EDITORIAL

HISTORY

Inflection points in urology as witnessed by Mark Soloway. Part 1: bladder cancer

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During my 53 years of practicing medicine in which urology was my subspecialty discipline I have been privileged to witness and have an impact on some important changes in the way we approach and manage a variety of clinical scenarios. Most of these relate to the management of patients with bladder, prostate, or kidney cancer. The purpose of this mini memoir is not to seek approval or be boastful but to allow others to understand the background and thinking behind the improvements in management of each of these cancers. Sometimes simple careful observations can lead to significant improvements on how we care for our patients.

The introduction of cisplatin for urothelial cancer

I had the good fortune to be one of five young surgeons to enter the class of 1970 at the Surgery Branch of the National Cancer Institute (NCI), National Institute of Health in Bethesda. Prior to acceptance each of us completed medical school and two years of general surgery residency. I graduated from Case Western Reserve University Medical School in Cleveland, Ohio and my two years of general surgery were at the University Hospitals of Cleveland. Our first year at the NCI was in a clinical setting taking care of cancer patients in the Surgical Oncology Branch of the NCI. In the second year we were expected to complete a research project. During the first year we were to design the project. My supervisor at the NCI was a urologist, George Myers. He gave me carte blanche to select a project. As we all know serendipity, luck, or coincidence can make a huge change in one's life.

As I was thinking of a project, I found an article in Cancer Research which described an animal model for bladder cancer (BC) [1]. Mice given a diet containing the carcinogen FANFT developed urothelial cancer of the bladder. I ordered several hundred C3H/He syngeneic female mice and fed them FANFT. I monitored their urine and when they had hematuria, I sacrificed them and examined the bladders. I also used urine cytology to detect BC [2]. Indeed, most developed BC and histologically this was urothelial cell carcinoma, identical to human BC (Figure 1).

In the 1970s the prognosis for locally advanced BC was poor. The survival in the few small case series

of cystectomy for stage C-D BC was 30%. The addition of preoperative radiation did not provide much benefit. Most of these cases were locally advanced at diagnosis and the surgery was challenging. Perioperative morbidity was high, and the operative mortality approached five percent. The only systemic chemotherapy was 5-fluorouracil which did not improve survival.

I had this animal model for BC and planned to test any potential investigative chemotherapy agent in these mice with BC (Figure 2). I approached Randy Johnson, PhD, a pharmacologist at the NCI, who was involved in new drug development, and he suggested I might test a new drug, cis-diammine-dichloro-platinum II. I vividly recall his telling me that this agent was unlikely to make it to the clinic because of its toxicity, mainly nephrotoxicity. I determined a dose the mice could tolerate and then performed an experiment in which some mice received this new drug, now called cisplatin, and others did not. When I knew a high percentage of the mice should have developed BC I removed the bladder of each animal and determined the percentage with BC and the size of any resulting tumors. The result was dramatic! Cisplatin, had a remarkable effect on reducing the number of mice with BC and the size of those that did develop.

While I was treating my mice with cisplatin medical oncologists at Memorial Sloan Kettering Hospital in NYC had learned how to minimize the nephrotoxicity of this new compound by a mannitol induced diuresis.

I presented my laboratory results with cisplatin at the Surgical Forum of the American College of Surgeons Meeting [3]. Alan Yagoda, one of the most respected medical oncologists in the US, was in the audience. He was impressed by my results and began to treat his BC patients at Sloan Kettering with cisplatin. His initial clinical experience was published in 1978 [4]. The occasional complete response and 30% partial response was far superior to that achieved with fluorouracil or adriamycin.

In 1975 when I moved to Memphis, Tennessee to join the Urology Department. I was a new faculty member and was one of the few in this region of the USA with a fellowship in urologic oncology. I was quite familiar with the newly approved chemotherapeutic drug, cisplatin. At that time the medical oncologists in Memphis did not have experience with cisplatin. Therefore, I began to treat my patients with locally advanced and metastatic BC when chemotherapy was indicated. As I was spending most of my day caring for patients in the clinic or operating room, I employed a nurse practitioner to help with the delivery and care of these patients [5]. I am indebted

