Mini review

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Prognostic indicators for treatment outcome in cervical cancer: a mini review

Abstract

While the advancements in treatment options for cervical cancer patients have improved treatment outcomes, treatment related toxicity and recurrence remain a significant issue to overcome. Research has focused on identifying significant indicators for treatment outcomes, but studies have not yet established accepted indicators for the field. The current mini-review provides a summary of toxicity and recurrence outcomes, in addition to both clinical and biological indicators for improved treatment outcome for cervical cancer.

Keywords: cervical cancer, indicators, treatment outcome, biomarkers

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Abbreviations: RT, radiotherapy; CCRT, concomitant chemoradiotherapy; BT, brachytherapy; PET, positron emission tomography; SUV, standard uptake value; MTV, metabolic tumor volume; TGV, tumor glycolytic volume

Introduction

Over 50years ago, the Papanicolaou (Pap) smear was introduced in the US which has resulted in significant declines in cervical cancer incidences and deaths. However, cervical cancer remains the third most prevalent cancer in females worldwide.[1,2] At advanced stages of the disease, treatment with radiotherapy (RT) alone decreases 5year survival rates leading to the implementation of multiple randomized clinical studies.[3] Advancements found that combining chemotherapy and RT resulted in increased progression-free and overall survival with improved local control.[3–5] As a result, in 1999 the US National Cancer Institute announced concomitant chemotherapy and RT (CCRT) as the standard of care for cervical cancer.[4,6] Since the acceptance of CCRT, the most significant advancement in treatment of cervical cancer over the last 20years has been brachytherapy (BT), which further improved survival rates.[5] Dose and fractionation determination have been improved due to greater understanding of tumor biology and radiation effects, but remain limited by tolerance of normal tissue for late effects and therefore also limiting the cure rate.[3,5] While CCRT involving BT advanced treatment outcomes, the improved survival rates have come at the cost of increased acute and late toxicity rates.[4,6]

The current standard of care for locally advanced cervical cancer is a combination of external beam radiotherapy and intracavitary BT with concurrent chemotherapy. High dose rate BT is an important component in the curative management of cervix carcinoma and is most commonly delivered in five fractions using tandem&ring or tandem&ovoids applicators.[7] Despite advanced treatment plans, treatment-related toxicity and recurrence still occur in a significant number of patients after treatment due to chemotherapy agents increasing radiosensitivity and ultimately the radiation hazard.[8,9] Although local control and toxicity rates have been slightly improving, recurrence rates remain as high as one-third, and toxicity rates remain as high as one-half among cervical cancer patients.[10,11] Therefore, it has been of great clinical importance to investigate early indicators for optimal therapeutic response based on which treatments can be adjusted to minimize recurrence or toxicity outcomes. Once prognostic factors are identified, the aggressiveness of treatment can be properly determined. The current mini-review provides a summary of toxicity and recurrence outcomes, in addition to both clinical and biological indicators for improved treatment outcomes of cervical cancer patients.

Discussion

Randomized studies of locally advanced cervical cancer patients showed CCRT improves long-term survival when compared to RT alone, though concurrent treatments result in more frequent acute toxicity and a 5% chance of late stage pelvic complications.[3] The most effective cytotoxic agent for enhancing RT treatment is Cisplatin, which provides lower toxicities compared to other agents, while still remaining as effective.[3] However, the proposed mechanism for doing so involves the drug inhibiting lethal or sub lethal damage repair and increasing hypoxic cell sensitization.[3–5] This inability to repair radiation damage increases the importance of mitigating treatment related toxicity.

