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European Association of Urology



Words of Wisdom

Re: Financial Conflicts of Interest Among Authors of Urology Clinical Practice Guidelines

Carlisle A, Bowers A, Wayant C, Meyer C, Vassar M

Eur Urol 2018;74:348–54

Experts' summary:

The objective of the study was to assess disclosed and undisclosed financial conflicts of interest (COI) among authors of clinical practice guidelines (CPGs) in urology [1]. Given the lack of a mandate for disclosure of industry payments outside of the USA, the study was largely focused on guidelines published by the American Urological Association (AUA). The authors assessed author disclosures for a small sample of five CPGs published by this organization from 2014 to 2016 and cross-referenced them against the Open Payments database mandated by the Physician Payment Sunshine Act. Among 54 guideline authors, 32 (59.3%) received at least one payment from industry; 20 (37.0%) received more than \$10 000 and six (11.1%) more than \$50 000 in payment. They also found 20 incidents of discrepant disclosure with failure to report industry payment. However, the authors' ability to establish direct relevance to the particular guideline topic was limited.

Experts' comments:

CPGs have become increasingly influential, affecting the care of thousands of patients. While content experts are critical to the guideline development process, any suggestion of less than complete transparency around financial COI disclosure is of major concern. As pointed out in the accompanying editorial by Lightner and Wolf [2], this study has considerable limitations, namely the inability to verify information provided by the Open Payment database and the lack of granularity with regard to payments made. It also leaves readers with the wrong impression that this problem is unique to the AUA. In fact, given the lack of similar reporting mechanisms for industry payments to physicians outside the USA, one might speculate that the issue of incomplete or inaccurate disclosure by guideline panelists may in fact be magnified for other professional organizations.

What makes this study stand out is its timeliness, mapping to a major debate across medical specialties

[3,4]. In an influential opinion piece, John Ioannidis has since made the radical proposal that professional societies abstain from authorship of guidelines altogether [5]. Instead, methodologists and patients might write the recommendations, consulting content experts only as needed, or transfer guideline leadership to nonspecialists with a more unbiased perspective. Moving forward, guideline developers should use this opportunity to rethink how COI might best be managed. This relates both to overall panel composition and panelist interactions when it comes to formulating recommendations. Strengthening the rigor and transparency of the guideline development process will be essential to preserving and growing public trust.

Conflicts of interest: Philipp Dahm reports serving as a member of the US GRADE Network, coordinating editor of Cochrane Urology, and a member of the University of Minnesota Evidence Practice Center (EPC) and the Veterans Administration Evidence Synthesis Team. In this capacity he has engaged in developing evidence reports for guideline developers including the AUA, European Association of Urology, and Canadian Association of Urology Canadian Urological Association (CUA). Shahnaz Sultan reports serving as a member of the US GRADE Network and a member of the University of Minnesota EPC and Veterans Administration Evidence Synthesis Team. In this capacity she has engaged in training of guideline developers for the CUA.

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Re: Bladder Preservation with Twice-a-day Radiation plus Fluorouracil/Cisplatin or Once Daily Radiation plus Gemcitabine for Muscle-invasive Bladder Cancer: NRG/RTOG 0712—A Randomized Phase II Trial

Coen JJ, Zhang P, Saylor PJ, et al

J Clin Oncol 2019;37:44–51

Experts' summary:

This multicenter randomized phase 2 study compared chemoradiation (CRT) with fluorouracil/cisplatin and twice daily radiation (the RTOG “standard”, arm 1) versus gemcitabine and once daily radiation (arm 2) in fit patients with nonmetastatic advanced bladder cancer. After 40-Gy CRT (induction phase), biopsy-proven complete responders went on to 64 Gy while nonresponders underwent surgery. All patients were offered adjuvant chemotherapy. Two groups of 33 patients had median follow-up of 5.1 yr. Complete responses after induction were found in 88% in arm 1 and 78% in arm 2. Adjuvant chemotherapy was given in 18 patients in arm 1 and 17 in arm 2. Grade 3 and 4 toxicity was not significantly different: 64% in arm 1, although more in the adjuvant chemotherapy phase, versus 55% in arm 2, with more toxicity in the CRT phase. After 3 yr, freedom from distant metastasis was 78% for arm 1 versus 84% for arm 2, with corresponding metastasis-free survival rates of 67% and 72%. In conclusion, both regimens achieved a high response rate. Patients receiving gemcitabine with once daily radiation experienced less toxicity, as expected, and efficacy was at least as good as in the arm with fluorouracil/cisplatin and twice daily radiation.

Experts' comments:

Since the outcomes from radical cystectomy have not improved over several decades, treatment strategies other than radical cystectomy are gaining in popularity for nonmetastatic invasive bladder cancer with the aim of less invasive procedures and/or better outcomes with regard to survival and quality of life. Some improvement seems possible with extended node dissection, although only in a subset of patients [1]. Neoadjuvant chemotherapy appears to improve overall survival by 5–8% in trials, but the advantage in real life seems very limited [2].

Bladder preservation with CRT is one such strategy. The 2018 European Association of Urology guideline on metastatic and muscle-invasive bladder cancer mentions CRT or multimodal treatment as the only realistic form of bladder preservation, and the recommendation is to consider CRT in highly selected, well-informed, and compliant patients, since long-term survival is comparable to the results after radical cystectomy. It is also a good

option when patients are unfit for cystectomy. Some selection is indeed necessary. The tumor should not be too large and ideally resected radically. Furthermore, carcinoma in situ and hydronephrosis are relative contraindications. However, multiple studies show good local control and long-term bladder function, low rates of salvage cystectomy, and high survival rates after CRT [3]. Whether long-term survival is similar to that after cystectomy remains unknown [4].

Even after patient selection, cisplatin-based chemotherapy can be an issue. The average age of patients with invasive bladder cancer is the mid-seventies. Many have a smoking history, and performance status and renal function are often impaired. No comparative radiosensitizer data exist, and CRT is currently administered with cisplatin, 5-fluorouracil/mitomycin C, carbogen-nicotinamide, and gemcitabine. These authors are to be complemented for succeeding in a randomized controlled trial that compares not only two chemotherapy regimens but also once and twice daily radiotherapy. Toxicity data for the two chemotherapy regimens show that grade 3 and 4 toxicity was somewhat higher in arm 1 (21/33 patients, 64%), although it was seen more in the adjuvant chemotherapy phase. In arm 2, grade 3 and 4 toxicity was seen in 18/33 patients (55%) and observed more often in the CRT phase. So even in this healthy patients cohort (61/66 patients had a performance status of 0) CRT has a significant risk of side effects, predominantly caused by chemotherapy, and this did not differ between the two arms. The efficacy results in both arms exceeded the goal set for the trial, which was 3-yr freedom from distant metastasis of >75%, with 78% in arm 1 and 84% in arm 2 achieving this result, and corresponding metastasis-free survival at 3 yr of 67% and 72%. It must be realized that the selected patients were above average: 44/66 were younger than 70 yr and all were fit for radical surgery and radiation. Moreover, nonresponders went on to cystectomy, although this was only performed for three patients in arm 1 and five in arm 2. What also increased the results, although it is not standard therapy, was the use of adjuvant chemotherapy after consolidation CRT or cystectomy, which was done for 18 patients in arm 1 and 17 patients in arm 2.

An interesting issue is the contribution of the initial tumor resection. In this trial a “maximally safe transurethral tumor resection” is mentioned. It seems obvious that better initial tumor resection should lead to better CRT results, but this remains to be proven.

My conclusion is that CRT is gaining interest. This trial confirms good efficacy results, although the positive patient