Indian J Med Res 154, August 2021, pp 319-328
DOI: 10.4103/ijmr.IJMR_339_21

Quick Response Code:

Review Article

Contribution of Tata Memorial Centre, India, to cervical cancer care: Journey of two decades

Anuj Kumar[1], Supriya Chopra[1] & Sudeep Gupta[2]

Departments of [1]Radiation Oncology & [2]Medical Oncology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

Received February 1, 2021

Cervical cancer continues to be a major public health concern in India and other low- and middle-income countries. Tata Memorial Centre, India, has been at the forefront in providing treatment, developing best practice guidelines for low-cost efficacious interventions, conducting practice-changing randomized trials and engaging in regional and international collaborations for education and research in cervical cancer. This review summarizes how cervical cancer research and clinical care has evolved over the past two decades at the Tata Memorial Centre, right from testing low-cost public health screening of cervical cancers to the incorporation of the latest technological advancements and providing high-quality evidence for therapeutic management of cervical cancer. The various ongoing strategies for improving survival, toxicity reduction, translational research studies, educational activities and teaching programmes initiated by the Tata Memorial Centre at both national and international levels are discussed.

Key words Brachytherapy - cervical cancer - early detection - education - NACT - prevention - research

Cervical cancer is one of the major health problems and the second most common cancer among women in India. The number of new cases of cervical cancer in India in 2020 was 1,23,907, contributing to 18.3 per cent of all cancers in women[1]. Although the incidence of cervical cancer continues to decrease, most women are still diagnosed in a locally advanced stage due to the lack of population-based screening programmes in India[2]. In the past two decades, Tata Memorial Centre in India has made substantial contributions towards advancing education and research related to prevention, vaccination and therapeutic intervention for cervical cancer and continues to conduct clinical and community trials that may be practice-changing worldwide[3]. Here we summarized the contribution of Tata Memorial Centre towards the development of key evidence for various aspects of clinical management of pre-invasive, invasive and recurrent cervical cancer. The review also highlights the role of Tata Memorial Centre in shaping a broader policy on the detection and management of cervical cancer including contribution towards resource assessment and building needs for education and research nationally and internationally.

Contribution of Tata Memorial Centre

Early detection and prevention of cervical cancer: Cervical cancer screening is one of the time-tested strategies known to reduce mortality from cervical cancer[4]. However, wide-scale population-level screening programmes have been challenging to implement in India and other low and middle-income countries (LMICs). This has been attributed not only to the cost involved (like in HPV DNA tests) but also the need to have trained and skilled personnel to report on cytology[5]. Low-cost and high-fidelity techniques such as visual inspection with acetic acid (VIA) have been tested at the Tata Memorial Centre from 1998–2011 within a cluster phase III randomized trial in 142,701 women aged 30-59 yr to assess the efficacy of screening with VIA in cervical cancers[6]. The procedure of VIA was performed by primary healthcare workers [unlike trained cytologists or pathologists needed for Papanicolaou (Pap) staining]. The clusters were randomized to the screening group (four rounds of cancer education and screening with VIA at 24 months interval) (n=75,360) and the control group (cancer education at entry alone) (n=76,178). The screening group showed a significant 31 per cent reduction in cervical cancer mortality. The reduction in mortality achieved by VIA (a low cost and resource screening test) suggests that this may be a good low-cost option for both high- and low-income countries and LMICs[7].

In another cluster-randomized study of 131,746 women from 52 villages in India, HPV DNA test, VIA, cytology and standard of care for the existing healthcare system were compared. The results of the cluster-randomized study concluded that even a single round of HPV DNA testing was associated with a significant reduction in the number of advanced cervical cancers and deaths from cervical cancer[8]. This study, for the first time has demonstrated that if resources are limited, even a single round of testing can effectively reduce mortality. This is a major knowledge advancement as population-based screening programme for cervical cancer necessitate repeat testing at predefined intervals and have significant cost investment.

Another study concluded that further costs of population-based screening could be reduced using a two-step screening model combining VIA for primary screening followed by HPV DNA detection as a secondary test[9]. In this study, VIA positive women were tested for the presence of oncogenic HPV types by hybrid capture II (HC2) and with colposcopy. VIA had a high sensitivity to detect CIN grade 2+ lesions and HPV DNA and colposcopy were reserved as secondary tests that had a high specificity for detecting CIN2 + lesions[9]. In a subsequent study, the HPV HC2 test was shown to be a better triage test in VIA-positive women to detect >CIN2[10].

Tata Memorial Centre also participated in a study that investigated the detection of HPV from menstrual blood. Menstrual pads were collected from women of 30-50 yr age group from rural regions within the State of Maharashtra followed by HPV testing and colposcopy. The menstrual pad method showed acceptable sensitivity and specificity providing an alternative option for a non-invasive and simple method of cervical cancer screening[11]. The aforementioned trials lay a foundation for cost-effective strategies that can be implemented at national levels both within India and other countries. With the development and testing of low-cost, rapid molecular-assay technologies for HPV DNA detection, this may become viable as a primary screening tool in LMICs in the future[12].

The Tata Memorial Centre also participated in a multicentric HPV vaccination study that was prematurely closed with some participants receiving only one or two doses of vaccine. This premature closure of the study provided an opportunity to study the immunogenicity of girls who received one or two doses of HPV vaccination. A seven-year follow up of this study demonstrated no persistent HPV infection in two dose cohort which was similar to a three-dose cohort suggesting that a two-dose recommendation could be safely extended to girls from 15 to 18 yr of age[13]. Furthermore, data on the cohort that received only one dose with a median follow up of 4.7 yr indicated similar rates of cumulative incident and persistent infections suggesting that even a single dose schedule could be an effective option for HPV vaccination[14]. However, there is a need for further follow up for immunogenicity and safety.