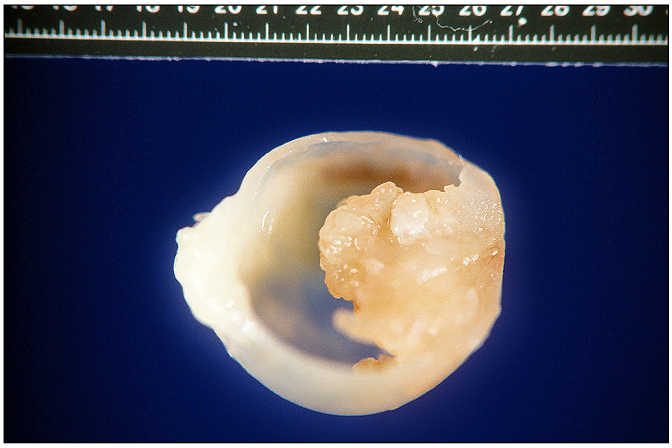

Figure 1. *Urothelial cancer induced in the C3H/He mouse bladder by the carcinogen FANFT.*

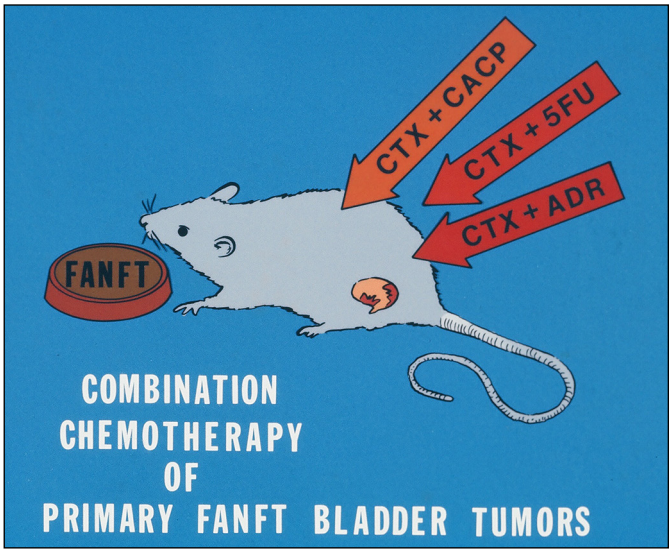

Figure 2. *One of my first powerpoint slides showing mice eating FANFT and developing bladder cancer. CACP is cisplatin. CTX is cyclophosphamide.*

to Cora Sternberg and Alan Yagoda, pioneers in the use of cisplatin for bladder cancer, for holding my hand as I embarked on this aspect of care for my patients. Our initial experience in Memphis was published in 1978 with an update in 1981 [6, 7].

The implantation hypothesis and intravesical chemotherapy

After my second year at the NCI, I returned to Cleveland (Figure 3). I brought many mice with me as well as the cell lines which were used for the metastatic model. The latter was started when I injected tumor cells from the bladder cancer from one animal into the hind limb of another syngeneic

mouse. In this way I developed two transplantable cell lines, MBT-2 and MBT-409. This was a model for metastatic BC. I could monitor tumor growth by measuring the growth of BC cells injected into the mouse hind limb and compare the growth following single and combination chemotherapy [8, 9, 10]). I was fortunate to have my own research laboratory during my three-year urology residency. Working with a technician I was able to continue working on this project while completing my urology training.

During this time (1972–1975) and later I utilized my animal model and cell lines to investigate the concept of implantation of BC tumor cells on the altered or damaged urothelial surface. There is a high rate of subsequent bladder cancer, often termed a 'recurrence', after an initial transurethral resection of bladder tumour (TUR BT). Are they a true recurrence of the same tumor, e.g., because of tumor implantation, or are they a new tumor because of the carcinogenic process that caused the first BC or because of a prior incomplete resection? I thought my animal model might prove whether BC tumor cells could preferentially implant on an altered or damaged urothelial surface. I learned how to reliably cauterize the posterior bladder of female mice which would simulate a TUR BT. I selected three groups of mice fed a normal diet. In the first group I only cauterized the bladder. As expected, none developed BC. In the second group I instilled a solution containing MBT-2 BC cells into the bladder but did not cauterize the bladder. None developed BC. In the third group I cauterized the posterior wall and instilled the same number of cancer cells. When sacrificed 80% of these mice had BC. Thus, cauterizing the bladder urothelium allowed for preferential implantation and growth of instilled BC cells [11, 12]. This animal study provided evidence for the concept of tumor implantation and thus a theoretical rationale for early post TUR BT intravesical chemotherapy. A chemotherapy drug placed into the bladder would have the potential to kill any floating viable tumor and reduce implantation. The object would be to lower the recurrence rate. In 1975 thiotepa was the only chemotherapy drug occasionally used for intravesical therapy. This drug was absorbed so there is a risk of myelosuppression. Based on my laboratory results I advocated for the use of intravesical chemotherapy for prophylaxis post TUR BT [13, 14]. After I moved to Memphis, as a new member of the faculty at The University of Tennessee Medical Center, I started to use intravesical mitomycin for intravesical chemotherapy [15, 16]. It took several years before a prospective randomized clinical trial was performed in the UK and proved the benefit of early instillation of mitomycin C in reducing the recurrence rate. To this day this remains as a guideline particularly following a TUR BT of stage Ta BC.