The main scoring systems for toxicity include RTOG/ARMSC and NCI/CTC for both acute and late effects. Acute effects occur during treatment, are often reversible, and resolve without medical intervention, whereas late effects are delayed months or evenyears after treatment, are typically permanent, and can decrease overall quality of life. The most common resulting toxicity is gastrointestinal (GI) involving symptoms such as diarrhea, abdominal cramps and pain, proctitis, and another leading toxicity is genitourinary (GU) involving symptoms such as frequency and dysuria. Late GI toxicity typically occurs within 2years of treatment in 10% of patients who have symptoms, and GU toxicity typically occurs within 1year in 33% of patients who show symptoms.[3] Moderate and severe toxicity rates can be as high as 10% and rise over time, and morbidity rates remain at 5-7% for GI and 1-4% for GU.[3]

To reduce treatment related toxicity and recurrence, prognostic indicators have been studied. Pathological prognostic factors known to have an effect on treatment outcomes in cervical cancer patients include presence of lymph node metastasis, age, histological tumor type and grade, tumor size, FIGO stage, lympho-vascular space invasion, and anemia.[6,12,13] Clinical parameters were also explored for their effects on treatment outcomes, including disease staging, prescribed dose, dosimetric values for tumor and organs at risk volumes, and total treatment duration.[13–17] These clinical and pathological prognostic

factors have been studied extensively and deemed important for prediction of survival outcomes. Despite optimizing treatments based on these factors, the recurrence rates remain among 30-40% in patients having locally advanced cervical cancer.[6] Successive research efforts to further optimize therapeutic treatment involved studying tumor microenvironments. Characteristics including hypoxia, interstitial fluid pressure, angiogenesis, and immune landscape have shown to pose increased risks leading to recurrence and mortality.[6]

Biological parameters have also been studied for their prognostic abilities. While the use of F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has shown importance and improvement in detecting lymph node metastasis and determining disease extent due to higher sensitivity and specificity, it has also shown an importance in anatomical and functional metabolic prediction of treatment outcomes.[12] High FDG uptake of the primary tumor, based on the standard uptake value (SUV), indicates poor prognosis and clinical outcome.[12] Researchers have begun to investigate the prognostic value in biological parameters from PET imaging used for determining tumor aggressiveness and staging of disease.[18] Biomarkers of interest have included SUV mean and maximum, metabolic tumor volume (MTV), and tumor glycolytic volume (TGV) for the prediction of therapeutic response as defined by overall survival, disease free survival, loco-regional control, and recurrence after treatment.[6,8,12,19,20] MTV takes into account the amount of active metabolic tumor cells, whereas TGV takes into account both tumor volume and metabolic activity. Utilizing functional parameters may advance contouring capabilities for the tumor volume by having biologically relevant and heterogeneity information to improve treatment plans.[6] However, these biomarkers only provide a single value to describe the tumor, thus it is necessary to find parameters to understand the metabolism of sub-volumes of the tumor and provide early evaluation of a patient's risk for recurrence or toxicity.

Conclusion

Over the last 20years there has been great progress and advancements made in the treatment of locally advanced cervical cancer. The standard of care has become concurrent chemoradiotherapy, which has improved survival rates and decreased recurrence rates, but has come at the cost of increased acute and late toxicity rates. Even with such advancements, the recurrence and toxicity rates in these patients still remain high. As a result, it is important to find indicators for improving treatment outcomes. While clinical and pathological parameters have been studied extensively and were found to play a role in optimizing treatments, further reductions in recurrence and toxicity rates are still necessary. Biological parameters have also been included in recent studies for their anatomical and functional metabolic prediction of treatment outcomes. Still, these only provide a single value to describe the tumor rather than a metabolic understanding of sub-volumes of a tumor. It is imperative that research for indicators is continued to discover a greater understanding of early evaluations in determining a patient's risk for recurrence or toxicity.

Acknowledgements

Conflict of interest

Author declares that there is no conflict of interest.

References

1. Health N. I. o. NIH Fact Sheets. *Cervical Cancer*. 2010.

2. Bodurka-Bevers D, Morris M, Eifel PJ, et al. Posttherapy Surveillance of Women with Cervical Cancer: An Outcomes Analysis. *Gynecologic Oncology*. 2000;78(2):187–193.

3. Maduro JH, Pras E, Willemse PH, et al. Acute and long-term toxicity following radiotherapy alone or in combination with chemotherapy for locally advanced cervical cancer. *Cancer Treatment Reviews*. 2003;29(6):471–488.

4. Green JA, Kirwan JM, Tierney JF, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet*. 2001;358(9284):781–786.

5. Kirwan JM, Symonds P, Green JA, et al. A systematic review of acute and late toxicitiy of concomitant chemoradiation for cervical cancer. *Radiother Oncol*. 2003;68(3):217–226.

