Interruption of Bone-Targeting Agents Before Tooth Extraction and Risk of Osteonecrosis of the Jaw in Patients With Bone Metastases A Nationwide Target Trial Emulation Study

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Background

Bone-targeting agents (BTAs) reduce skeletal complications in patients with bone metastases but may increase osteonecrosis of the jaw (ONJ) risk after tooth extraction. Whether pre-extraction BTA interruption reduces ONJ risk, and which patients may benefit, remains uncertain. We estimated the effect of pre-extraction BTA interruption on ONJ risk and identified patient characteristics associated with differential benefits.

Method

In this nationwide target trial emulation, we included patients with bone metastases receiving oncologic-dose BTAs who underwent tooth extraction between 2007 and 2020. BTA interruption was defined as no recorded BTA exposure within 30 days before extraction, and ONJ was assessed within 120 days after extraction. Risk differences (RDs) were estimated using doubly robust augmented inverse probability weighting with cross-fitted machine-learning models. Data-driven heterogeneity analyses identified clinically selected characteristics associated with differential interruption benefit.

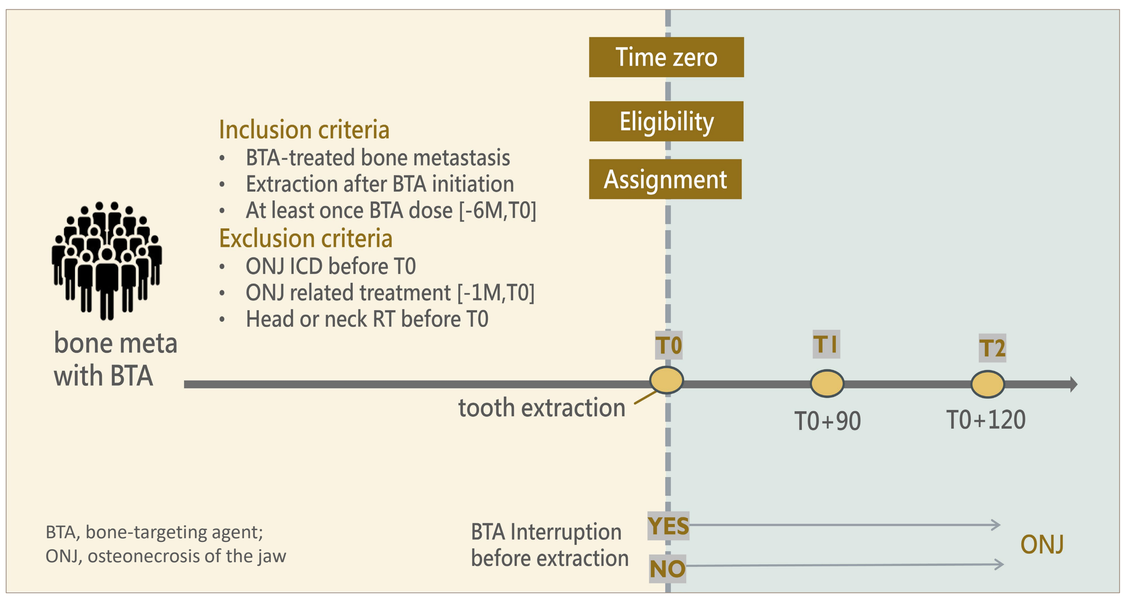

Figure1 Study design

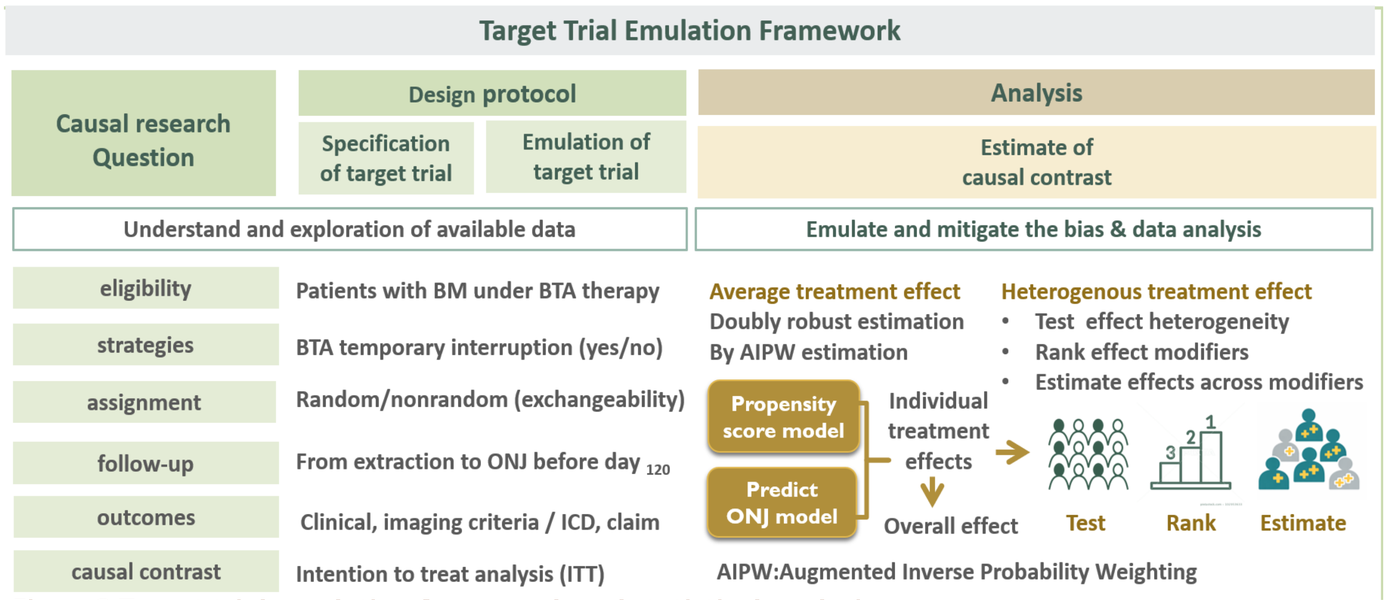

Figure2 Target trial emulation framework and statistical analysis

Result

Among 5,427 patients, 2,379 had pre-extraction BTA interruption and 3,048 did not. The estimated 120-day ONJ risk was 2.237% with interruption and 2.491% without interruption, corresponding to an RD of −0.00254 (95% CI, −0.00717 to 0.00209), with greater risk reduction as off-treatment intervals increased. Estimated benefit varied across patient characteristics, with stronger protective patterns among patients with 1–3 years of prior BTA exposure, bisphosphonate use, and diabetes-related characteristics, whereas patterns were attenuated among those with anemia or proton pump inhibitor use.

