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Planning for the impact of XX trial on spine stereotactic body radiotherapy (SBRT) utilization at a tertiary cancer centre

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ABSTRACT

Purpose: The goal of this study was to assess the potential real-world impact of the recently reported XX trial on spine SBRT utilization. We estimated the proportion of patients treated with conventional radiotherapy (CRT) who would have been eligible for spine SBRT per trial inclusion criteria and analysed the potential estimated increased costs to our institution.

Materials/Methods: This was a retrospective review of patients who received spine CRT at our institution between August to October 2020. Data abstracted included demographics, XX eligibility

criteria, provider-reported pain response and survival. A cost analysis and time survey was performed using institutional and provincial data.

Results: Of 73 patients reviewed, 24 (33%) patients were eligible. The most common exclusion factors included irradiation of ≥3 consecutive spinal segments (n=32, 44%), Eastern Cooperative Oncology Group (ECOG) performance status >2 (n=17, 23%), and symptomatic spinal cord compression (n=13, 18%). Of eligible patients, the mean age was 68.92 years, median Spinal Instability in Neoplasia Score (SINS) was 8 (IQR: 7–9), and median ECOG was 2 (IQR: 1–2). The most common primary cancer types among eligible patients were lung (n=10) and breast (n=4). The median survival of eligible patients was 10 months (95% CI: 4 months–not reached) with 58% surviving longer than 3 months. Of patients who had subjective pain documented after CRT, 54% had at least some response. The cost of spine SBRT was estimated to $4,764.80 compared to $3,589.10 for CRT, and tasks for spine SBRT took roughly three times as long as those for CRT.

Conclusions: One third of patients who received palliative spine CRT met eligibility criteria for XX. This possible expanded indication for spine SBRT can have a substantial impact on resource utilization. These data may be useful in guiding resource planning at institutions looking to commence a spine SBRT program.

INTRODUCTION

Bone metastases are common among patients with cancer, occurring in up to 70% of those with certain solid tumours such as breast and prostate cancer (1). It is the most common cause of pain in patients with cancer and can cause other debilitating manifestations including spinal cord compression and hypercalcemia. Conventional radiotherapy (CRT) is most often used to palliate symptoms related to bone metastases, though the complete response rate of pain with CRT is unsatisfactory. A 2007 systematic review of clinical trials evaluating palliative CRT for bone metastases showed both single fraction and multiple fraction regimens were correlated with overall response rates of 58 and 59% respectively, and complete response rates of 23 and 24% (2).

Compared to CRT, stereotactic body radiotherapy (SBRT) plans are more conformal and higher in biological effective dose. This can confer improved local control, especially in radioresistant disease (3), and is a particularly important outcome for spinal metastases where local recurrences can result in significant morbidity. Furthermore, within the oligometastatic paradigm where all sites of limited metastases are treated, the capability of administering spine SBRT is integral. In the SABR-COMET trial, which demonstrated an overall survival benefit with delivering SBRT to all sites of oligometastases, bone metastases were common with 35% of the patients receiving SBRT to 1 or more bony targets (4). Therefore, the comprehensive treatment of oligometastatic patients depends on an established spine SBRT program.

It is unclear in addition to improved local control whether spine SBRT improves pain response rate. A previous randomized phase 2 trial published in 2018 of 55 patients compared spine SBRT (24 Gy in 1 fraction) to CRT (30 Gy in 10 fractions) (5). The investigators found that the single fraction regimen was associated with lower pain scores compared to CRT at 6 months. While there was not a significant difference in pain scores at the 3-month primary endpoint, a trend favoring the SBRT arm was observed. Another randomized phase 3 trial of 339 patients that compared spine SBRT to a dose of 16–18 Gy in 1 fraction to CRT to a dose of 8 Gy in 1 fraction did not observe a difference in pain scores at 3 months (6).