Figure 3. *With my chair of urology in Cleveland, Ohio, University Hospitals of Cleveland, Lester Persky, MD.*

Cisplatin and radiation

The next question I embarked on in my laboratory and subsequently in the clinic was the synergistic effect of cisplatin and radiation. The effectiveness of radiation in BC had limitations and yet many patients were receiving this for treatment of muscle invasive urothelial cancer of the bladder (MIBC). Since cisplatin had impressive activity in BC, I thought that if it could be tolerated along with radiation there might be an additive or synergistic effect. I used the MBT-2 metastatic model. Tumor cells were injected into the hind legs of mice. Once the tumors reached a given size they were treated with radiation. Half of them also received cisplatin. There was clearly an additive effect with the combination. Tumors either did not grow or were substantially smaller [17]. This led to a clinical trial among my patients [18]. I was a member of The National Bladder Cancer Group chaired by George Prout. Based on our murine study this multi institutional cooperative group completed a clinical trial evaluating the safety of the combination of cisplatin and radiation for patients with muscle invasive BC who were either not suitable for or refused cystectomy. The combined treatment was well tolerated, and the response rate seemed to be superior to historical data of radiation alone [19]. A subsequent randomized study confirmed this benefit [20]. The combination of cisplatin with radiation remains as a guideline for suitable patients who elect radiation instead of cystectomy for locally advanced BC.

Neoadjuvant chemotherapy

In 1985 I advocated for the use of preoperative systemic cisplatin based chemotherapy before cystectomy for patients with muscle invasive BC [21, 22]. A subsequent prospective randomized trial performed by the Southwest Oncology Group proved the modest survival benefit of this approach. Harry Herr recently wrote a nice review of the history of neoadjuvant chemotherapy for MIBC [23].

Flexible cystoscopy

I had the opportunity to visit the endoscopic equipment manufacturing facility of Winter and Ibe in Hamburg, Germany in the 1980s. They later became part of the Olympus company based in Japan. I was impressed with their rigid lens equipment. In the mid 1980s I was asked to try a new instrument made by Olympus in Japan - a flexible cystoscope. Olympus was an established manufacturer of flexible endoscopic equipment for the upper and lower GI tract and decided to manufacture a smaller endoscope for the use in the lower urinary tract. I was one of the first to use this new instrument [24]. Although the optics were not as sharp as a rigid lens it was apparent that the extent of discomfort, i.e., pain, for the male patient was much less than a rigid cystoscope. Olympus presented the instrument and a video of a procedure at the annual AUA meeting. Many urologists were initially reluctant to embrace this new tool as the optics required a learning curve. For the first few years one had to look directly through the eyepiece. A few years later the manufacturers devised a camera attached to the head piece to transmit the image to a monitor. Subsequently the camera was built into the scope. A few years ago, I had to use an earlier model in a Veteran Administration Clinic and this flexible cystoscope did not have a camera. I had a difficult time adjusting (Figure 4).

The flexible cystoscope has become an integral part of the urologists' armamentarium. As I learned from colleagues in some countries where office equipment is not reimbursed by the health care system patients needing diagnostic cystoscopy still undergo either rigid cystoscopy in the office or alternatively flexible or rigid cystoscopy but in a hospital setting.

