

Palliative Treatment of Intractable Hematuria in Context of Advanced Bladder Cancer

A Systematic Review

Seyed Mohammad Ghahestani, Nasser Shakhssalim

Introduction: In a patient with bladder urothelial cancer that is not suitable for or does not choose curative treatment, intractable hematuria is a disastrous condition. In this article, we tried to review the literature and extract a stepwise approach for palliative treatment of hematuria in these patients.

Materials and Methods: The MEDLINE was searched with the help of the Medical Subject Headings system using different combinations of terms *urinary bladder neoplasm, hematuria, carboprost, cyclophosphamide, cystitis, alum, and hyperbaric oxygenation*. The articles were separately reviewed by the two authors and verified by each other. Eventually, a decision tree was developed for management of gross hematuria in patients with bladder cancer.

Results: Although, there was not any reported randomized controlled trial or prospectively designed study, the available case series were rather expressive to draw out a logical approach. Formalin has a grave adverse effect profile and is recommended only in special circumstances. For management of each case of gross hematuria in bladder cancer, the etiology of bleeding is the most important determinant.

Conclusion: Hematuria in the context of advanced bladder neoplasms can now be effectively treated with fewer side effects using all available modalities in a logical holistic approach. We proposed a decision tree for management of hematuria in this context. However, regarding lack of well-designed trials, a treatment method should be based on individualized scenarios and clinical experience, bringing into account the patient's preferences.

Keywords: urinary bladder neoplasms, hematuria, alum compounds, hyperbaric oxygenation, intravesical administration, cyclophosphamide

*Urol J. 2009;6:149-56.
www.uj.unrc.ir*

INTRODUCTION

A patient is considered for palliative care when he or she is not a candidate for any form of curative treatment or does not wish to accept the related morbidity. Palliative care might be needed in patients with advanced bladder cancer who suffer from gross hematuria. Gross hematuria in the context of bladder cancer may have a host of etiologies. The probable causes can be sloughing

tumoral mass, radiation cystitis, cyclophosphamide-induced hemorrhagic cystitis (CIHC), and also other sources of bleeding such as the prostate. In a patient who is a candidate for palliative care and unfit in the curative treatment criteria, intractable hematuria can be a disastrous condition. Associated conditions such as already present or impending obstructive azotemia may require simultaneous treatment. In this

Urology and Nephrology Research Center, Shahid Labbafinejad Medical Center, Shahid Beheshti University (MC), Tehran, Iran

*Corresponding Author:
Nasser Shakhssalim, MD
Urology and Nephrology Research Center, No 101, 9th Boustan St, Pasdaran Ave, Tehran, Iran
Tel: +98 21 2256 7222
Fax: +98 21 2256 7282
E-mail: slim456@yahoo.com*

article, we tried to collect all available data in the literature concerning this condition, and then, to develop a logical diagram out of the available data, regarding the pitfalls of a lack of randomized controlled trials.

MATERIALS AND METHODS

The systematic review of the literature was performed in January 2008 through searching the MEDLINE. We employed a search strategy using a combination of the Medical Subject Headings of *urinary bladder neoplasm* and *hematuria*; *carboprost* and *hematuria*; *cyclophosphamide* and *cystitis* and *alum*; and *cyclophosphamide* and *cystitis* and *hyperbaric oxygenation*. The latter three were completed to cover those aspects of CIHC in the setting of other malignancies and the benign conditions. The first one was planned to perform the most sensitive search including all aspects of hematuria in bladder cancer. Initially, 763 results were retrieved, of which 92 were selected and reviewed by 2 urologists. The selected articles were those concerning palliative treatment of gross hematuria in the background of either bladder cancer or radiation cystitis, and also the application of carboprost, alum, or hyperbaric oxygenation in CIHC in the background of any other malignancies or even benign conditions, for instance, Wegener granulomatosis. The term *palliative* was formally used for that group of patients who were not suitable for curative treatment, but temporized with a better quality of life. The search was limited to only humans. No date or language limitations were employed. The two urologists reviewed the full texts and extracted the data and each verified the accuracy of the data extracted by the other. No randomized clinical trials were found among the articles. Regarding the lack of high-quality studies and also expert recommendations surrounding all treatment modalities and situations, a tree diagram for making a logical decision was developed by the authors.