The Canadian Cancer Trials Group recently reported results from XX, a randomized phase 2/3 trial of 229 patients that demonstrated superior complete response rates for pain following spine stereotactic body radiotherapy (SBRT; 24 Gy in 2 daily fractions; 35%) compared to CRT (20 Gy in 5 fractions; 14%) (7). It

was the first trial to compare a fractionated SBRT dose regimen and accounted for spinal instability in the assessment and enrolment of patients. These findings support a practice-changing paradigm shift whereby a subset of eligible patients with painful spine metastases may be offered upfront spine SBRT over CRT. At many institutions, this may potentially result in an increase in spine SBRT cases.

The goal of this study was to assess the potential real-world implications of XX by estimating the proportion of patients treated with CRT who would have been eligible for spine SBRT per XX inclusion criteria and performing a cost and time analysis to estimate the potential impact on institutional system resource use in the Canadian health care context.

MATERIALS AND METHODS

This study was a retrospective cohort review. Approval was obtained from our institution's research ethics board. Adult patients who received palliative spine CRT at our institution between August to October 2020 were identified using our radiation electronic medical record (EMR). These dates were chosen because they were prior to the presentation of the XX study.

One researcher (XX or XX) extracted data from patient records in the EMR. Variables included demographic information, functional status, primary cancer type, eligibility criteria of the XX study, provider-reported pain response, and overall survival.

Descriptive statistics were used to summarize data. T-tests and chi-square tests were used to compare baseline characteristics. Survival analysis was performed using the Kaplan–Meier method and a log-rank test.

A cost analysis was performed using institutional and provincial data. The breakdown of costs from the perspective of the institution is listed in Table 1. The personnel costs for the consult, treatment, and follow up are based on provincial funding estimates for each course of treatment, accounting for the complexity of treatment. Follow-up costs are estimated for the first year after treatment. The equipment costs were calculated by dividing the annual costs by the annual volume of patients treated at our institution. Factors that were not included were capital costs and costs associated with workup, diagnosis, or follow-up imaging. These costs also assume that patients only have a single treatment

course. Additional costs to the government billed outside of the cancer program (e.g., physician fees, follow-up imaging) were not accounted using this analysis as this would not be incurred by the institution.

We performed a survey of radiation oncologists, physicists, dosimetrists, CT therapists and treatment therapists to assess time costs associated with CRT and spine SBRT. Participants were asked the time required to complete various treatment planning and delivery tasks at minimum, on average, and at maximum. Surveys were distributed to participants via institutional mailing lists.

RESULTS

Between August and October 2020, 73 patients received palliative CRT to the spine. The baseline characteristics of all patients are detailed in Table 2.

Twenty-four (33%) patients met eligibility criteria for XX. Of eligible patients, the mean age was 69 years (SD 14), median Spinal Instability in Neoplasia Score (SINS) was 8 (interquartile range [IQR]: 7–9) and median ECOG was 2 (IQR: 1–2). The most common primary cancer types among eligible patients were lung (n=10) and breast (n=4). The median dose delivered to eligible patients was 20 Gy in 5 fractions (IQR: 8–20 Gy). Fifteen (63%) eligible patients had additional radiation to a site other than the spine at the same time.

Exclusion criteria are listed in Table 3. Forty-nine (67%) patients met at least one exclusion criterion, though most met multiple. The most common exclusion factors included irradiation of more than 3 consecutive spinal segments (n=32, 44%), Eastern Cooperative Oncology Group (ECOG) performance status greater than 2 (n=17, 23%), symptomatic spinal cord compression (n=13, 18%), and frank mechanical instability (n=12, 16%) as measured using the SINS. The SINS was indeterminable in 7 cases (10%) of epidural-only disease, which also renders a patient ineligible; otherwise, the median SINS was 9 (IQR: 7–10). Four (5%) patients had prior surgery and 8 (11%) patients had prior overlapping radiation to the area, also rendering them ineligible.

The median survival of eligible patients was 10 months (95% CI: 4 months–not reached) with 58% surviving longer than 3 months (Figure 1). Survival was not significantly different between eligible and

ineligible patients (p = 0.6). Subjective pain following radiation was documented in 55 of 73 patients (75%) and of these, 37 patients (54%) had at least some response after CRT.