Development and validation of FIGO/TNM staging system: Experts from Tata Memorial Centre contributed to the revised International Federation of Gynecology and Obstetrics (FIGO) staging for cervical cancer in 2018[15]. In a study of 632 locally advanced cervical cancer (LACC) patients, the investigators categorized outcomes as per the old and new FIGO and the AJCC (American Joint Committee on Cancer)

staging system. The three-year disease-free survival (DFS) for stages IB, IIA, IIB, IIIA, IIIB, IIIC1, IIIC2 and IVA were 100, 93, 84, 53, 77, 74, 61 and 61 per cent, respectively. Patients with lymphadenopathy had significantly inferior outcomes when compared to node-negative patients (62.9 *vs*. 77.8%, *P*=0.002) validating the importance of nodal involvement in cervical cancer. However, DFS was poorer in patients with ≥3 para-aortic and pelvic nodes than <3 para-aortic and pelvic nodes (13.6% *vs*. 56.3%, *P*=0.001). Patients with primary tumour volume >30 cm^3 also had worse three-year DFS than those with ≤30 cm^3 volume (67.4 *vs*. 78.5%, *P*=0.002)[16]. The results of the validation study[16] suggest that further refinement of staging is needed with the incorporation of tumour and nodal volume. Based on the observations within this large cohort, modification of the existing TNM and FIGO system was suggested to allow reclassification of patients in four different stage groupings with high fidelity[16]. These observations in the future may help with further evolution of the FIGO and TNM staging.

Practice changing therapeutic trials: National Cancer Institute alert in 1999 recommended that concurrent chemoradiation should be the standard of care for the management of LACC[17]; however, the clinical trials testing the role of concurrent chemoradiation had under-representation of patients in stage III B[18]. A Phase III trial (NCT 00193791) was initiated at the Tata Memorial Centre to test the benefit of concurrent chemoradiation in stage III B and accrued 850 patients from 2003 to 2011. After a median follow up of 88 months, the study reported in 2018 that the five-year DFS was significantly higher in the chemoradiation arm (52.3%) when compared to RT alone arm (43.8%). Eight per cent overall survival (OS) benefit was observed in the chemoradiation arm (54 *vs*. 46%). This study provided level one evidence in favour of concurrent weekly cisplatin chemotherapy when compared to RT alone in stage III B patients[19]. The absolute benefit observed within this phase III trial was eight per cent as compared to three per cent reported by the individual patient data meta-analysis[20].

Tata Memorial Centre was also among the first ones to test and report the role of neoadjuvant chemotherapy (NACT) and surgery as compared to chemoradiation in stage IB2-IIB cervical cancer. A phase III randomized controlled trial of 635 patients with FIGO stage IB2, IIA and IIB cervical cancer was designed to test the superiority of NACT-surgery ± adjuvant chemo-radiation over chemoradiation[21]. However, at the final analysis, inferior outcomes for the primary end point of DFS were observed in the NACT-surgery arm. At a median follow up of 58.5 months, five-year DFS of 69.3 per cent was observed in NACT-surgery and 76.7 per cent in chemoradiation arm (*P*=0.03)[21]. The results provided an important answer about the lack of role of NACT-surgery in the management of stage IB2-IIB cervical cancer. The results were later corroborated by the EORTC trial[22].

Pattern of care and implementation studies

In addition to performing randomized trials, the Tata Memorial Centre has consistently reported outcomes of patients treated outside clinical trials. In a large retrospective study, outcomes of 6234 patients with stage IB-IIIB cervical cancer treated with radical intent between 1979 and 1994 were reported[23]. At a median follow up of 68 months, the DFS for stage IB-IIA was 60-62 per cent at eight years with either surgery, radical radiation therapy or pre-operative radiation followed by surgery. For stage IIB and IIIB, a DFS of 56 and 40 per cent, respectively, was achieved at eight years[23]. Concurrent chemoradiation results in a five-year OS rate of 66 per cent and DFS of 58 per cent in LACC[24]. In another study, five-year outcomes were reported for patients treated in 2010. Overall, a five-year DFS of 62 per cent was observed in stage II and 45 per cent in stage III suggesting improvement over the historical series. Grade 3 or higher late toxicity was seen in only five per cent of the patients[25].

From 2014, Tata Memorial Centre adopted radiation dose escalation through brachytherapy and reported three-year outcomes in 2018. In a series of 339 patients of LACC, the audit reported three-year local control, DFS and OS of 94.1, 83.3 and 82.7 per cent, respectively, in stage IB-IIB (FIGO 2009). For stage III-IVA, the corresponding rates were 85.1, 60.7 and 69.6 per cent, respectively[26]. These studies reported improvement in outcomes as a result of the effective delivery of clinical care for all patients. In another study of 632 patients, there was a further reduction in local (6.1%), pelvic nodal (4.9%), para-aortic nodal (6.9%) and distant relapse (9.4%), suggesting efficient adoption of full course concurrent chemoradiation, primary and nodal dose escalation in routine clinical practice. It was noteworthy that the three-year DFS in pelvic and para-aortic node positive and stage IV A disease (III C1 and III C2) patients was 74, 61 and 61 per cent, respectively[16].

Selected studies from Tata Memorial Centre have reported the outcomes of patients who are poorly represented in LACC clinical trials. Outcomes of patients with lower vaginal involvement are not adequately reported in the literature and these patients are often not included in prospective clinical trials. In an audit study that reported 118 patients with lower third vaginal involvement, the three-year DFS and OS of FIGO stage IIIA patients were significantly better than IIIB patients (71 *vs.* 56%, *P*=0.02 and 76 *vs.* 66%, *P*=0.01) after a median follow up of 30 months. The overall three-year DFS and OS rates were 61.5 and 69.8 per cent, respectively. Concurrent chemotherapy and the absence of persistent disease independently predicted survival on multivariate analysis[27]. Another study reported outcomes of LACC patients who present with obstructive uropathy at the time of initial diagnosis[28]. In this group of patients, percutaneous nephrostomy and double-J stenting was performed. Only 50 per cent of patients could receive radical chemoradiation. While the median survival was 10 months for all the overall patients, select patients with good performance status, small tumour size and serum creatinine <3 mg/dl who could complete chemoradiation had superior clinical outcomes as compared to others (30 *vs*. 10 months). The study identified a small number of patients with advanced stage who could potentially become long-term survivors and the clinical features listed above to assist in patient selection[28].