RESULTS

The most widely used modalities for treatment of gross hematuria due to bladder cancer were arterial occlusion, intravesical formalin

instillation, intravesical alum instillation, hyperbaric oxygenation, urinary diversion, chemoradiation, and intravesical carboprost instillation. Here, we orderly discuss the obtained results for each modality through the aforesaid comprehensive search strategy.

Arterial Occlusion

There were 7 studies, in total, about arterial occlusion for treatment of intractable hematuria, 2 of which were case reports and the rest were case series.⁽¹⁻⁷⁾ In all of the studies, endovascular techniques had been used, except for one in which endovascular technique had been compared to open ligation retrospectively.⁽¹⁾ In 1 case report, superselective endovascular technique had been used.⁽²⁾ The full text of a Russian article was not available.⁽¹⁾ Overall, arterial occlusion had been performed in 34 patients in different studies. In one study, the technique had been debated with no follow-up except for 2 of the patients. Of 32 patients with follow-up information, 29 had responded completely, defined as complete cessation of gross hematuria. Another patient had responded with less transfusion requirements. The reported side effects were postembolization syndrome and transitory gluteal claudication.⁽³⁾ The etiologies were heterogeneous including sloughing tumoral mass, radiation cystitis, and of the prostate origin. These figures showed a more than 90% rate of response. Despite the lack of homogenous well-designed studies, acceptable response rate could be expected.

Formalin Instillation

There were 5 studies concerning hematuria treatment with formalin instillation in the literature.⁽⁸⁻¹²⁾ All of them were case series, and formalin instillation had been performed in a total of 61 patients due to an intractable hematuria in the context of bladder cancer. A 10% solution had been used for irrigation for a period of about 5 to 30 minutes,^(8,9) except in one study, in which a 1% solution had been used instead, but we could not find a full text of the article. The data of 3 patients were not available. Fifty-two of 58 patients had responded with complete disappearance of gross hematuria and another

one had a decrease in the amount of the required transfusion. Two similar studies had debated the prevalence and the significance of complications.^(8,9) Of 24 patients in these two studies, 10 died ultimately of kidney failure, 9 developed bladder capacities below 100 mL, 2 had retroperitoneal fibrosis, 3 had incontinence, 4 had severe lower urinary tract symptoms, and 11 died within 3 to 4 months after the treatment or before arresting the hemorrhage. Regarding these data, a severe toxicity and morbidity could be attributed to formalin instillation with the 10% solution. The 1% solution had been studied even less.

Alum Instillation

There was only 1 case series concerning alum instillation in the context of bladder cancer in this search, with 15 recruited patients.⁽¹³⁾ A 66% rate of complete response and a 15% rate of partial response had been reported. There was another case report of a death after alum instillation in a patient with chronic kidney failure,⁽¹⁴⁾ and a case report of a tuberculosis-like reaction and retroperitoneal fibrosis.⁽¹⁵⁾ There were also a case series of 4 patients with CIHC and concomitant renal insufficiency in the setting of a blood malignancy who suffered aluminum encephalopathy after intravesical alum instillation.⁽¹⁶⁾ Nonetheless, alum instillation seemed to be effective in both radiation cystitis and sloughing tumoral mass.⁽¹³⁾

Hyperbaric Oxygen Therapy

In 3 case series, 108 patients had been recruited, all with radiation cystitis.⁽¹⁷⁻¹⁹⁾ At least, 20 sessions of 100% oxygen had been completed, with a pressure of 3 bars, each lasting for 90 minutes. Overall, 92 patients had responded with the complete cessation of their gross hematuria that establishes an 85% success rate. The treatment seems to have no adverse effect; however, economical disadvantages and the need for multiple treatment sessions are the major concerns.⁽¹⁷⁻¹⁹⁾

Intravesical Carboprost Tromethamine Instillation

Five articles were found in literature concerning carboprost (prostaglandin F₂ alpha) instillation

in the setting of hematuria.⁽²⁰⁻²⁴⁾ There were 2 case series recruiting 18 and 4 patients, respectively, with different protocols; however, the majority of them had received 0.4 mg/dL to 1.0 mg/dL of carboprost tromethamine for 2 hours, 4 times per day, alternating with continuous saline bladder irrigation for 2 hours, during 4 to 5 days.^(20,21) Both of these case series included CIHC and the only 2 studies concerning radiotherapy-induced cystitis were case reports. In 2 case series, 12 of 22 patients had responded completely, of whom 5 patients had required multiple courses of treatment to establish a success rate of 54%, and 8 of 22 patients had responded with decreased transfusion requirement, establishing a success rate of 36% for partial response. With the exception of a bladder spasm, no other side effects had been reported in those studies.