We received 22 responses on our time survey, including 3 CT therapists, 4 dosimetrists, 7 physicists, 5 radiation oncologists and 4 treatment therapists. The results of the survey are listed in Table 4. Most tasks were felt to take twice as long for spine SBRT compared to CRT except for therapy-related tasks such as simulation or patient setup. Notably, dosimetrists felt that spine SBRT plans can take at least 8 times as long to create than CRT plans.

Extrapolating from these data, we estimate that 219 patients would receive spine CRT at our institution in one year. At a cost of $2,908.65 per patient, the total estimated cost for spine CRT is $636,994.35 per year. With 33% of patients being eligible for XX and at an increased cost of $1,045.00 per patient with spine SBRT, we estimate a theoretical maximum increase of $75,522.15 to the institution per year. From a radiation programmatic perspective, our centre saw 4,754 consults, delivered 4,456 treatment courses and had an overall budget of $14,469,534. Thus, the projected increase would represent approximately 5.22% of the total radiation budget.

DISCUSSION

We found that 33% of patients who received spine CRT within the study period would have been eligible for XX. Common exclusion criteria included irradiation of more than 3 consecutive spinal segments, poor performance status, and symptomatic cord compression. Despite meeting inclusion criteria for XX, not all eligible patients would undergo spine SBRT in real world practice. Other factors that affect what treatment a patient undergoes include prognosis, urgency to start treatment (e.g., patients with pain crisis), and patient preference. Our cost analysis showed that each spine SBRT treatment increased costs by $1,045.00 per patient, or a 35.9% relative increase in cost compared to CRT. It was felt that radiation tasks for spine SBRT took more than three times as long as those for CRT with the largest time increase in dosimetry.

Previous estimates of costs of spine SBRT have ranged from US$7,728.62 to 11,813.00 (8, 9). The difference in these estimates compared to our findings likely reflect differences in payment schemes between countries and across jurisdictions, and additional fees not included in our calculations (e.g.,

physician fees, imaging fees that are not incurred by our institution). Comparisons of spine SBRT compared to CRT have typically found a relative increase in cost of 33.9 to 40% (9, 10), which is similar to our findings.

Though at an increased cost per treatment, spine SBRT has higher response rates and purported improved durability of response to pain demonstrated in two separate randomized trials. Improved durability of response may lead to cost-savings from less retreatment, especially for patients with longer life expectancy, which was not factored into our cost analysis.

A recent cost effectiveness analysis compared 2-fraction spine SBRT, 1-fraction SBRT, 1-fraction CRT and radiofrequency ablation (RFA) for painful spine metastases (11). The authors found that in most cases, 2-fraction SBRT and RFA were not more cost effective than 1-fraction CRT, whereas 1-fraction SBRT was.

The XX trial showed superior 3-month complete response rates to pain with 24 Gy in 2 daily fractions of SBRT compared to 20 Gy in 5 fractions of CRT (35 vs 14%, p = 0.0002) (7). In another trial, Sprave et al. compared pain response rates with 24 Gy in 1 fraction of spine SBRT compared to 30 Gy in 10 fractions of CRT (5). Although the trial did not meet its prespecified endpoint of significant rates of pain response at 3 months, they did show significantly lower pain scores at 6 months for the SBRT group (p = 0.002).

In addition to the inclusion criteria for XX, other factors may be further considered to select patients that may benefit the most from SBRT, such as those with longer survival or those with oligometastases who may have survival benefit from SBRT. Zeng et al. recently published prognostic factors associated with dying within 3 months or living greater than 3 years following spine SBRT (12). Non-breast or prostate primaries, ECOG performance status ≥ 2, polymetastatic disease, painful lesions and paraspinal disease were prognostic for dying within 3 months.

This study was unique in assessing trial eligibility in a real-world scenario and assessing the cost and time impact of a change in practice. Limitations of this study include its retrospective nature and associated biases, and that it does not account for patients who received spine SBRT prior to the trial results being presented. This study also presents data from a single institution in Canada and may not be applicable to other centers, especially in other jurisdictions with different payment schemes. Our study also did not account for financial toxicity for patients, including time costs, loss of income, or transportation costs,

which are increasingly being studied (13). Further, our costs only account for a single treatment course per patient, though 45% of all patients received radiation to other sites at the same time. The time period of three months was chosen for practical reasons, as we felt that the number of patients included were enough to complete our primary goal of assessing the proportion of eligible patients. We felt that even with increased numbers, the retrospective nature of this study and the availability of prospective data with XX would not make our survival or subgroup analyses more impactful. Future studies could examine the optimal dose and fractionation for spine SBRT, and a cost effectiveness analysis for the various schemes.