Clinical audits of outcomes have also been reported of patients with neuroendocrine histology and special clinical circumstances as coexisting HIV infection[29-31]. As a proportion of patients with cervical cancer also present with very advanced disease, a report from the institution summarises the outcomes following extreme hypofractionation for palliation for very advanced cervical cancer. A study evaluating the outcomes of 100 patients with palliative RT reported 100, 49 and 33 per cent response to bleeding, discharge and pain respectively, with a single fraction of 10 Gy. By second fraction, more than 50 per cent pain relief was reported in up to 60 per cent of patients with a median survival of seven months[32]. In another study in patients with locally advanced metastatic rectal cancer use of a hypofractionated schedule of 25 Gy in 5#, we observed control of pain and bleeding in up to 80 per cent of patients[33]. A phase III randomized study has recently been initiated to test the superiority of rapid palliation schedule (25 Gy/5#/one week) over a protracted schedule of 30 Gy/3#/7-8 wk. A total of 230 patients will be included[34].

Tata Memorial Centre is actively involved as a part of the National Cancer Grid of India initiative for treatment homogenization. Institutional representatives participated in the development of resource stratified treatment guidelines. Furthermore, a national resource assessment was undertaken to study the feasibility of broader implementation of guidelines[35]. A multi-institutional study is presently underway to evaluate the implementation of guidelines which will provide valuable information about the broader level implementation of these policies.

Studies investigating advances in external beam technology

In a phase II randomized trial of 200 patients that evaluated dose escalation in LACC through a combination of intensity-modulated radiotherapy (IMRT) and standard brachytherapy, patients were randomized into IMRT and brachytherapy [50 Gy/25#/5 wk followed by 5# of 7 Gy high-dose rate (HDR) weekly brachytherapy to point A] (Study arm) or 3D conformal radiation and brachytherapy (40 Gy/20#/4 wk with midline shielding at 20 Gy followed by 7 Gy HDR brachytherapy to point A x 5# weekly) (standard arm). After a median follow up of 62 months, no difference was observed in locoregional control (LRC), DFS and acute toxicities between the two arms. However, late rectal toxicity was significantly higher in the study arm as compared to the standard arm secondary to dose escalation. [grade III/IV: 15 versus 2 per cent (*P*<0.005)][36].

The Centre has also recently published the results of a phase III randomized trial comparing 3DCRT with image-guided IMRT (IG-IMRT) in patients receiving post-operative radiation for cervical cancer. The trial was designed to detect a reduction in grade ≥2 late bowel toxicity with the application of IG-IMRT[37]. At a median follow up of 46 months, the three year cumulative incidence of grade ≥2 late GI toxicity was 21.1 *vs* 42.4 per cent (*P*<0.01) in IG-IMRT arm and 3DCRT arm respectively[38]. In a sub-analysis from this study, the feasibility of bone marrow sparing was reported[39]; however, simultaneous bowel and bone marrow sparing needs further investigation.

A previous study compared the performance of two techniques of IMRT delivery [volumetric modulated arc therapy (VMAT) and fixed field IMRT], and reported improved performance of VMAT in terms of dose homogeneity and conformity with significant improvements in organs at risk sparing[40]. Further investigators compared two different techniques

of VMAT (halcyon *vs*. tomotherapy). Essential equivalence was noticed between halcyon and helical tomotherapy based plans for IMRT in cervical cancer[41]. The role of machine learning in improving IMRT planning process fidelity and efficiency was studied. A prospective study reported no difference between clinical and machine learning generated treatment plans inferring that the automated machine-based plans were robust[42]. These observations may be important and facilitate the transition of high-quality care delivery with high fidelity in high volume centres.

Contribution to brachytherapy

Brachytherapy is an integral part of cervical cancer treatment, and Tata Memorial Centre has been actively involved in prospective clinical studies at national and international trials[43]. In a phase III randomized study of 830 patients that compared low-dose rate to HDR, no significant difference was observed in LRC, survival or toxicity between the two[44]. Tata Memorial Centre was also a major contributor to the phase III randomized study, initiated by the International Atomic Energy Agency (IAEA), across seven countries in 601 patients to compare two fractionation regimens for HDR brachytherapy. Of the 601 patients, 257 patients studied at Tata Memorial Centre contributed. The study compared 7 Gy × 4# with 9 Gy × 2#. Local control was significantly higher for the arm using 7 Gy × 4#. No differences in OS or adverse effects were found between the arms. This was the first trial that reported benefit of brachytherapy dose escalation[45].

Experts from Tata Memorial Centre have also contributed to the international publication of International Commission on Radiation Units and Measurements (ICRU) Report 89[46]. Within an international collaborative framework advanced brachytherapy principles (EMBRACE and EMBRACE II) were tested at the centre. In collaboration with the medical university of Vienna, Tata Memorial Centre piloted a technical modification in brachytherapy technique to improve brachytherapy coverage in patients with a poor response to external radiation. Close to 90 per cent of patients in this study had a residual disease in the distal parametrium/pelvic wall following external radiation. The results showed local control, DFS and OS of 76/72, 56/50, 62/54 for three and five years, respectively, with acceptable toxicities even in patients with poor response[47]. A simulation study was conducted to evaluate the macroeconomic benefits with MR-IGBT over conventional brachytherapy that demonstrated significant economic gains with IGBT[48]. There is a lack of level I evidence supporting the wide-scale implementation of image-guided brachytherapy. While Tata Memorial Centre is presently conducting a phase III randomized study to test the superiority of 2D over image guided brachytherapy[49].

