agent' cisplatin in CCRT would not be able to curtail distant relapses. Since they believed that the 'radiosensitizing dose of single agent cisplatin' would not be effective against systemic metastatic disease, they suggested that intensive combination chemotherapy, rather than single agent, would be beneficial for patients at high risk of distant failure (as per SCCAg, stage and nodal status) [92].

A very recent study by Ryu *et al.* compared the weekly cisplatin at 40mg/m^2 vs. triweekly cisplatin at 75mg/m^2 for CCRT. Their observations revealed better outcomes with the tri-weekly regimen, which could be hypothesized as due to the higher peak concentrations achievable with triweekly-higher dose cisplatin, which could be effective for local control and in elimination of micrometastases [181].

The addition of paclitaxel or gemcitabine to cisplatin in CCRT has been investigated with promising results [182-183]. The status of non-cisplatin agents for CCRT is also in active consideration. A recent Cochrane analysis suggested that benefit exists with non-platinum agents too, mainly deriving from the data of Lorvidhaya *et al*. [180-184].

The status of novel targeted monoclonal agents and tyrosine-kinase inhibitors will also be the focus of future research. Pre-clinical data suggests benefit with cetuximab even in the absence of EGFR overexpression, given that it would negate the radiation induced upregulation of EGFR and in inhibiting the phosphorylation of EGFR [185].

Overall Treatment Time as a Prognostic Factor

Overall treatment time (OTT) is considered to be an independent prognostic factor with regards to cervical carcinoma. It has been recommended that OTT should not exceed 56 days. Loss of local control after exceeding OTT is rather dramatic, with an expected 1% decrement in LC for every additional day beyond 56 days [186-189].

The knowledge of accelerated tumor cell repopulation initiated research into modification of dose and fractionation with an attempt to improve outcomes. Clinical evidence has hinted that accelerated repopulation in cervical carcinoma begins at an average of 19 days of treatment initiation [84].

Various methods of acceleration of treatment to counter tumor repopulation include- the use of RT for 6 days in a week rather than 5 days (reduces overall treatment time by a week, and intensifies weekly dose by around 20% [84]), the early integration of brachytherapy and aggressive symptom management to avoid breaks due to toxicity. Hyperfractionation and concomitant boost have also been tried, both showing good local control, albeit with increased toxicity [190-191]. Moreover, toxicities often have the potential to force treatment breaks which could ultimately increase OTT [192].

Neoadjuvant Chemotherapy (NACT) and Prognosis

NACT prior to RT has no proven benefit, and may even be detrimental. NACT could lead to the induction of accelerated-repopulation. If overall-treatment time can be calculated from Day-1 of NACT, and assuming 3 cycles of NACT prior to definitive CCRT are given, it can be assumed that the effective OTT could well exceed 15-16weeks, more than double the recommended 7-8week. Two phase-3 trials have in-fact demonstrated poorer outcomes with the use of NACT [193].

Adjuvant Consolidation Chemotherapy and Prognosis

The use of additional cycles of chemotherapy after completion of definitive CCRT has been shown to be beneficial in nasopharyngeal carcinoma, where the methodology was adopted in an intention to prevent distant relapses, a common event with nasopharyngeal carcinoma.

With CC, there could be specific subsets of patients who could benefit from this approach, such as those with a high risk of distant or local relapse, adenocarcinomas and in patients with residual foci of unknown significance. As per the metaanaysis by the Cochrane collaboration, adjuvant chemo after chemoradiotherapy seems to improve survival; however they called for new RCT to find out conclusive results [180,194].

IMRT and its Benefit on Survival Outcome

The benefit of IMRT with para-aortic nodal irradiation and in the post-hysterectomy setting is unquestionable. However, the adoption of IMRT for treatment of the intact cervix is quite recent, and the consensuses are a work in progress [195-197].

It must be remembered that the use of conventional RT techniques offers a luxury to the planning clinician in that all structures within the portals are irradiated. However with IMRT, an error or oversight with delineation could cause geographical misses and subsequent local failure. The cervix and uterus is a fairly mobile organ, often undergoing displacements secondary to changes in bowel and bladder filling. Without regular image-guidance, there is a likelihood that OARs and CTVs may take turns in occupying the initially planned ‘PTV’.

There indeed have been studies elucidating the reduction of bowel, bladder and marrow toxicity with the use of IMRT in LACC [198-199]. But randomized studies are needed to enable definitive statements regarding impact on pelvic control and survival. However, image-guided IMRT can be expected to improve outcomes by dose-escalation to LN in pelvic or paraaortic areas.

Particulate RT to Improve Prognosis

Proton-beam RT, long known for their unique dose-distribution characteristics are rarely used owing to their limited availability. Song *et al.* [200] compared conformal proton beam therapy with IMRT. They noted that three beam proton RT could achieve superior marrow sparing ability in comparison to an eight-field IMRT. Kagei *et al.* [201] reported excellent long term results of proton beam RT and additionally stated that benefit could be especially gained among patients ineligible for ICBT.

Neutrons have been used in therapy of CC by the utilization of ^{252}Cf sources for ICBT. Tacev *et al.* [202] reported better 5-year survival with ^{252}Cf brachytherapy in comparison to conventional source ICBT. Impressive

results were also reported from China by Lei *et al.* [203].

CONCLUSIONS

Prognostification of cancer patients is necessary for optimizing choices and intensity of therapy. Staging of patients is an important prognostic exercise. However, in the case of LACC, given the very high possible heterogeneities that may exist within individual stage groups, a proper picture of prognosis can only be had with the help of various factors of significance, as reviewed in this article. In the future, we may expect modifications in the FIGO stage, most likely to integrate nodal status as a factor. In addition, other parallel staging systems and nomograms are likely to evolve, which could be applied parallel to the FIGO staging system to provide additional vital information. Infact, attempts at improved staging are already underway, as exemplified by the designation of nodal-involvement as 'Stage-IIIB' under the 7th edition of the TNM-AJCC system [27]. Also, promising new nomograms are also under development [204]. Proper prognostification would be vital for the success of 'tailored therapy' in the future, where specific patients would benefit most from specific therapeutic plans. After-all, one size does not fit all, as illustrated by the discovery of heterogeneity within breast cancers, where the therapeutic options vary with hormonal and her2neu receptors. It is very probable that carcinoma of the cervix too is a heterogenous disease, which would need categorization of patients into groups who would benefit from specific management plans.

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