Urinary Diversion

Urinary diversion excludes the bladder from the urinary tract, making it a relatively closed system with internal blood tamponade and preventing further blood loss. It also averts continuous contact of the fragile hemorrhagic mucosa of the bladder with urine urokinase. Moreover, it makes the bladder amenable to other treatment modalities such as formalin instillation that otherwise encounter with cumbersome complications, namely, bladder contracture and ureteral fibrosis. There was only 1 study recruiting 16 patients with heterogeneous etiologies.⁽²⁵⁾ Eleven patients had responded with complete cessation of hematuria and 3 patients had experienced decreased transfusion requirements, establishing a response rate of 87%.

Chemoradiation

In 1 study, 7 people with either hematuria or progressive azotemia had been recruited, all of whom had responded to palliative doses of radiation.⁽²⁶⁾ Although the studies in this regard seemed even more scarce, it was logical that reducing the tumor mass would lead to a decrease in hematuria; however, the side effects of chemoradiation might provide further reasons for a new cascade of hematuria. Nevertheless, hematuria induced by radiation or alkylating

agents treatable by other measures is similarly debated.

Palliative Cystectomy

Many of the patients who were chosen for palliative care were those presumptively believed surgically unsuitable for cystectomy.⁽²⁷⁾ The point was that those patients were the cases in whom achieving a negative surgical margin or a tumor-free state was difficult or impossible. Some of those patients might be suitable for palliative cystectomy, or probably, we had to accept the difficulties and complications because of the disastrous consequences of the tumor. In this search, we found 1 study by Zebic and colleagues,⁽²⁷⁾ published in 2005, in which 53 patients had been recruited for cystectomy, 6 of whom for a palliative goal. Two of the patients died early and the other 5 suffered grave complications. Nonetheless and as a last resort, palliative cystectomy might be inevitable. The concept of palliative cystectomy has changed recently with the advent of neoadjuvant chemotherapy.

Treatment of Cyclophosphamide-induced Hemorrhagic Cystitis

Cyclophosphamide-induced hemorrhagic cystitis occurs in 2% to 40% of patients treated with cyclophosphamide.⁽²⁸⁾ Histologically, cyclophosphamide- and busulfan-induced bladder damage is similar to radiation cystitis.⁽²⁹⁾ Therefore, it is thought that the same modalities effective in radiation cystitis might be effective in CIHC, too. There was 1 case series comprising of 5 patients with follow-up periods ranging from 5 to 10 months for CIHC, who had been treated with alum. Three patients responded with complete remission of hematuria.⁽³⁰⁾ A similar case report has been published, as well.⁽³¹⁾ As previously mentioned, a case series of 4 patients with CIHC and renal insufficiency was available who had suffered from encephalopathy after alum instillation.⁽¹⁶⁾

Concerning hyperbaric oxygenation as a treatment method for CIHC in humans, there were 6 case reports in the context of the ovarian cancer, peripheral stem cell transplantation, and

Wegener granulomatosis.⁽³²⁻³⁷⁾ In addition, there were studies on hyperbaric oxygenation in rat and guinea pig models with CIHC.^(38,39) In some of the studies, a preventive effect for hyperbaric oxygenation was denied and a healing-promoting effect was confirmed.^(38,39) In some other studies, a preventive and therapeutic effect was confirmed in conjunction with mesna.^(28,39,40)