Currently image-guided brachytherapy is desirable, there is a considerable deficit in imaging scanners throughout the country as compared to developed countries[50]. In an online survey conducted among radiation oncologists of India, it was noted that many of the centres commonly carried out CT and X-ray imaging with Point A prescription being the most common methodology for planning[51]. Low-cost imaging modalities such as CT and ultrasonography (USG) were more in practice compared to MRI. In a prospective study that evaluated CT based target and organs-at-risk (OAR) delineation with the help of MRI at diagnosis and real-time transrectal ultrasound (TRUS) information during brachytherapy planning, the results were comparable to MRI-based approach[52,53]. In a feasibility study of using transabdominal ultrasound for brachytherapy planning, 60 patients of stage IIB to III B cervical cancer were included. Brachytherapy was performed with ultrasound guidance. Reference points were defined on sonography as a surrogate for target and extrapolated on to CT. Point A planning with OAR optimization was done. With a median follow up of 49 months, the five-year local and pelvic control, DFS and OS were 93.3, 85, 71.7, and 71.7 per cent, respectively. Hence, USG may be an acceptable alternative to MRI brachytherapy[54].

In addition to the above techniques, our institution has developed innovative techniques in brachytherapy of cervical cancer. A novel technique using a single ovoid and a central tandem was reported for patients who have reduced vaginal space that limits standard intracavitary procedures. During the first application, central tandem and a single ovoid is inserted, the other ovoid being replaced by a rubber tube. For the subsequent application, contralateral ovoid is inserted[55]. This modified high dose rate (HDR) intracavitary technique may prove an alternative for centres where interstitial brachytherapy for cancer of the cervix is not available.

Tata Memorial Centre undertook a nationwide audit to understand brachytherapy availability for cervical cancer and estimated the burden of LACC in each State and the required infrastructure

for EBRT and brachytherapy to meet the current needs of cervical cancer[56]. Brachytherapy deficit was noted in 14 Indian States, and it was estimated that additional 58 brachytherapy units would be needed. It was estimated that, with the current BT deficit, approximately 14,000 women in India may have delayed or no access to brachytherapy. As the infrastructural deficit may take time to expand, various strategies to improve brachytherapy access including altered abbreviated brachytherapy fractionation schedules are being investigated[57].

Recurrent cancers

Local recurrences following suboptimal surgery without appropriate adjuvant treatment are not uncommon in patients with cervical cancer in India and in many other LMICs where adequate surgical expertise or referral practices for adjuvant radiotherapy may not be in place[58]. Even after definitive non-surgical treatments, 30-50 per cent relapse rates have been reported in the literature[59]. In a retrospective study of patients with recurrent vault/vaginal cancers treated with interstitial brachytherapy from 2000 to 2008, modest clinical outcomes with three-year locoregional relapse-free survival, DFS and OS of 62.4, 59.5 and 73.4 per cent, respectively, with acceptable late toxicities were seen[60]. A prospective phase II study integrating tomotherapy-based intensity-modulated radiotherapy (IMRT), interstitial brachytherapy and 3D planning for all patients reported five-year actuarial DFS and OS of 75 and 71 per cent with grade III/IV rectal and genitourinary toxicity in five and three per cent patients, respectively[61]. In a phase II study of MRI and PET-guided interstitial brachytherapy for post-surgical vaginal recurrences of cervical cancer, patients were recruited with residual or recurrent disease after hysterectomy. Patients underwent baseline T2W MRI, 18 F-FDG, 18 F-FLT and 18 F-F Miso PET and received EBRT 50 Gy/25#. MRI was performed at brachytherapy and utilized for the delineation of clinical target volume. While patients with parametrial disease at baseline received interstitial brachytherapy (16-20 Gy/4-5#), those with vaginal disease received intracavitary brachytherapy (12-14 Gy/2-4#). Image-guided radiation and brachytherapy was associated with good-to-excellent local control, DFS and OS of 84, 73 and 74.5 per cent, respectively, in patients with vaginal recurrences of cervical cancer[62]. Functional score stability was observed from baseline till 24 and 60 months. For the symptom domain, at two and five years post-radiotherapy, the difference in toxicities were not significant.

Only a few studies worldwide have focussed on re-irradiation of gynaecological cancers with brachytherapy ± external radiation. The Centre has published outcomes in this setting using individualized intracavitary/interstitial brachytherapy techniques. With a median follow up of 25 months, two-year local control, DFS and OS were 44, 42, and 52 per cent, respectively. This study also showed that the outcome was better with higher doses[63]. An update of this series showed two-year local control, DFS and OS of 54, 50 and 64 per cent, respectively. Grade 3 or higher toxicity was seen in 22.4 per cent patients[64]. This was superior to systemic chemotherapy, targeted therapy or immunotherapy for treating central relapses that were not amendable for surgery[65].

Toxicity reduction studies

In a series of studies, dose-volume response has been reported for various normal pelvic organs with an aim to reduce long-term toxicity. The relationship between dose-volume parameters and severe bowel toxicity was analyzed in a study of 71 patients undergoing post-operative radiation for cervical cancer. Grade 2 or higher bowel toxicity was seen in 30.9 per cent grade 3 or higher bowel toxicity in 12.6 per cent patients. On univariate analysis, V15 small bowel (SB) <275 ml, V30 SB <190 ml, and V40 SB <150 ml and V15 large bowel (LB) <250 ml and V40 LB <90 ml predicted for the absence of grade 3 or higher toxicity. On multivariate analysis, only V15 SB and V15 LB were significant[66]. In another study of 103 patients, V30 peritoneal cavity ≥900 ml and use of concurrent chemotherapy independently predicted acute toxicity. The presence of acute grade ≥III toxicity independently predicts late toxicity[67]. While the QUANTEC essentially reported a correlation of radiation dose with acute toxicity, our study was the first to report a correlation of radiation dose with late toxicity and possible potential of advanced techniques in toxicity reduction which was subsequently tested and validated in a phase III trial (PARCER NCT 01279135)[38]. Other studies have focussed on reporting dose-volume and toxicity correlation for rectum, duodenum, bone marrow and vagina[68,69]. Prospective work from the institution has also focussed on reporting the temporal trends of late toxicity after pelvic radiation. This reporting of temporal trends may help in providing better understanding of reporting late toxicity as prevalence rather than incidence.