Office cauterization

Once I felt comfortable with flexible cystoscopy, I began to cauterize low grade (LG) Ta bladder tumors in the office with topical anesthesia. Thus, when I saw a patient with small LG Ta appearing

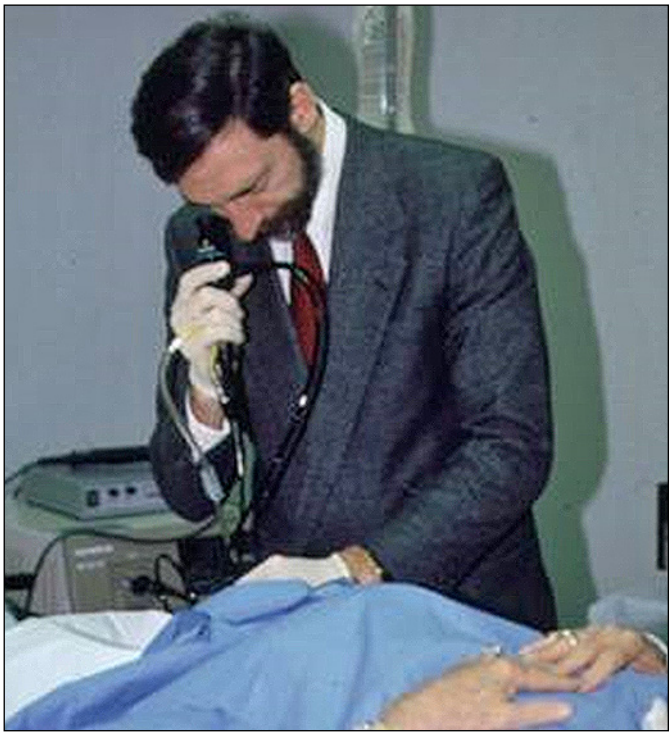

Figure 4. *I was one of the first to use flexible cystoscope.*

tumors and a history of similar tumors I either observed them or cauterized the tumors in the office outpatient setting. Historical data established that patients with LG Ta BC very infrequently develop subsequent invasive BC. In 1984 I published a paper suggesting that patients with LG Ta tumors could be followed primarily by cytology alone If they did not have any high grade cancer cells in the urine cystoscopy might be avoided [25]. This eventually evolved into the concept of active surveillance (AS) for recurrent LG Ta BC. Urologists are quite accurate identifying the stage of a small papillary BC. Harry Herr, a respected urologic oncologist and friend, has been an advocate of a minimally invasive approach for LG Ta BC for years. Office cautery or active surveillance is time and cost saving for the patient and the urologist. Many of these patients are elderly and have co morbid conditions and thus it is in their best interest to minimize treatment when we are dealing with an essentially "benign" neoplasm.

I published my initial series of patients with recurrent LG Ta BC on active surveillance in 2003 [26]. Several others have confirmed the safety and benefit of active surveillance to minimize the inconvenience and expense related to a formal TUR BT for small asymptomatic LG Ta BC. I updated my experience in 2015 [27]. I have had concerns about the current accepted classification of recurrent LG Ta BC as in-

termediate risk. The only BC in the low risk category is an initial, solitary, less than 3 cm LG Ta BC. Any subsequent LG Ta tumors are termed intermediate risk even though there is agreement that these patients are at almost no risk of having an invasive BC. This, in the view of myself and many of my colleagues, leads to overtreatment [28–32].

TUR checklist

A TUR BT is one of the more common urologic procedures yet, until very recently, there have been few guidelines or publications discussing the details of the procedure. The number of publications describing the technical aspects of a radical prostatectomy is far higher than a TUR BT although the latter is a more common operation. In an effort to formalize the details of a TUR BT, David Pan, a urologic oncology fellow now working in Australia, and I co-authored an article proposing a checklist for a TUR BT [33]. This is a step-by-step checklist beginning with the initial patient encounter followed by an immediate preoperative checklist which includes the type of anesthesia, the availability of the necessary operating room equipment, and the details of the TUR BT which includes documenting the location, number, size and configuration of the tumors, and the extent of the resection. Recent publications have demonstrated the advantage of having a checklist in terms of ensuring a thorough procedure. The TUR BT is an often-underappreciated common operation which is the foundation for the management of the BC patient [34–38]. Only recently do I notice an interest in papers and courses devoted to the TUR BT.