DISCUSSION

Intractable hematuria in the context of bladder cancer is a rather disastrous condition. Candidates for curative treatment are planned for an immediate treatment to be unburdened of both hematuria and cancer at the same time. Those not suitable for curative treatment still have to face the diverse aspects of hematuria. A host of etiologies for hematuria in these cases could be logically speculated. Sloughing tumoral mass and the side effects of treatment, such as radiation cystitis and CIHC are of potential causes. There may also be other sources of bleeding such as the prostate or simultaneous ureteropelvic cancer. The most debated modalities for treatment of this condition are: arterial occlusion (either endovascular selective or superselective and the open technique), intravesical formalin instillation, intravesical alum instillation, hyperbaric oxygen therapy, and intravesical carboprost instillation (prostaglandin F₂ alpha) in CIHC. In cases of sloughing tumoral mass, palliative-dose radiation has been proposed, too. No randomized controlled trial or well-designed prospective studies on this subject were found in this review, presumably because of the relative rarity of the occasion or urologists' focus on curative strategies of bladder cancer. Furthermore, no comprehensive review was found covering all modalities and aspects of treatment in the literature. Nevertheless, the available data seemed guiding to a logical deduction determining a step-by-step approach to these patients.

Arterial occlusion seems a modality coping with all etiologies with a response rate of about 90%. The endovascular technique is a less-invasive method with minimal complications in both selective and superselective approaches.⁽²⁾ The open technique can be applied when other

concomitant problems (eg, azotemia) is needed to be treated with urinary diversion either with an ileal conduit or bilateral cutaneous ureterostomy. This is what is called “a combined approach” or “bladder urovascular segregation” which also makes the bladder amenable to further otherwise aggressive treatment, namely intravesical formalin instillation. This approach is a way to evade the more morbid treatment of palliative cystectomy.

Formalin instillation seemed to result in a response rate of 90% with consecutive instillations; however, it is associated with roughly 100% rate of significant complications such as kidney failure, retroperitoneal fibrosis, considerable reduced bladder capacity, and severe lower urinary tract symptoms. In one study, a 1% solution was suggested instead of the usual 10% solution to reduce the complications, but we were unable to find the full text of the article.⁽¹⁰⁾

Overall, we do not recommend formalin instillation in case of the availability of other measures except in the following scenarios: (1) if a previous combined approach or urinary diversion has been used to evade the potential complications of formalin instillation; and (2) in cases of radiation cystitis if severe fibrosis of the bladder wall is already present and surgical handling of the abdomen is difficult and other measures have failed.

The articles concerning alum instillation comprised the etiologic spectrum of sloughing tumoral mass, radiation cystitis, and CIHC. The achieved response rate was around 80% with sparse reports of complications such as ureteral fibrosis and tuberculosis-like reactions.⁽¹⁵⁾ Yet, 6 cases of aluminum toxicity and death were reported, all harboring a component of renal insufficiency. Hence, in the cases of concomitant renal insufficiency, we recommend that using of alum instillation be avoided, and other effective measures be exploited instead. Otherwise, alum instillation seems a very effective and inexpensive method with the least morbidity.

Hyperbaric oxygenation has been reported to be effective in cases of radiation cystitis and CIHC. However, no reports of its application in the case of sloughing tumoral mass were available. Overall, 108 patients had been assigned for

hyperbaric oxygenation with a response rate of 85%. All these patients had radiation cystitis. There were also 6 case reports on the patients with CIHC. The preventive role of hyperbaric oxygenation in cases of CIHC, with or without mesna, remains controversial in spite of promising studies on animals.^(28,38-40) However, this modality is not ubiquitous, and also it is expensive and needs at least 20 sessions of treatment.

Carboprost was mainly used in cases of CIHC with a response rate of about 90%. Overall, 22 patients had undergone carboprost instillation, of whom 12 responded completely, 5 required multiple treatment courses, and 8 responded with decreased transfusion requirements. There were only 2 case reports of its usage in radiation cystitis; therefore, the evidence is too frail to recommend its usage in such circumstances, but considering the histological similarities of CIHC and radiation cystitis, its efficacy in cases of radiation cystitis seems likely.

Hyperbaric oxygenation and carboprost have not been used in cases of sloughing tumoral mass, but alum and formalin instillation have been shown effective in these circumstances. In only 1 study on 16 patients, urinary diversion was used with a response rate of 87%. Despite lack of extensive studies in this area, it looks practical because of two obvious advantages: (1) this procedure simultaneously treats present or imminent obstructive azotemia that is also a source of significant associated morbidity; and (2) the procedure leave us free to use other kinds of treatment modalities that are otherwise strongly morbid, ie, formalin instillation or extensive intravesical cauterization.