Translational research studies

Tata Memorial Centre also has actively contributed to translational research in cervical cancer in patients undergoing treatment. Some of the notable contributions include the role of viral integration site (episomal) and persistent HPV viral load as a predictor of recurrence after chemoradiation[70]. In a prospective study, patients with persistent HPV 16/18 infection had a significantly higher overall and locoregional relapses (49 and 32%) as compared to those who had clearance of HPV by nine months (28 and 11% with P=0.024 and P=0.02, respectively). Furthermore, persistent HPV infection by 24 months showed a significant impact on LRC and recurrence-free survival (RFS)[71,72].

Our institution was also one of the few institutions to prospectively test the impact of cancer stem cells on outcomes of cervical cancer following chemoradiation. Pre-treatment and post biopsies were performed for 150 patients. At baseline, moderate-to-strong immunohistochemical expression of SOX-2, OCT-4, Nanog, CD44 and Podoplanin was observed in 12.8, 4.8, 24.4, 15.5 and 1.3 per cent patients, respectively. At a median follow up of 30 months, locoregional and distant relapse was observed in 12.2 and 23.1 per cent patients. The three-year DFS was 87 per cent. Moderate-to-high CSC expression and CD44 low status (P<0.04) independently predicted for locoregional relapse-free survival[73]. The results of these studies have also been incorporated in to the international multicentric study BIOEMBRACE-1[74], which is investigating markers of epithelial–mesenchymal translation, stemness and immune response with disease recurrence in patients treated with chemoradiation for LACC recruited within EMBRACE studies.

Research and education

The Tata Memorial Centre has contributed towards training and education in gynaecological cancers within the framework of educational collaborations with the IAEA conducting training of international participants for gynaecological brachytherapy. In collaboration with Elekta, the Centre conducts the brachytherapy training school Brachy Academy[75], and the institution also accepts scholars from global health programmes.

Conclusion & future directions

Tata Memorial Centre is presently leading the investigation of the role of HIV protease and Protein kinase B (Akt) inhibitor Nelfinavir in improving disease-free survival in patients receiving chemoradiation for LACC in an ongoing randomized trial[76]. In another ongoing randomized trial optimal fractionation for the palliation of advanced cervical cancer is being studied[34].

To summarize, Tata Memorial Centre has provided substantial contributions in various aspects of cervical cancer prevention, treatment and research over the past three decades. This includes contribution towards prevention through screening, practice-changing therapeutic trials, advancing radiation technologies, brachytherapy, educational and training activities and national and international collaborations.

***Financial support & sponsorship*:** None.

***Conflicts of Interest*:** None.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; *71* : 209-49.
2. Sankaranarayanan R, Budukh AM, Rajkumar R. Effective screening programmes for cervical cancer in low- and middle-income developing countries. *Bull World Health Organ* 2001; *79* : 954-62.
3. Shrivastava SK, Lewis S, Sastri SC, Lavanya G, Mahantshetty U, Engineer R. Cancer cervix: Establishing an evidence-based strategy, an experience of a tertiary care centre in India. *Curr Probl Cancer* 2018; *42* : 137-47.
4. World Health Organization. *Screening for cervical cancer*. Available from: *https://www.who.int/cancer/detection/cervical_cancer_screening/en/*, accessed on January 24, 2021.
5. School of Public Health, Postgraduate Institute of Medical Educational & Research, Chandigarh, India. *Health technology assessment of strategies for cervical cancer screening in India.* Available from: *https://dhr.gov.in/sites/default/files/HTA_CaCx%20Screening%20in%20India.pdf*, accessed on January 24, 2021.
6. Shastri SS, Mittra I, Mishra GA, Gupta S, Dikshit R, Singh S, *et al.* Effect of VIA screening by primary health workers: Randomized controlled study in Mumbai, India. *J Natl Cancer Inst* 2014; *106* : dju009.
7. Legood R, Gray AM, Mahé C, Wolstenholme J, Jayant K, Nene BM, *et al*. Screening for cervical cancer in India: How much will it cost a trial based analysis of the cost per case detected. *Int J Cancer* 2005; *117* : 981-7.
8. Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, *et al*. HPV screening for cervical cancer in rural India. *N Engl J Med* 2009; *360* : 1385-94.
9. Pimple S, Shastri SS. Comparative evaluation of human papilloma virus-DNA test verses colposcopy as secondary cervical cancer screening test to triage screen positive women on primary screening by visual inspection with 5% acetic acid. *Indian J Cancer* 2014; *51* : 117-23.