Orthotopic bladder

In 1985 another trip to Germany was most helpful. I visited Richard Hautmann in Ulm as I wanted to see how he constructed the orthotopic neobladder (Figure 5). I was not enamored with the other alternative to an ileal conduit, a continent cutaneous urinary diversion, since, in my view, this was a compromise between the standard ileal conduit and the orthotopic neobladder. The patient had to catheterize the stoma and the stoma occasionally leaked. After my visit in Ulm, I returned to Memphis and began performing the procedure on a regular basis. This is an excellent form of urinary diversion for men or women who want to avoid a stoma and are willing to catheterize the neobladder if needed. They must also accept the high possibility of some nocturnal enuresis. Although with the advent of robotic cystectomy the percent of diversions that are orthotopic has declined to less than 20% it has not changed in my practice. I perform all cystoprostatectomies with an open approach and 30% elect an orthotopic neobladder. Utilization of the ERAS perioperative protocol and the intraoperative use of the Enseal device has significantly reduced the perioperative morbidity and particularly blood loss.

Figure 5. *Richard Hautmann. One of my closest urology colleagues. In 1985 I visited him to see him performing the neobladder. We have been close friends ever since.*

CONFLICTS OF INTEREST

The author declare no conflicts of interest.

References

1. Ertürk E, Cohen SM, Price JM, Bryan GT. Pathogenesis, histology, and transplantability of urinary bladder carcinomas induced in albino rats by oral administration of N-(4-(5-nitro-2-furyl)-2-thiazolyl)formamide. Cancer Res. 1969; 29: 2219-2228
2. Soloway MS, Myers GH Jr, Marrone JA, Del Vecchio PR, Malmgren RA. Evaluation of urinary cytology as an indicator of bladder neoplasia in mice. J Urol. 1973; 109: 249-252.
3. Soloway MS, deKernion JB, Rose D, Persky L. Effect of chemotherapeutic agents on bladder cancer: a new animal model. Surg Forum. 1973; 24: 542-544.
4. Yagoda A, Watson RC, Kemeny N, Barzell WE, Grabstald H, Whitmore WF Jr. Diamminedichloride platinum II and cyclophosphamide in the treatment of advanced urothelial cancer. Cancer. 1978; 41: 2121-2130.
5. Soloway MS, Ikard M, Tidwell M. Role of nurse clinician in urologic oncology. Urology. 1978; 12: 685-688.

6. Soloway MS. Cis-diamminedichloroplatinum II in advanced urothelial cancer. J Urol. 1978; 120: 716-719.

7. Soloway MS, Ikard M, Ford K. Cis-diamminedichloroplatinum (II) in locally advanced and metastatic urothelial cancer. Cancer. 1981; 47: 476-480.

8. Dekernion JB, Soloway MS, Persky L. Chemotherapy of experimental transitional-cell carcinoma. Urology. 1974; 4: 63-68.

9. Soloway MS. Single and combination chemotherapy for primary murine bladder cancer. Cancer. 1975; 36: 333-340.

10. Crabtree WN, Soloway MS, Matheny RB Jr, Murphy WM. Metastatic characteristics of four FANFT-induced murine bladder tumors. Urology. 1983; 22: 529-531.

11. Soloway MS, Masters S. Urothelial susceptibility to tumor cell implantation: influence of cauterization. Cancer. 1980; 46: 1158-1163.

12. Weldon TE, Soloway MS. Susceptibility of urothelium to neoplastic cellular implantation. Urology. 1975; 5: 824-827.

13. Soloway MS. Rationale for intensive intravesical chemotherapy for superficial bladder cancer. J Urol. 1980; 123: 461-466.

14. Soloway MS. The management of superficial bladder cancer. Cancer. 1980; 45: 1856-1865.

15. Soloway MS, Murphy WM, DeFuria MD, Crooke S, Finebaum P. The effect of mitomycin C on superficial bladder cancer. J Urol.1981; 125: 646-648.

16. Soloway MS. Treatment of superficial bladder cancer with intravesical mitomycin C: analysis of immediate and long-term response in 70 patients. J Urol. 1985; 134: 1107-1109.

17. Soloway MS, Morris CR, Sudderth B. Radiation therapy and cis-diammine-dichloroplatinum (II) in transplantable and primary murine bladder cancer. Int J Radiat Oncol Biol Phys. 1979; 5: 1355-1360.