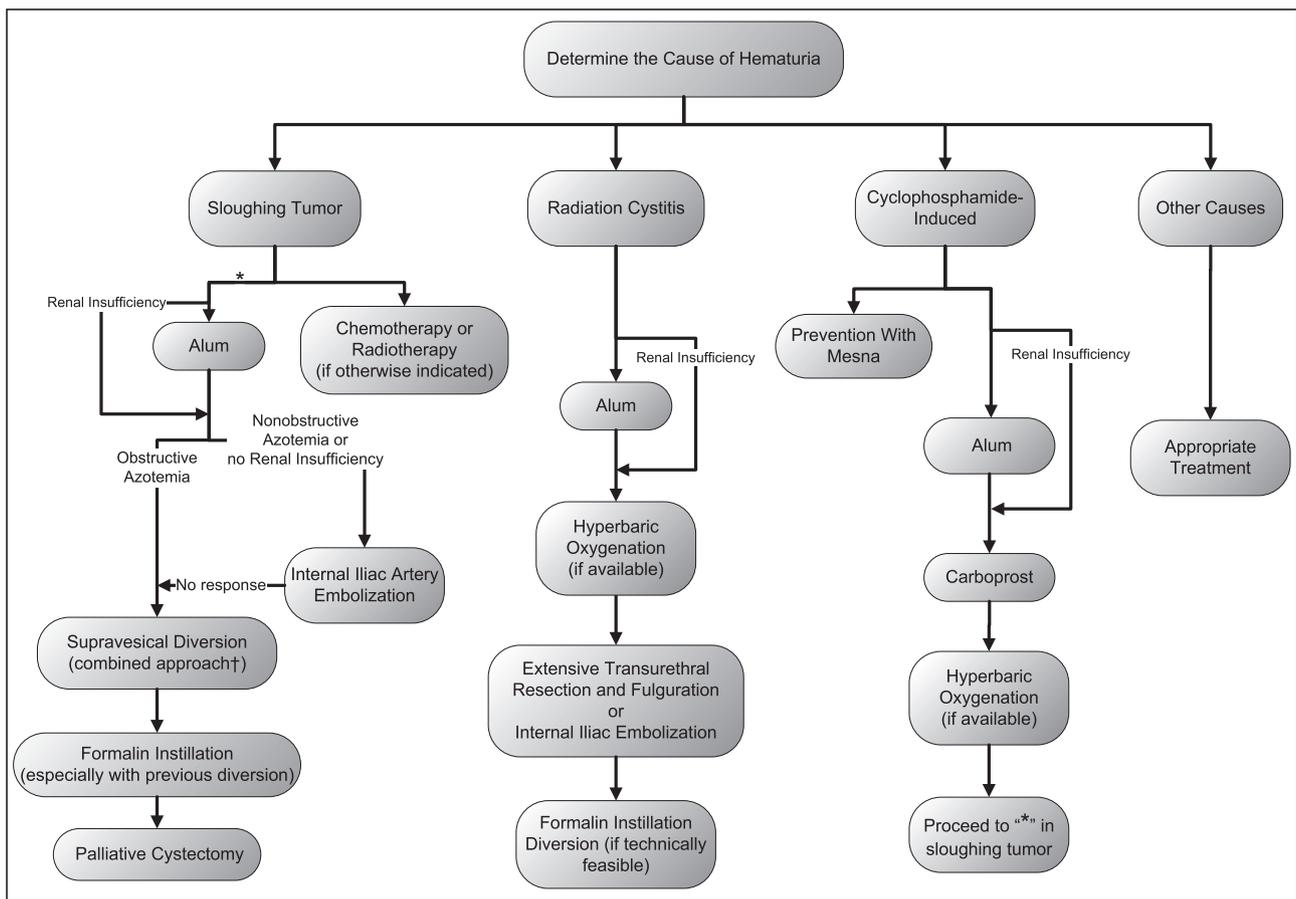
Palliative cystectomy remains as the last resort to be considered. Although, by definition, achieving a free surgical margin with a curative intent may be impossible in most of these patients, a rough ablative procedure may be inevitable. However, in one study, cystectomy was a morbid and lethal procedure.⁽²⁷⁾ We must keep in mind that many cases previously thought to be inoperable are now suitable candidates for the curative surgery after neoadjuvant chemotherapy. In the only one available study, 7 patients underwent a radiotherapy session with a single dose of 1000