10. Mishra GA, Pimple SA, Gupta SD. Cervical cancer screening in low resource settings: Cytology versus HPV triage for VIA positive women. *Int J Prev Med* 2019; *10* : 138.
11. Budukh A, Palayekar V, Maheshwari A, Deodhar K, Purwar P, Bagal S, *et al*. Menstrual pad, a cervical cancer screening tool, a population-based study in rural India. *Eur J Cancer Prev* 2017; *27* : 1.
12. Qiao YL, Sellors JW, Eder PS, Bao YP, Lim JM, Zhao FH, *et al.* A new HPV-DNA test for cervical-cancer screening in developing regions: A cross-sectional study of clinical accuracy in rural China. *Lancet Oncol* 2008; *9* : 929-36.
13. Basu P, Muwonge R, Bhatla N, Nene BM, Joshi S, Esmy PO, *et al.* Two-dose recommendation for human papillomavirus vaccine can be extended up to 18 years – Updated evidence from Indian follow-up cohort study. *Papillomavirus Res* 2019; *7* : 75-81.
14. Sankaranarayanan R, Prabhu PR, Pawlita M, Gheit T, Bhatla N, Muwonge R, *et al*. Indian HPV Vaccine Study Group. Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study. *Lancet Oncol* 2016; *17* : 67-77.
15. Bhatla N, Berek JS, Cuello Fredes M, Denny LA, Grenman S, Karunaratne K, *et al.* Revised FIGO staging for carcinoma of the cervix uteri. *Int J Gynecol Obstet* 2019; *145* : 129-35.
16. Raut A, Chopra S, Mittal P, Patil G, Mahantshetty U, Gurram L, *et al*. FIGO classification 2018: Validation study in patients with locally advanced cervix cancer treated with chemo-radiation. *Int J Radiat Oncol Biol Phys* 2020; *108* : 1248-56.
17. McNeil C. New standard of care for cervical cancer sets stage for next questions. *J Natl Cancer Inst* 1999; *91* : 500-1.
18. Gupta S. Adjuvant chemotherapy in locally advanced cervical cancer: The ceiling remains unbroken. *J Gynecol Oncol* 2019; *30* : 54-6.
19. Shrivastava S, Mahantshetty U, Engineer R, Chopra S, Hawaldar R, Hande V, *et al*. Cisplatin chemoradiotherapy vs radiotherapy in FIGO stage IIIB squamous cell carcinoma of the uterine cervix: A randomized clinical trial. *JAMA Oncol* 2018; *4* : 506-13.
20. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol* 2008; *26* : 5802-12.
21. Gupta S, Maheshwari A, Parab P, Mahantshetty U, Hawaldar R, Chopra S, *et al*. Neoadjuvant chemotherapy followed by radical surgery versus concomitant chemotherapy and radiotherapy in patients with stage IB2, IIA, or IIB squamous cervical cancer: A randomized controlled trial. *J Clin Oncol* 2018; *36* : 1548-55.
22. Kenter G, Greggi S, Vergote I, Katsaros D, Kobierski J, Massuger L, *et al*. Results from neoadjuvant chemotherapy followed by surgery compared to chemoradiation for stage Ib2-IIb cervical cancer, EORTC 55994. *J Clin Oncol* 2019; *37* (Suppl 15) : 5503.
23. Shrivastava S, Mahantshetty U, Engineer R, Tongaonkar H, Kulkarni J, Dinshaw K. Treatment and outcome in cancer cervix patients treated between 1979 and 1994: A single institutional experience. *J Cancer Res Ther* 2013; *9* : 672-9.
24. Kumar L, Gupta S. Integrating chemotherapy in the management of cervical cancer: A critical appraisal. *Oncology (Switzerland)* 2016; *91* : 8-17.
25. Chopra S, Gupta M, Mathew A, Mahantshetty U, Engineer R, Lavanya G, *et al.* Locally advanced cervical cancer: A study of 5-year outcomes. *Indian J Cancer* 2018; *55* : 45-9.
26. Mittal P, Chopra S, Pant S, Mahantshetty U, Engineer R, Ghosh J, *et al*. Standard chemoradiation and conventional brachytherapy for locally advanced cervical cancer: Is it still applicable in the era of magnetic resonance-based brachytherapy? *J Glob Oncol* 2018; *4* : 1-9.
27. Gurram L, Patil R, Chopra S, Maheshwari A, Shylasree TS, Gupta S, *et al.* Evaluation of outcomes in patients of cervical cancer with lower one third vaginal involvement: A single institutional experience. *Gynecol Oncol* 2020; *159* : 359-64.
28. Salunkhe R, Chopra S, Kulkarni S, Shetty N, Engineer R, Mahantshetty U, *et al.* Outcomes of locally advanced cervical cancer presenting with obstructive uropathy: An institutional audit. *Indian J Cancer* 2020; *57* : 416-22.
29. Rekhi B, Patil B, Deodhar KK, Maheshwari A, Kerkar RA, Gupta S, *et al.* Spectrum of neuroendocrine carcinomas of the uterine cervix, including histopathologic features, terminology, immunohistochemical profile, and clinical outcomes in a series of 50 cases from a single institution in India. *Ann Diagn Pathol* 2013; *17* : 1-9.
30. Dhir AA, Sawant S, Dikshit RP, Parikh P, Srivastava S, Badwe R, *et al.* Spectrum of HIV/AIDS related cancers in India. *Cancer Causes Control* 2008; *19* : 147-53.
31. Shrivastava SK, Engineer R, Rajadhyaksha S, Dinshaw KA. HIV infection and invasive cervical cancers, treatment with radiation therapy: Toxicity and outcome. *Radiother Oncol* 2005; *74* : 31-5.
32. Mishra SK, Laskar S, Muckaden MA, Mohindra P, Shrivastava SK, Dinshaw KA. Monthly palliative pelvic radiotherapy in advanced carcinoma of uterine cervix. *J Cancer Res Ther* 2005; *1* : 208-12.
33. Jain S, Engineer R, Ostwal V, Ramaswamy A, Chopra S, Desouza A, *et al*. Addition of short course radiotherapy in newly diagnosed locally advanced rectal cancers with distant metastasis. *Asia Pac J Clin Oncol* 2021; *17* : e70-6.
34. National Institute of Health. US National Library of Medicine. ClincalTrails.gov. *Pallaiative radiation for adraced cervical cancer (RAPPAL)*. Available from: *https://clinicaltrials.gov/ct2/show/NCT03997110*, accessed on January 24, 2021.
35. Chopra SJ, Mathew A, Maheshwari A, Bhatla N, Singh S, Rai B, *et al.* National cancer grid of India consensus guidelines on the management of cervical cancer. *J Glob Oncol* 2018; *4* : 1-15.
36. Gudi S, Naga P, Mahantshetty U, Chopra S, Engineer R, Ghadi Y, *et al*. Clinical outcome with dose escalation using IMRT in Cervical Cancer: A phase II randomized trial. Radiother Oncol 2018; *127* : S199-200.
37. Chopra S, Engineer R, Mahantshetty U, Misra S, Phurailatpam R, Paul SN, *et al.* Protocol for a phase III randomized trial of image-guided intensity modulated radiotherapy (IG-IMRT) and conventional radiotherapy

for late small bowel toxicity reduction after postoperative adjuvant radiation in Ca cervix. *BMJ Open* 2012; *2* : e001896.

