The Effect of Metformin Use on Survival in Soft Tissue Sarcoma Patients: A Surveillance Epidemiology and End Results - Medicare Database Study

Ian D. Hutchinson MD, Ashar Ata MBBS PhD & Matthew R. DiCaprio MD.
Division of Orthopaedic Surgery, Albany Medical Center, Albany, NY 12208, USA.

BACKGROUND

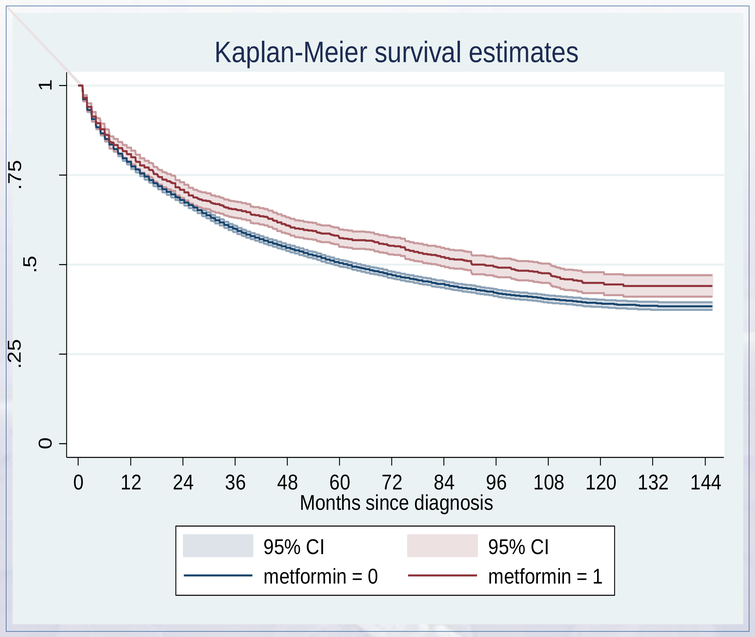
- Soft tissue sarcomas are rare malignancies of mesenchymal origin comprising about 1% of all adult cancers.
- Metformin use has been associated with prolonged cumulative survival in patients with various visceral carcinomas (non-small cell lung, pancreas, colon, head and neck).
- Preclinical studies demonstrate that metformin impairs tumor cellular metabolism, alters matrix turnover and suppresses oncogenic signaling pathways, including receptor tyrosine kinase, PI3K/Akt, and mTOR pathways.

The objective of this study was to investigate the association between metformin use and overall survival in soft tissue sarcoma patients.

METHODS

- The Surveillance Epidemiology and End Results (SEER) - Medicare database was used to identify patients who were diagnosed with a soft tissue sarcoma from 2007-2016.
- ICD-9 primary site codes and HCPCS codes identified cancer treatment, comorbidities and procedures within the Medicare claims files.
- Concomitant medication use was identified with the National Drug Codes using the Medicare Part D event files.
- Survival was assessed comparing metformin users to non-users using a Log Rank Test for Equality of Survivor functions.
- Covariate analysis was performed for patient-related (age, gender), tumor specific (grade) and treatment-related (radiation modality, surgery and the timing of radiation with surgery) factors.

RESULTS



- The SEER database identified 13843 patients eligible for interpretation.
- Of these, 12,138 patients were not taking metformin, while 1705 were taking it at the time of diagnosis and throughout the disease course.
- Patient follow up duration for the patients without metformin was 51.6 ±41.4 months and for those taking metformin was 56.3 ±42.2 months.
- Log Rank Test for the Equality of Survival was significantly different between the groups with patients taking metformin experiencing prolonged survival ($p< 0.001$).
- 50% mortality was seen in the metformin group at 90.5 months, compared to 61.9 months in the group without metformin.
- The 5-year survival: with metformin 57% versus 50% in the patients without metformin.
- The overall hazard ratio for patients on metformin was 0.83 ($P< 0.001$).
- The patient groups (taking metformin versus without metformin) did not differ significantly with respect to tumor grade, age at diagnosis, surgery, radiation modality, and timing of radiation relative to surgery.
- Only gender differed significantly between the study groups with more males taking metformin compared to females (12.95% vs 11.5%)
- Adjusted for these covariates, the hazard ratio for patients on metformin was 0.84 ($p<0.01$).
- Interestingly, the hazard ratios for patients receiving preoperative radiation only and those receiving postoperative radiation only were identical, 0.28, ($p<0.001$).

DISCUSSION

- These preliminary findings are suggestive that metformin use may be associated with increased cumulative survival in patients with soft tissue sarcoma.
- Future analysis of this dataset will focus on isolating the effect of metformin use by comparing outcomes to diabetics not using metformin, controlled for comorbidity including the diabetes severity index.
- Overall, prolonged survival in patients with soft tissue sarcoma on metformin is consistent with similar effects seen in other visceral carcinomas.
- Ultimately, formulation of robust data will serve the basis to support clinical trials regarding the use of metformin to prolong survival of soft tissue sarcoma patients.

REFERENCES

1. *Amin S, Mhango G, Lin J, et al. Am J Gastroenterol. 2016;111(9):1350-1357.*
2. *Ben Sahra I, Laurent K, Loubat A, et al. Oncogene. 2008;27(25):3576-3586.*
3. *Cazzaniga M, DeCensi A, Pruneri G, et al. Br J Cancer. 2013;109(11):2792-2797.*
4. *Chang SH, Luo S, O'Brian KK, et al. Lancet Haematol. 2015;2(1):e30-36.*
5. *Garcia C, Yao A, Camacho F, Balkrishnan R, Cantrell LA. Gynecol Oncol. 2017;146(2):346-350.*
6. *Garrett CR, Hassabo HM, Bhadkamkar NA, et al. Br J Cancer. 2012;106(8):1374-1378.*
7. *Lin JJ, Gallagher EJ, Sigel K, et al. Am J Respir Crit Care Med. 2015;191(4):448-454.*
8. *Stokes WA, Eguchi M, Amini A, et al. Oral Oncol. 2018;84:12-19.*

Albany Medical Center