rad for either intractable hematuria or azotemia that yielded a good response rate.⁽²⁶⁾ However, chemoradiation may cause a new cascade of events leading again to hematuria. Therefore, this method is particularly suitable when there are other indications for chemoradiation such as bothersome metastases.

Can We Have a Decision Tree With Present Knowledge?

Concerning the lack of well-designed controlled studies comparing the efficacy of the available modalities for treatment of hematuria in bladder cancer, our choices can be prioritized with respect to the adverse effects, expenses, and usages reported in the literature. Among the modalities alum instillation seemed the least expensive and the most innocuous, subject to taking precautions in cases of renal insufficiency. As mentioned, alum has been used in cases of sloughing tumoral

mass, radiation cystitis, and CIHC. Hyperbaric oxygenation, on the other hand, has not been used in cases of sloughing tumoral mass. This modality is expensive and needs multiple sessions. Moreover, concomitant problems in these cases, such as azotemia or urinary incontinence, may need to be addressed simultaneously with an open approach. If there is no such a concomitant problem, radiologic hypogastric artery occlusion seems the least invasive. Formalin instillation, though the first thought passing the minds of urologists encountering with such patients, has a grave adverse profile, and thus, should be considered as the last resort here. Nevertheless, when previous diversion has been done, many of these complications can inherently be avoided. Formalin instillation can also be used in an already fibrotic bladder after radiation with least additional side effects; however, the danger of bladder perforation and retroperitoneal fibrosis



Decision tree for therapeutic approach to intractable hematuria in advanced bladder malignancy.

†Combined approach includes simultaneous Supravesical diversion and hypogastric artery ligation through a single inferior midline incision or laparoscopy.

is still present. In cases of radiation cystitis, open approaches are pushed to the end of the row, due to difficulties of open surgical technique and healing in these patients. In CIHC, carboprost instillation is an alternative worth to be considered. Collecting these data in a diagram, a decision tree can be developed despite the mentioned paucity of data in this regard (Figure).

Until stronger evidence in the form of well-designed randomized controlled trials are available, decision on a treatment method should be based on individualized scenarios and the clinical experience, also bringing into account the patients' preferences. Nonetheless, on the way of decision-making process, the general health and also the consent of the patient should be strongly taken into consideration.

CONCLUSION

A single-modality approach to palliative treatment of hematuria in bladder cancer must be discarded now. In any specific case, the exact etiology of bleeding is the most important determinant. Comorbidities are other significant factors in making a decision. Formalin should no longer be universally used except in those cases with previous urinary diversion or failed combined approach. Alum should not—if ever—be used in patients with renal insufficiency. Hyperbaric oxygenation has not been used in patients with sloughing tumoral mass yet. Present or imminent azotemia is a strong determinant and must be taken into consideration for a holistic approach. We hope with the proposed decision tree, fewer persons fall in the category of more morbid treatment options and are benefited with a better quality of life.

CONFLICTS OF INTEREST

None declared.