CONCLUSION

Around one third of patients who received palliative conventional spine radiotherapy met eligibility criteria for XX. This possible expanded indication for spine SBRT can have a substantial impact on resource utilization, including contouring, planning and quality assurance resources. These data may be useful in guiding resource and workforce planning at institutions looking to commence or expand a spine SBRT program.

REFERENCES

1. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006;12(20 Pt 2):6243s-9s.

2. Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol. 2007;25(11):1423-36.

3. Yamada Y, Katsoulakis E, Laufer I, Lovelock M, Barzilai O, McLaughlin LA, et al. The impact of histology and delivered dose on local control of spinal metastases treated with stereotactic radiosurgery. Neurosurg Focus. 2017;42(1):E6.

4. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet. 2019;393(10185):2051-8.

5. Sprave T, Verma V, Forster R, Schlampp I, Bruckner T, Bostel T, et al. Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy. Radiother Oncol. 2018;128(2):274-82.

6. Ryu S, Deshmukh S, Timmerman RD, Movsas B, Gerszten PC, Yin FF, et al. Radiosurgery Compared To External Beam Radiotherapy for Localized Spine Metastasis: Phase III Results of NRG Oncology/RTOG 0631. Int J Radiat Oncol Biol Phys. 2019;105(1):S2-S3.

7. Sahgal A, Myrehaug SD, Siva S, Masucci GL, Maralani PJ, Brundage M, et al. Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: an open-label, multicentre, randomised, controlled, phase 2/3 trial. Lancet Oncol. 2021;22(7):1023-33.

8. Papatheofanis FJ, Williams E, Chang SD. Cost-utility analysis of the cyberknife system for metastatic spinal tumors. Neurosurgery. 2009;64(2 Suppl):A73-83.

9. Haley ML, Gerszten PC, Heron DE, Chang YF, Atteberry DS, Burton SA. Efficacy and cost-effectiveness analysis of external beam and stereotactic body radiation therapy in the treatment of spine metastases: a matched-pair analysis. J Neurosurg Spine. 2011;14(4):537-42.

10. Boyce-Fappiano D, Ning MS, Thaker NG, Pezzi TA, Gjyshi O, Mesko S, et al. Time-Driven, Activity-Based Cost Analysis of Radiation Treatment Options for Spinal Metastases. JCO Oncol Pract. 2020;16(3):e271-e9.

11. Kowalchuk RO, Mullikin TC, Kim DK, Morris JM, Ebner DK, Harmsen WS, et al. Cost-Effectiveness of Treatment Strategies for Spinal Metastases. Pract Radiat Oncol. 2022;12(3):236-44.

12. Zeng KL, Sahgal A, Tseng CL, Myrehaug S, Soliman H, Detsky J, et al. Prognostic Factors Associated With Surviving Less Than 3 Months vs Greater Than 3 Years Specific to Spine Stereotactic Body Radiotherapy and Late Adverse Events. Neurosurgery. 2021;88(5):971-9.

13. Prasad RN, Royce TJ, Chino F, Jagsi R, Palmer JD. Financial Toxicity as an End Point in Prospective Clinical Trials Involving Radiation Therapy. Adv Radiat Oncol. 2022;7(6):100970.