Table1 AIPW-estimated counterfactual ONJ risks and risk difference (RD)

	No. patients	AIPW-estimated ONJ risk, % (95% CI)	AIPW-estimated RD (95% CI)
Risk estimatesrisk of developing ONJ			
If all patients followed the interruption strategy	5427	2.237% (1.844%, 2.630%)	
If all patients had followed the no interruption strategy	5427	2.491% (2.076%, 2.906%)	
Overall risk difference			
Interruption versus No interruption			-0.00254 (-0.00717, 0.00209)

Table2 BTA off-treatment interval analysis

	No. patients	AIPW-estimated RD (95% CI)
BTA interruption duration		
30–60 days versus no interruption	956	−0.0020 (−0.0126, 0.0086)
60–90 days versus no interruption	529	−0.0038 (−0.0175, 0.0098)
90–120 days versus no interruption	427	−0.0177 (−0.0281, −0.0074)
>120 days versus no interruption	467	−0.0194 (−0.0284, −0.0105)

AIPW, augmented inverse probability weighting; BTA, bone-targeting agent; CI, confidence interval; ONJ, osteonecrosis of the jaw

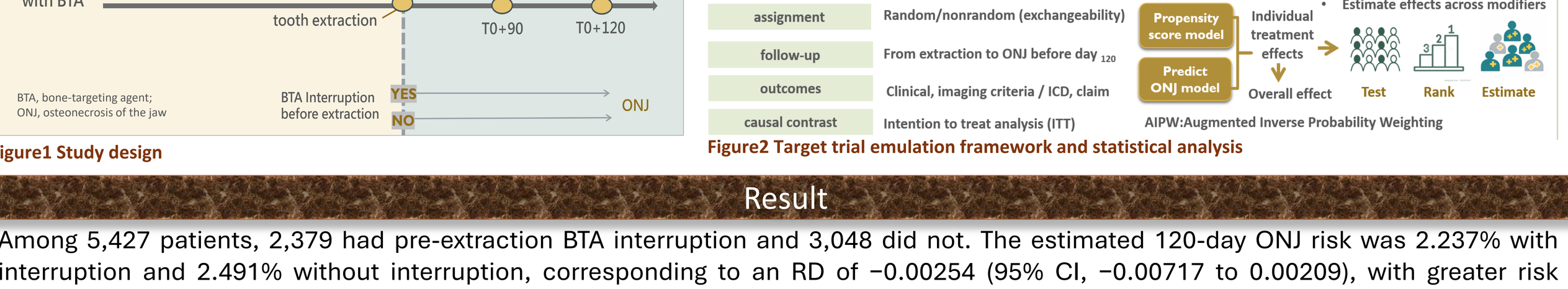

Figure4 Heatmap of risk difference by BTA duration and other potential modifiers (A) BTA type (B) Diabetes (C) Anemia (D) Proton pump inhibitors (PPIs)

Tile values represent mean individual-level AIPW risk differences (RDs) for BTA interruption versus no interruption; n indicates subgroup size. Negative values and blue colors indicate more favorable estimated interruption effects, whereas positive values and red colors indicate less favorable effects. Lighter colors indicate estimates closer to the null. Asterisks and bold outlines indicate 95% CIs excluding zero. AIPW, augmented inverse probability weighting; RD, risk difference; BTA, bone-targeting agent; BP, bisphosphonate; Deno, denosumab; Both, exposure to both BP and denosumab. DM, diabetes mellitus; PPI, Proton pump inhibitor

Conclusion

Pre-extraction BTA interruption did not significantly reduce ONJ risk overall, but benefits varied by patient characteristics, supporting individualized peri-extraction BTA management rather than a uniform interruption strategy.

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