18. Soloway MS, Ikard M, Scheinberg M, Evans J. Concurrent radiation and cisplatin in the treatment of advanced bladder cancer: a preliminary report. J Urol. 1982; 128: 1031-1033.

19. Shipley WU, Coombs LJ, Einstein AB Jr, Soloway MS, Wajsman Z, Prout GR Jr. Cisplatin and full dose irradiation for patients with invasive bladder carcinoma: a preliminary report of tolerance and local response. J Urol. 1984; 132: 899-903.

20. Shipley WU, Prout GR Jr, Einstein AB, et al. Treatment of invasive bladder cancer by cisplatin and radiation in patients unsuited for surgery. JAMA. 1987; 258: 931-935.

21. Soloway MS. Learning to integrate systemic chemotherapy into a treatment plan for patients with advanced bladder cancer. J Urol. 1985; 133: 440-441.

22. Soloway MS. Is there a role for induction therapy for locally advanced bladder cancer? Urology. 1987; 29: 577-583.

23. Herr H, Soloway M. History of neoadjuvant chemotherapy for muscle invasive bladder cancer is presented by two individuals who lived through this era and contributed to its concept and success. Urology. 2021; 159: 2-5.

24. Soloway MS. Flexible cystourethroscopy: alternative to rigid instruments for evaluation of lower urinary tract. Urology. 1985; 25: 472-474.

25. Morrison DA, Murphy WM, Ford KS, Soloway MS. Surveillance of stage O, grade I bladder cancer by cytology alone--is it acceptable? J Urol. 1984; 132: 672-674.

26. Soloway MS, Bruck DS, Kim SS. Expectant management of small, recurrent, noninvasive papillary bladder tumors. J Urol. 2003; 170(2 Pt 1): 438-441.

27. Smith ZL, Soloway MS. Expectant Management of Low-Risk Bladder Cancer. Curr Urol Rep. 2015; 16: 82.

28. Klaassen Z, Soloway MS. European Association of Urology and American Urological Association/Society of Urologic Oncology Guidelines on risk categories for non – muscle invasive bladder cancer may lead to overtreatment for low – grade Ta bladder tumors. Urology. 2017; 105: 14-17.

29. Soloway MS. Active surveillance or office fulguration for low grade Ta bladder tumors: a win-win for patients and urologists. J Urol. 2018; 199: 1120-1122.

30. Soloway MS, Matulay JT, Kamat AM. A case for risk adapted management of low-grade bladder tumors. Eur Urol Oncol. 2020; 3: 128-129.

31. Matulay JT, Soloway M, Witjes JA, et al. Risk - adapted management of low - grade bladder tumours: recommendations from the International Bladder cancer Group (IBCG). Brit J Urol Int. 2020; 125: 497-505.

32. Lokeshwar SD, Rahman SN, Press BH, Khan AI, Soloway MS. Surveillance and office management of low-grade Ta bladder tumors. Actas Urol Esp (Engl Ed). 2022; 46: 613-618.

33. Pan D, Soloway MS. The importance of transurethral resection in managing patients with urothelial cancer in the bladder: proposal for a transurethral resection of bladder tumor checklist. Eur Urol. 2012; 61: 1199-1203.

34. Mostafid H, Kamat AM, Daneshmand S, et al. Best practices to optimize transurethral resection of bladder tumors (TURBT). Eur Urol Onc. 2021; 4: 12-19.

35. Adiyat KT, Katkoori D, Soloway CT, De Los Santos R, Manoharan M, Soloway MS. 'Complete transurethral resection of bladder tumor': Are the guidelines being followed? Urology. 2009; 75: 365-367.

36. Lokeshwar SD, Ruiz-Cordero R, Hupe MC, Jorda M, Soloway MS. Impact of 2004 ISUP/WHO classification on bladder cancer grading. World J Urol. 2015; 33: 1929-1936.

37. Soloway MS, Matulay JT, Kamat AM. A case for risk adapted management of low-grade bladder tumors. Eur Urol Oncol. 2020; 3: 128-129.

38. Matulay JT, Soloway M, Witjes JA, et al. Risk – adapted management of low – grade bladder tumours: recommendations from the International Bladder cancer Group (IBCG). Brit J Urol Int. 2020; 125: 497-505.