FIGURES

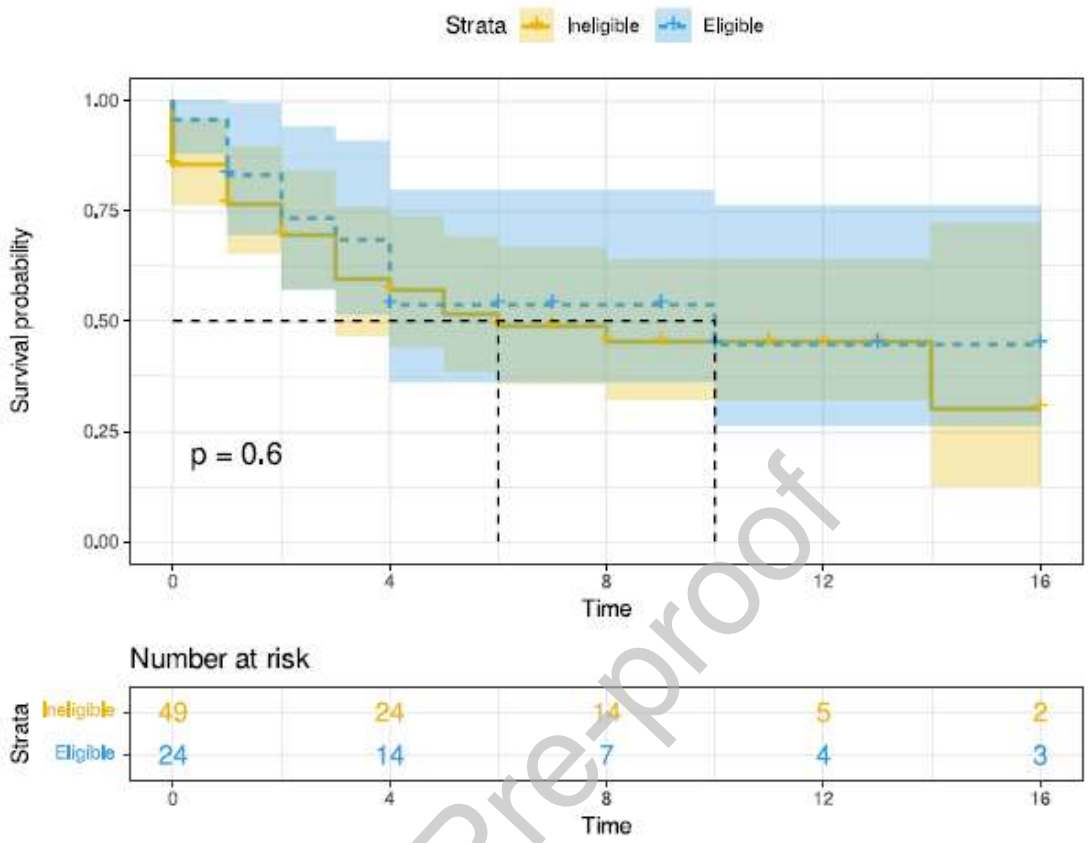

Figure 1. Overall survival stratified by eligibility.

TABLES

Table 1. Breakdown of costs for spine CRT and SBRT per treatment course. All costs are quoted in Canadian dollars.

Domain	Cost	CRT	SBRT
Consult	Nursing	97.00	97.00
	Radiation therapist	20.00	20.00
	Clerical	46.00	46.00
Treatment-Personnel	Radiation therapy and dosimetry	952.00	1,794.00
	Physicist	240.00	264.00
	Physics associate	33.00	27.00
	Nursing	63.00	114.00
	Clerical	92.00	161.00
	Supplies	51.00	61.00
Treatment-Equipment	Equipment support	693.67	693.67
	Software	282.55	282.55
	Parts, labour and upgrades	96.16	96.16
	Minor equipment and replacements	45.27	45.27
Follow-up	Nursing	86.00	110.00
	Clerical	93.00	119.00
	Clinic supplies	18.00	23.00
Total		2,908.65	3,953.65

Abbreviations: CRT = conventional radiotherapy. SBRT = stereotactic body radiotherapy.

Table 2. Baseline characteristics of all patients, patients that would have been eligible for XX trial, and patients that would have been ineligible for XX trial.