38. Chopra S, Gupta S, Kannan S, Dora T, Engineer R, Mangaj A, *et al*. Late toxicity after adjuvant conventional radiation versus image-guided intensity-modulated radiotherapy for cervical cancer (PARCER): A randomized controlled trial. *J Clin Oncol* 2021; *39* : 3682-92.
39. Lewis S, Chopra S, Naga P, Pant S, Dandpani E, Bharadwaj N, *et al*. Acute hematological toxicity during post-operative bowel sparing image-guided intensity modulated radiation with concurrent cisplatin. *Br J Radiol* 2018; *91* : 20180005.
40. Cozzi L, Dinshaw KA, Shrivastava SK, Mahantshetty U, Engineer R, Deshpande DD, *et al.* A treatment planning study comparing volumetric arc modulation with RapidArc and fixed field IMRT for cervix uteri radiotherapy. *Radiother Oncol* 2008; *89* : 180-91.
41. Panda S, Swamidas J, Chopra S, Mangaj A, Fogliata A, Kupelian P, *et al*. Treatment planning comparison of volumetric modulated arc therapy employing a dual-layer stacked multi-leaf collimator and helical tomotherapy for cervix uteri. *Radiat Oncol* 2020; *15* : 22.
42. Swamidas J, Pradhan S, Chopra S, Panda S, Gupta Y, Sood S, *et al*. Development and clinical validation of Knowledge-based planning for Volumetric Modulated Arc Therapy of cervical cancer including pelvic and para aortic fields. *Phys Imaging Radiat Oncol* 2021; *18* : 61-7.
43. Kumar A, Chopra S, Mahantshetty U, Reddy VA. Brachytherapy in India: Learning from the past and looking into the future. *Brachytherapy* 2020; *19* : 861-73.
44. Mahantshetty U, Lewis S, Engineer R, Swamidas J, Chopra S, Gurram L, *et al*. Low-dose-rate versus high-dose-rate intracavitary brachytherapy in cervical cancer - Final results of a phase I randomized trial. *Brachytherapy* 2021; *20* : 1146-55.
45. Hendry J, Jones GW, Mahantshetty U, Sarria G, da Motta NW, Fidarova E, *et al*. Radiobiological analysis of outcomes using external beam radiotherapy plus high dose-rate brachytherapy (4x7 Gy or 2x9 Gy) for cervical cancer in a multi-institution trial. *Intl J Rad Oncol Biol Phys* 2017; *99* : 1313-4.
46. The International Commission on Radiation Units and Measurements Report 89. Prescribing, recording, and reporting brachytherapy for cancer of the cervix. *J ICRU* 2013; *13* : 1-10.
47. Mahantshetty U, Sturdza A, Naga Ch P, Berger D, Fortin I, Motisi L, *et al.* Vienna-II ring applicator for distal parametrial/ pelvic wall disease in cervical cancer brachytherapy: An experience from two institutions: Clinical feasibility and outcome. *Radiother Oncol* 2019; *141* : 123-9.
48. Chakraborty S, Mahantshetty U, Chopra S, Lewis S, Hande V, Gudi S, *et al.* Income generated by women treated with magnetic resonance imaging-based brachytherapy: A simulation study evaluating the macroeconomic benefits of implementing a high-end technology in a public sector healthcare setting. *Brachytherapy* 2017; *16* : 981-7.
49. National Institute of Health. US National Library of Medicine. *Image based brachytherapy in locally advanced cervical cancers - A randomized controlled trial (COMBAT-Cx)*. Available from: *https://clinicaltrials.gov/ct2/show/NCT03005743*, accessed on January 16, 2021.
50. Schlemmer HP, Bittencourt LK, D'Anastasi M, Domingues R, Khong PL, Lockhat Z, *et al.* Global challenges for cancer imaging. *J Glob Oncol* 2018; *4* : 1-10.
51. Chatterjee A, Grover S, Gurram L, Sastri S, Mahantshetty U. Patterns of cervical cancer brachytherapy in India: Results of an online survey supported by the Indian brachytherapy society. *J Contemp Brachytherapy* 2019; *11* : 527-33.
52. Mahantshetty U, Naga Ch P, Khadanga CR, Gudi S, Chopra S, Gurram L, *et al.* A Prospective comparison of computed tomography with transrectal ultrasonography assistance and magnetic resonance imaging-based target-volume definition during image guided adaptive brachytherapy for cervical cancers. *Int J Radiat Oncol Biol Phys* 2018; *102* : 1448-56.
53. Mahantshetty U, Khanna N, Swamidas J, Engineer R, Thakur MH, Merchant NH, *et al.* Trans-abdominal ultrasound (US) and magnetic resonance imaging (MRI) correlation for conformal intracavitary brachytherapy in carcinoma of the uterine cervix. *Radiother Oncol* 2012; *102* : 130-4.
54. Nayak AS, Engineer R, Mahantshetty UM, Sastri S, Swamidas J, ShrivastavaSK, *et al*. Transabdominal ultrasonography based high dose rate conformal intracavitary brachytherapy in cervical carcinoma. *Intl J Radiat Oncol Biol Phys* 2017; *99* : E304.
55. Sharma V, Mahantshetty U, Menon V, Sharma D. A modified technique for high-dose-rate intracavitary brachytherapy in advanced cancer of the cervix. *Brachytherapy* 2003; *2* : 246-8.
56. Chopra S, Shukla R, Budukh A, Shrivastava SK. External radiation and brachytherapy resource deficit for cervical cancer in India: Call to action for treatment of all. *J Glob Oncol* 2019; *5* : 1-5.
57. Mahantshetty U, Gurram L, Bushra S, Ghadi Y, Aravindakshan D, Paul J, *et al*. Single application multifractionated image guided adaptive high-dose-rate brachytherapy for cervical cancer: dosimetric and clinical outcomes. *Int J Radiat Oncol Biol Phys* 2021; *111* : 826-34.
58. Saibishkumar EP, Patel FD, Ghoshal S, Kumar V, Karunanidhi G, Sharma SC. Results of salvage radiotherapy after inadequate surgery in invasive cervical carcinoma patients: A retrospective analysis. *Int J Radiat Oncol Biol Phys* 2005; *63* : 828-33.
59. Hong JH, Tsai CS, Lai CH, Chang TC, Wang CC, Chou HH, *et al*. Recurrent squamous cell carcinoma of cervix after definitive radiotherapy. *Int J Radiat Oncol Biol Phys* 2004; *60* : 249-57.
60. Mulye G, Gudi S, Gurram L, Chopra S, Scaria L, Kadam S, *et al*. Clinical outcomes of patients treated with template based high dose rate interstitial brachytherapy boost for gynaecological cancers- A retrospective analyses. *Brachytherapy* 2019; *18* : S58.
61. Engineer R, Chopra S, Mahantshetty U, Maheshwari A, Kerkar R, Phurailatpam R, *et al* . OC-0353: EBRT and interstitial brachytherapy for recurrent vault carcinomas: Factors influencing the outcomes. *Radiother Oncol* 2016; *119* : S162-63.