REFERENCES

- Granov AM, Anisimov VN, Grinval'd VA, Ryzhkov VK, Borisova NA. [Roentgenological-endovascular occlusion and ligation of internal iliac arteries in bleeding tumors of the bladder]. *Vestn Khir Im I I Grek*. 1985;135:51-5. Russian.
- De Berardinis E, Vicini P, Salvatori F, Sciarra A, Gentile V, Di Silverio F. Superselective embolization of bladder arteries in the treatment of intractable bladder haemorrhage. *Int J Urol*. 2005;12:503-5.
- Rodriguez-Patron Rodriguez R, Sanz Mayayo E, Gomez Garcia I, et al. [Hypogastric artery embolization as a palliative treatment for bleeding secondary to intractable bladder or prostate disease]. *Arch Esp Urol*. 2003;56:111-8. Spanish.
- Arguelles Salido E, Medina Lopez RA, Iglesias Lopez A, Congregado Ruiz CB, Peiro de las Heras J, Pascual del Pobil Moreno JL. [Selective arterial embolization in the treatment of intractable hematuria]. *Arch Esp Urol*. 2005;58:453-7. Spanish.
- Li BC. [Internal iliac artery embolization for the control of severe bladder and prostate haemorrhage]. *Zhonghua Wai Ke Za Zhi*. 1990;28:220-1, 53. Chinese.
- McIvor J, Williams G, Southcott RD. Control of severe vesical haemorrhage by therapeutic embolisation. *Clin Radiol*. 1982;33:561-7.
- Bruhl P, Thelen M. [Selective transfemoral embolization of the internal iliac artery in carcinoma of the bladder (author's transl)]. *Dtsch Med Wochenschr*. 1978;103:737-9, 47. German.
- Giannakopoulos X, Grammeniatis E, Chambilomatis P, Baltogiannis D. Massive haemorrhage of inoperable bladder carcinomas: treatment by intravesical formalin solution. *Int Urol Nephrol*. 1997;29:33-8.
- Ferrie BG, Rundle JS, Kirk D, Paterson PJ, Scott R. Intravesical formalin in intractable haematuria. *J Urol (Paris)*. 1985;91:33-5.
- Proca E, Popescu E. [Formolization of the bladder mucosa for hemostatic purposes]. *Rev Chir Oncol Radiol O R L Oftalmol Stomatol Chir*. 1980;29:253-7. Romanian.
- Servadio C, Nissenkorn I. Massive hematuria successfully treated by bladder irrigations with formalin solution. *Cancer*. 1976;37:900-2.
- Kumar S, Rosen P, Grabstald H. Intravesical formalin for the control of intractable bladder hemorrhage secondary to cystitis or cancer. *J Urol*. 1975;114:540-3.
- Arrizabalaga M, Extramiana J, Parra JL, Ramos C, Diaz Gonzalez R, Leiva O. Treatment of massive haematuria with aluminous salts. *Br J Urol*. 1987;60:223-6.
- Shoskes DA, Radzinski CA, Struthers NW, Honey RJ. Aluminum toxicity and death following intravesical alum irrigation in a patient with renal impairment. *J Urol*. 1992;147:697-9.
- Braam PF, Delaere KP, Debruyne FM. Fatal outcome of intravesical formalin instillation, with changes mimicking renal tuberculosis. *Urol Int*. 1986;41:451-4.
- Murphy CP, Cox RL, Harden EA, Stevens DA, Heye MM, Herzig RH. Encephalopathy and seizures induced by intravesical alum irrigations. *Bone Marrow Transplant*. 1992;10:383-5.
- Corman JM, McClure D, Pritchett R, Kozlowski P, Hampson NB. Treatment of radiation induced hemorrhagic cystitis with hyperbaric oxygen. *J Urol*. 2003;169:2200-2.
- Bevers RF, Bakker DJ, Kurth KH. Hyperbaric oxygen

