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The potential "additive" thromboembolic risk of radiotherapy

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To Editor,

We read with interest the meta-analysis of primary prevention of thromboembolism (TE) in ambulatory lung cancer patients receiving chemotherapy recently published in *APJCO* (2018 Jun;14(3):210-216). This analysis confirms previously reported findings of the benefit of primary thromboprophylaxis for TE prevention during chemotherapy but with high number needed to treat warranting a more targeted approach, as currently being investigated in ongoing trials.

Contributions of therapeutic modality to TE risk are not the same and not well elucidated to date. In particular the potential "additive" TE risk of radiotherapy remains an important unanswered question given that radiotherapy continues to be a mainstay therapeutic modality for many tumours in both the curative and palliative setting.

The limited and and largely retrospective data (Table 1) suggests TE rates among patients with cancer receiving radiotherapy as the sole modality are lower comparatively to chemotherapy or combination chemoradiotherapy. But there is a lack of high quality prospective data truly estimating incidence and cumulative risk.

We identified only one study evaluating TE among patients receiving single modality radiotherapy.[1] Other studies indiscriminately included patients receiving radiotherapy in conjunction with systemic therapies (Table 1).[2–5] In a prospective registry study, 13% (1202/9284) of patients who suffered TE in the setting of active cancer received radiotherapy.[2] However, nearly three quarters received concomitant therapies; 65% chemotherapy and 9% hormone therapy.

We have recently completed a prospective study (BIOTEL, biomarkers of thromboembolism in lung cancer), in which patients were longitudinally profiled to assess TE risk and incident rates (under review). This study included a small cohort of patients receiving single modality radiotherapy (*n* = 34). Despite 88% demonstrating a procoagulant thrombogenic biomarker profile (thromboelastography and fibrinogen/D-dimer studies), only one patient developed TE over 12-month follow-up period.

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We also retrospectively assessed TE incidence in a larger cohort of patients with lung cancer treated with single modality radiotherapy enrolled in a local prospective cohort study. Patients received either curative or palliative intent single modality primary, mediastinal, or chest wall radiotherapy from 2012 to 2016. Enrolment was from the commencement of radiotherapy to the earliest date of death, loss to follow-up, commencement of chemotherapy or surgery, or end of study (3 months). Patients receiving concurrent chemotherapy or therapeutic anticoagulation were excluded. Among 441 patients with lung cancer, 18 (4%) developed TE (13 venous and 5 arterial); median time to TE was 30 days (range 1–77). While TE incidence in this study (4%) was similar to the small prospective BIOTEL study (3%) and the previously described retrospective study of single modality radiotherapy (3–6%)[1] and lower than the 10–20% incidence reported among lung cancer patients receiving chemotherapy, findings should be confirmed in a larger prospective design.

Accordingly, as part of a recently opened phase III trial of targeted primary thromboprophylaxis (TARGET-TP), we have extended eligibility to patients receiving single modality radiotherapy (ANZCTRN12618000811202). While limited to an observation cohort only, this represents a prospective opportunity to assess longitudinal thrombogenic biomarker profiles and correlative thrombohemorrhagic clinical outcomes for this under researched and clinically relevant treatment setting.

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Table 1 - Summary of studies reporting thromboembolism among patients receiving radiotherapy

Study	Design	No. treated with RT	RT alone[a]	Cancer diagnosis	VTE rate	VTE risk (95%CI) for RT vs. no RT or other TX[2]
Alexander 2018	P	35	100%	NSCLC	3%	HR 0.14 (0.02–1.05)[b]
Alexander 2018	R	441	100%	NSCLC	3%	NR[c]
Cherkashin et al. (2017)[1]	R	323	100%	Mixed	6% brain 3% other[d]	5% increased VTE risk with RT, *P* = 0.018

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Guy et al. (2017)[2]	P	1202	26%[e]	22% LC	NR[f]	RR 1.72 (1.52–1.95)
Ashrani et al. (2015)[3]	R	54	NR[g]	12% LC[h]	NR[f]	OR 1.77 (1.00–3.15)
Lee et al. (2014)[4]	R	582	NR[g]	NSCLC	6% Cur 13% Pal	Cur HR 1.4 (0.7–2.7) Pal HR 3.4 (2.4–5.0)
Blom et al. (2006)[5]	R	12261	NR[g]	14% LC[h]	1% stage I-III 1% stage IV	Stage I–III HR 0.8 (0.6–1.0) Stage IV HR 0.7 (0.4–1.1)

[a]Remaining cohort treated with concomitant chemotherapy; [b]Hazard ratio for single modality radiotherapy versus chemoradiotherapy or chemotherapy; [c]Cohort included only patients treated with radiotherapy; [d]Sits of radiation included abdomen, pelvis, chest, and breast; [e]Calculated from published data; [f]Cohort included only patients with VTE (registry or case control study); [g]Concomitant chemotherapy included but breakdown not reported; [h]Proportion of lung cancer patients in overall study cohort may not reflect proportion treated with radiotherapy. CI, confidence interval; CHT, chemotherapy; Cur, curative intent radiotherapy; LC, lung cancer; NR, not reported; P, prospective, Pal, palliative intent radiotherapy; R, retrospective; RT, radiotherapy; Tx, treatment; VTE, venous thromboembolism.

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