62. Chopra S, Engineer R, Shah S, Shukla R, Dora T, Gupta P, *et al*. MRI and PET guided interstitial brachytherapy for post-surgical vaginal recurrences of cervical cancer: Results of phase II study. *Int J Radiat Oncol Biol Phys* 2019; *106* : 310-19.

63. Mahantshetty U, Kalyani N, Engineer R, Chopra S, Jamema S, Ghadi Y, *et al.* Reirradiation using high-dose-rate brachytherapy in recurrent carcinoma of uterine cervix. *Brachytherapy* 2014; *13* : 548-53.

64. Lewis S, Mahantshetty U, Engineer R, Chopra S, Kalyani N, Shrivastava SK.. Reirradiation with high-dose-rate brachytherapy in recurrent cervical cancer - An update. *Brachytherapy* 2016; *15* : S91.

65. Tewari KS, Sill MW, Penson RT, Huang H, Ramondetta LM, Landrum LM, *et al.* Bevacizumab for advanced cervical cancer: Final overall survival and adverse event analysis of a randomized, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet* 2017; *390* : 1654-63.

66. Chopra S, Krishnatry R, Dora T, Kannan S, Thomas B, Sonawone S, *et al.* Predictors of late bowel toxicity using three different methods of contouring in patients undergoing post-operative radiation for cervical cancer. *Br J Radiol* 2015; *88* : 20150054.

67. Chopra S, Dora T, Chinnachamy AN, Thomas B, Kannan S, Engineer R, *et al.* Predictors of grade 3 or higher late bowel toxicity in patients undergoing pelvic radiation for cervical cancer: Results from a prospective study. *Intl J Radiat Oncol Biol Phys* 2014; *88* : 630-5.

68. Singh R, Chopra S, Engineer R, Paul S, Kannan S, Mohanty S, *et al*. Dose-volume correlation of cumulative vaginal doses and late toxicity after adjuvant external radiation and brachytherapy for cervical cancer. *Brachytherapy* 2017; *16* : 855-61.

69. George G, Lewis S, Chopra S, Phurailatpam R, Engineer R. A retrospective study of the dosimetric parameters and duodenal toxicity in patients with upper gastrointestinal and gynaecological cancers treated with radiation therapy. *Clin Oncol (R Coll Radiol)* 2020; *32* : e53-9.

70. Das P, Thomas A, Kannan S, Deodhar K, Shrivastava SK, Mahantshetty U, *et al*. Humanpapillomavirus (HPV) genome status & cervical cancer outcome – A retrospective study. *Indian J Med Res* 2015; *142* : 525-32.

71. Mahantshetty U, Teni T, Naga P, Hotwani C, Umesh S, Kannan S, *et al*. Impact of HPV 16/18 infection on clinical outcomes in locally advanced cervical cancers treated with radical radio (chemo) therapy – A prospective observational study. *Gynecol Oncol* 2018; *148* : 299-304.

72. Hotwani C, Pawar S, Kannan S, Hande V, Kedar D, Chopra S, *et al*. Quantitative estimation of Hpv infection, viral load & its impact on clinical outcome in locally advanced cervical cancer treated with radical radio (chemo) therapy: An observational study. *J Can Res Therap* 2017; *13* (Suppl) : S362.

73. Chopra S, Deodhar K, Pai V, Pant S, Rathod N, Goda JS, *et al.* Cancer stem cells, CD44, and outcomes following chemoradiation in locally advanced cervical cancer: Results from a prospective study. *Int J Radiat Oncol Biol Phys* 2019; *103* : 161-8.

74. A pilot evaluation of prognostic molecular and serum biomarkers of disease recurrence after chemoradiation in patients with locally advanced cervical cancer from EMBRACE study group (BIO-EMBRACE-1). Available from: *https://www.embracestudy.dk/UserUpload/PublicDocuments/Docs/BIO-EMBRACE-1_Version_1.4_clean_14032018.pdf*, accessed on January 16, 2021.

75. BrachyAcademy. Available from: *https://www.brachyacademy.com/*, accessed on January 26, 2021.

76. National Institute of Health. US National Library of Medicine. *Radiosensitizing effect of nelfinavir in locally advanced carcinoma of cervix (NELCER)*. Available from: *https://clinicaltrials.gov/ct2/show/NCT03256916*, accessed on January 16, 2021.

For correspondence: Dr Supriya Chopra, Department of Radiation Oncology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai 400 012, Maharashtra, India
e-mail: supriyasastri@gmail.com