Characteristic	All patients (n=73)	Eligible patients (n=24)	Ineligible patients (n=49)	p
Age (mean ± SD)	70.14 ± 11.86	68.92 ± 13.84	70.73 ± 10.87	0.5761
Sex [n (%)]				
M	41 (56%)	9 (38%)	32 (65%)	0.046
F	32 (44%)	15 (62%)	17 (35%)	
ECOG [n (%)]				
0	1 (1%)	0	1 (2%)	*
1	30 (41%)	11 (46%)	19 (39%)	
2	25 (34%)	13 (54%)	12 (24%)	
3	15 (21%)	0	15 (31%)	
4	2 (3%)	0	2 (4%)	
Primary cancer type [n (%)]				
Lung	22 (30%)	10 (42%)	12 (24%)	0.78
Breast	11 (16%)	4 (17%)	7 (14%)	
Prostate	9 (12%)	2 (8%)	7 (14%)	
Hematologic	9 (12%)	1 (4%)	8 (16%)	
Other	22 (30%)	7 (29%)	15 (32%)	

Dose [median (IQR)]	20 (8–20)	20 (8–20)	20 (8–20)	0.47
Fractions [median (IQR)]	5 (1–5)	5 (1–5)	5 (1–5)	0.37

*Not calculated as this was a potential exclusion criterion. Abbreviations: ECOG = Eastern Cooperative Oncology Group performance status.

Table 3. Exclusion criteria for XX trial.

Characteristic	**N**	**%**
Irradiation of more than 3 consecutive spinal segments	32	44
ECOG > 2	17	23
Symptomatic spinal cord compression	13	18
SINS > 12	12	16
Previous overlapping radiation	9	12
SINS indeterminable	7	10
Previous overlapping surgery	4	5
Pacemaker	1	1
Previous radionuclide treatment	0	0

Abbreviations: ECOG = Eastern Cooperative Oncology Group performance status. SINS = Spinal Instability in Neoplasia Score.

Table 4. Results of time cost surveys of tasks associated with spine CRT and SBRT.

Task		**CRT**	**SBRT**
Contouring and/or field placement	Minimum	Up to 15 minutes	Between 16 and 30 minutes
	Average	Up to 15 minutes	Between 31 and 60 minutes
	Maximum	Between 16 and 30 minutes	Between 61 and 90 minutes
Peer review	Minimum	Up to 5 minutes	Up to 5 minutes
	Average	Up to 5 minutes	Between 6 and 10 minutes
	Maximum	Up to 5 minutes	Between 11 and 15 minutes
Plan review	Minimum	Up to 5 minutes	Up to 5 minutes
	Average	Up to 5 minutes	Between 6 and 10 minutes
	Maximum	Up to 5 minutes	Between 11 and 15 minutes
Simulation	Minimum	Up to 30 minutes	Up to 30 minutes
	Average	Up to 30 minutes	Up to 30 minutes
	Maximum	Up to 30 minutes	Between 31 and 60 minutes
Dosimetry	Minimum	Up to 30 minutes	Between 91 and 120 minutes

	Average	Up to 30 minutes	Between 120 and 240 minutes
	Maximum	Up to 30 minutes	More than 240 minutes
Plan QA	Minimum	Up to 30 minutes	Up to 30 minutes
	Average	Up to 30 minutes	Between 31 and 60 minutes
	Maximum	Between 31 and 60 minutes	Between 91 and 120 minutes
Patient setup	Minimum	Up to 5 minutes	Up to 5 minutes
	Average	Up to 5 minutes	Up to 5 minutes
	Maximum	Between 16 and 30 minutes	Between 11 and 15 minutes
Total	**Average**	**Up to 120 minutes**	**Up to 415 minutes**

Abbreviations: CRT = conventional radiotherapy. SBRT = stereotactic body radiotherapy.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Andrew Arifin reports a relationship with Canadian Association of Radiation Oncology that includes: board membership. Arjun Sahgal reports a relationship with Varian Medical Systems Inc that includes: consulting or advisory and speaking and lecture fees. Arjun Sahgal reports a relationship with Elekta that includes: consulting or advisory and speaking and lecture fees. Arjun Sahgal reports a relationship with AstraZeneca that includes: consulting or advisory and speaking and lecture fees. Arjun Sahgal reports a relationship with Medtronic that includes: consulting or advisory and speaking and lecture fees. Arjun Sahgal reports a relationship with Brainlab AG that includes: consulting or advisory and speaking and lecture fees.