- treatment for haemorrhagic radiation cystitis. *Lancet*. 1995;346:803-5.
19. Rijkmans BG, Bakker DJ, Dabhoiwala NF, Kurth KH. Successful treatment of radiation cystitis with hyperbaric oxygen. *Eur Urol*. 1989;16:354-6.
 20. Levine LA, Jarrard DF. Treatment of cyclophosphamide-induced hemorrhagic cystitis with intravesical carboprost tromethamine. *J Urol*. 1993;149:719-23.
 21. Levine LA, Kranc DM. Evaluation of carboprost tromethamine in the treatment of cyclophosphamide-induced hemorrhagic cystitis. *Cancer*. 1990;66:242-5.
 22. Miller LJ, Chandler SW, Ippoliti CM. Treatment of cyclophosphamide-induced hemorrhagic cystitis with prostaglandins. *Ann Pharmacother*. 1994;28:590-4.
 23. Hemal AK, Praveen BV, Sankaranarayanan A, Vaidyanathan S. Control of persistent vesical bleeding due to radiation cystitis by intravesical application of 15 (S) 15-methyl prostaglandin F2-alpha. *Indian J Cancer*. 1989;26:99-101.
 24. Hemal AK, Vaidyanathan S, Sankaranarayanan A, Ayyagari S, Sharma PL. Control of massive vesical hemorrhage due to radiation cystitis with intravesical instillation of 15 (s) 15-methyl prostaglandin F2-alpha. *Int J Clin Pharmacol Ther Toxicol*. 1988;26:477-8.
 25. Pomer S, Karcher G, Simon W. Cutaneous ureterostomy as last resort treatment of intractable haemorrhagic cystitis following radiation. *Br J Urol*. 1983;55:392-4.
 26. Chan RC, Bracken RB, Johnson DE. Single dose whole pelvis megavoltage irradiation for palliative control of hematuria or ureteral obstruction. *J Urol*. 1979;122:750-1.
 27. Zebic N, Weinknecht S, Kroepfl D. Radical cystectomy in patients aged > or = 75 years: an updated review of patients treated with curative and palliative intent. *BJU Int*. 2005;95:1211-4.
 28. Hader JE, Marzella L, Myers RA, Jacobs SC, Naslund MJ. Hyperbaric oxygen treatment for experimental cyclophosphamide-induced hemorrhagic cystitis. *J Urol*. 1993;149:1617-21.
 29. Capelli-Schellpfeffer M, Gerber GS. The use of hyperbaric oxygen in urology. *J Urol*. 1999;162:647-54.
 30. Gattegno B, Guilleminot F, Fiette P, et al. [Treatment of hemorrhagic cystitis caused by cyclophosphamide using intravesical instillation of potassium alum. Apropos of 5 cases]. *Ann Urol (Paris)*. 1990;24:190-2. French.
 31. Serrano Frago P, Allepuz Losa C, Gil Martinez P, et al. [Treatment of hemorrhagic cystitis secondary to cyclophosphamide. Literature review with regard to a case]. *Actas Urol Esp*. 2005;29:230-3. Spanish.
 32. Shameem IA, Shimabukuro T, Shirataki S, Yamamoto N, Maekawa T, Naito K. Hyperbaric oxygen therapy for control of intractable cyclophosphamide-induced hemorrhagic cystitis. *Eur Urol*. 1992;22:263-4.
 33. Kuroda I, Kuwata Y, Kakehi Y. Hyperbaric oxygen therapy for Wegener's granulomatosis with cyclophosphamide-induced hemorrhagic cystitis. *Int J Urol*. 2002;9:470-2.
 34. Alagoz T, Buller RE, Anderson B, et al. Evaluation of hyperbaric oxygen as a chemosensitizer in the treatment of epithelial ovarian cancer in xenografts in mice. *Cancer*. 1995;75:2313-22.
 35. Dar'ialova SL, Vedernikova NV, Bergut FL, Zel'vin BM. [Use of antitumor preparations under hyperbaric oxygenation in ovarian cancer]. *Akush Ginekol (Mosk)*. 1979;34:6. Russian.
 36. Zel'vin BM, Vedernikova NV. [Bioenergetic metabolism in ovarian cancer treated with cyclophosphane in combination with hyperbaric oxygenation]. *Vopr Onkol*. 1979;25:85-6. Russian.
 37. Hughes AJ, Schwarer AP, Millar IL. Hyperbaric oxygen in the treatment of refractory haemorrhagic cystitis. *Bone Marrow Transplant*. 1998;22:585-6.
 38. Oztas E, Korkmaz A, Oter S, Topal T. Hyperbaric oxygen treatment time for cyclophosphamide induced cystitis in rats. *Undersea Hyperb Med*. 2004;31:211-6.
 39. Korkmaz A, Oter S, Deveci S, Goksoy C, Bilgic H. Prevention of further cyclophosphamide induced hemorrhagic cystitis by hyperbaric oxygen and mesna in guinea pigs. *J Urol*. 2001;166:1119-23.
 40. Etlík O, Tomur A, Deveci S, Piskin I, Pekcan M. Comparison of the uroprotective efficacy of mesna and HBO treatments in cyclophosphamide-induced hemorrhagic cystitis. *J Urol*. 1997;158:2296-9.