6. Herrera FG, Thomas B, John OP, et al. [18F] FDG-PET/CT metabolic parameters as useful prognostic factors in cervical cancer patients treated with chemo-radiotherapy. *Radiation Oncology*. 2016;11:43.

7. Viswanathan AN, Beriwal S, De Los Santos JF, et al. The American Brachytherapy Society Treatment Recommendations for Locally Advanced Carcinoma of the Cervix Part II: High Dose-Rate Brachytherapy. *Brachytherapy*. 2012;11(1):47–52.

8. Park JJ, Kim CK, Park BK. Prognostic value of diffusion-weighted magnetic resonance imaging and 18F-fluorodeoxyglucose-positron emission tomography/computed tomography after concurrent chemoradiotherapy in uterine cervical cancer. *Radiation Oncology*. 2016;120(3):507–511.

9. Lan ML, Yu X, Xiao H, et al. Clinical outcomes and toxicity of postoperative intensity-modulated versus three-dimensional conformal radiation therapy in patients with cervical cancer. *Asia Pac J Clin Oncol*. 2016;12(4):430–436.

10. Gadducci A, Tana R, Cosio S, et al. Treatment Options in Recurrent Cervical Cancer (Review). *Oncol Lett*. 2010;1(1):3–11.

11. Roszak A, Wareńczak-Florczak Z, Bratos K, et al. Incidence of radiation toxicity in cerviacl cancer and endometrial cancer patients treated with radiotherapy alone versus adjuvant radiotherapy. *Reports of Practical Oncology and Rep Pract Oncol Radiother*. 2012;17(16):332–338.

12. Vural GU, Akkas BE, Demirel BB. Standardized uptake value and metabolic tumor volume measured by 18F FDG Pet/CT are sensitive biomarkers for the presence of lymph node metastasis in patients with cervical cancer carcinoma. *Rev Esp Med Nucl Imagen Mol*. 2014;33(5):268–273.

13. Chen CC, Wang L, Lin JC, et al. The prognostic factors for locally advanced cervical cancer patients treated by intensity-modulated radiation therapy with concurrent chemotherapy. *Journal of the Formosan Medical Association*. 2015;114(3):231–237.

14. Fyles A, Keane TJ, Barton M, et al. The effect of treatment duration in the local control of cervical cancer. *Radiotherapy and Oncology*. 1992;25(4):273–279.

15. Mazeron R, Castelnau-Marchand P, Dumas I, et al. Impact of treatment time and dose escalation on local control in locally advanced cervical cancer treated by chemoradiation and image-guided pulsed-dose rate adaptive brachytherapy. *Radiation Oncology*. 2015;114(2):257–263.

16. Shaverdian N, Gondi V, Sklenar KL, et al. Effects of Treatment Duration During Concomitant Chemoradiation Therapy for Cervical Cancer. *Int J Radiation Oncol Biol Phys*. 2013;86(3):562–568.

17. Hunter GK, Reddy CA, Klein EA, et al. Long-Term (10Year) Gastrointestinal and Genitourinary Toxicity after Treatment with External Beam Radiotherapy, Radical Prostatectomy, or Brachytherapy for Prostate Cancer. *Prostate Cancer*. 2012;2012:853487.

18. Nair VS, Gevaert O, Davidzon G, et al. Prognostic Pet 18F-FDG uptake imaging features are associated with major oncogenomic alterations in patients with resected non-small cell lung cancer. *Cancer Res*. 2012;72(15):3725–3734.

19. Nakamura K, Ikuo Joja, Takeshi Nagasaka, et al. Maximum standardized lymph node uptake value could be an important predictor of recurrence and survival in patients with cervical cancer. *European Journal of Obsterics & Gynecology and Reproductive Biology*. 2014;173:77–82.

20. Roman-Jimenez G, JD Ospina, J Leseur, et al. Investigating the contribution of pre- and per-treatment 18F-FDG PET-CT segmentation methodologies for post-treatment tumor recurrence prediction in cervical cancer. *IRBM*. 2013;34(4):274–277.