Renal damage induced by the treatment with non-opioid analgesics — theoretical assumption or clinical significance

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Poškodenie obličiek po liečbe neopioidnými analgetikami — teoretický predpoklad alebo klinický význam

Abstract

Fackovcova D, Kristova V, Kriska M:
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Non-opioid analgesics are some of the most widely used therapeutic agents in clinical practice today. The number of patients at risk for adverse events related to the use of these agents is rapidly expanding . While the gastrointestinal toxicity of these medications is well known, it has become increasingly apparent that the kidney is also an important target for untoward clinical events. Evidence of the nephrotoxicity of analgesic preparations is not sufficiently completed and available in our region.
Analgesic-related renal injury has been classified based on mechanism of action into "classic" analgesic nephropathy and NSAID-related renal toxicity. From clinical point of view the renal side effects induced by analgesics can be classified into hemodynamic (functional) side effects and idiosyncratic side effects.
The common link in both types of side effects seems to be renal ischemia related to prostaglandin synthesis inhibition. Key enzyme in this process is cyclooxygenase occurring in two isoforms: COX-1 and COX-2. Antiinflammatory effect of NSAIDs is mediated by COX-2 inhibition, while the side effects (gastrotoxicity, nephrotoxicity) by inhibition of COX-1.
COX-1 was more inhibited by indomethacin and piroxicam and COX-2 by 6-MNA (active metabolite of nabumetone), diclofenac and ibuprofen. Nimesulide and meloxicam selectively block COX-2 and are recommended to patients at risk or treated with diuretics. *(Tab. 2, Fig. 2, Ref. 38.)*
Key words: non-steroidal antiinflammatory drugs, cyclooxygenase, side effects, renal toxicity.

Abstrakt

Fačkovcová D., Kristová V., Kriška M.:
Poškodenie obličiek po liečbe neopioidnými analgetikami — teoretický predpoklad alebo klinický význam
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Neopioidné analgetiká patria medzi najčastejšie používané terapeutické prostriedky v dnešnej klinickej praxi. Počet pacientov vystavených riziku vedľajších účinkov následkom užívania týchto prostriedkov sa rýchlo zvyšuje. Kým gastrointestinálna toxicita týchto liekov je známa, čoraz viac je zrejmejšie, že takisto obličky sú dôležitým cieľom ich nepriaznivého klinického účinku. Nefrotoxicita analgetických preparátov nie je v našej oblasti dostatočne dokázaná.
Obličkové poškodenie následkom užívania analgetík bolo zatriedené na základe ich mechanismu účinku ako klasická analgetická nefropatia a renálna toxicita spôsobená NSA. Z klinického hľadiska môžu byť vedľajšie obličkové účinky vyvolané analgetikami klasifikované ako hemodynamické (funkčné) a idiosynkratické vedľajšie efekty.
Spojujúcim článkom medzi oboma typmi vedľajších efektov sa zdá renálna ischémia spojená s inhibíciou syntézy prostaglandínov. Kľúčovým enzýmom v tomto procese je cyklooxygenáza, ktorá sa vyskytuje v dvoch formách: COX-1 a COX-2. Protizápalový efekt NSA je sprostredkovaný inhibíciou COX-2, kým vedľajšie efekty (gastrotoxicita, nefrotoxicita) inhibíciou COX-1. COX-1 bola viac inhibovaná indometacínom a piroxikamom a COX-2 aktívnym metabolitom nabumetonu (6-MNA), diklofenakom a ibuprofenom. Nimesulid a meloxicam selektívne blokujú COX-2 a odporúčajú sa pacientom užívajúcim diuretiká. *(Tab. 2, obr. 2, lit. 38.)*
Kľúčové slová: nesteroidové protizápalové lieky, cyklooxygenáza, vedľajšie účinky, renálna toxicita.

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Non-opioid analgesics comprise heterogenous group of drugs inducing pain relief by central (e.g. amitriptyline, carbamazepine) and peripheral nervous systems paracetamol, acetylsalicylic acid and related compounds — nonsteroidal anti-inflammatory drugs (NSAIDs), local anaesthetics (Rang and Dale, 1991). Their classification is shown on table (Tab. 1).

The most frequently used non-opioid analgesics, at present, are nonsteroidal anti-inflammatory drugs (NSAIDs). In 1991 70 million prescriptions for these analgesics were prescribed in USA, at the price of 2,2 billion dollars. Since 1973 till 1981 the number of 30 million prescriptions doubled, and in 1987 attained the mentioned 70 million prescriptions yearly (Tomita, 1988). If acetylsalicylic acid is classified into the group of NSAIDs, then worldwide 30 million people at least, receive daily a drug of this group (O'Brien and Bagby, 1985). In France during 1970 to 1980 the number of prescribed NSAIDs doubled, though the incidence of rheumatic diseases increased only by 29 % (De Pourvourville, 1992). Available reviews show that 198,725 million Sk was paid for analgesics in 1995 in Slovakia, and 327,420 million Sk for antirheumatic, antiflogistic drugs (Gibala, 1997).

Epidemiological reviews on abuse of analgesics in Slovakia and on prevalence of analgesic nephropathies in our region are not sufficiently completed and available. Completion of data in National centre of organ transplantations in Bratislava, where database of persons on the waiting list for kidney transplantation is prepared, will be promising. Patients in terminal phase of renal failure of all dialysis centres in Slovakia are successively inscribed in the waiting list. To January 15th 1997 there were 1116 patients with renal failure, 29 of them with diagnosis of analgesic nephropathy due to abuse of analgesic drugs, and 41 with diagnosis of tubulointerstitial nephritis inscribed (data collection realized 6 years ago).

Classification of nephropathies

The National Kidney Foundation published classification of analgesic-related renal injury. Generally accepted classification is based on mechanism of action:

1. "Classic" analgesic nephropathy. This is a disease resulting from the habitual consumption over several years of a mixture containing at least two antipyretic analgesics and usually codeine or caffeine. It is characterized by renal papillary necrosis and chronic interstitial nephritis that leads to the insidious onset of progressive renal failure.

2. NSAID- related renal toxicity. This is a disorder characterized by one of several distinct presentations: acute renal failure secondary to renal vasoconstriction, interstitial nephritis often presenting as nephrotic syndrome due to minimal change glomerulopathy, hyperkalemia, sodium and water retention, and, rarely, papillary necrosis. There is a distinct "at-risk" population for the acute renal failure that develops secondary to renal vasoconstriction: Those individuals with underlying volume depletion from any cause and those individuals with chronic renal disease are particularly susceptible to this effect (National kidney foundation position paper, 1996)

From clinical point of view the primary renal side effects induced by analgesics can be classified into:

A) Hemodynamic (functional) side effects — characterized by acute renal failure, hyponatraemia, hyperkalemia, acute interstitial nephritis resulting from prostaglandin synthesis inhibition (Carmichael and Shankel, 1985; Schlegel, 1987; Buchanan and Brooks, 1991).

B) Idiosyncratic side effects — characterized by analgesic nephropathy and nephrotic syndrome (Buchanan and Brooks, 1991; Hardin and Longenecker, 1992), leading to chronic renal insufficiency with unknown underlying mechanism.

A) Hemodynamic (functional) side effects

It is to emphasize, that predicable in 1 % reversible side effects are involved. It has been accepted the mechanism of damage, described 25 years ago by John Vane, that these drugs interfere with arachidonic acid transformation into the thromboxane and prostaglandins by cyclooxygenase inhibition (Vane, 1971).

Most clinical effects of NSAIDs are mediated by prostaglandin synthesis inhibition. Under physiological circumstances are prostaglandins the mediators of inflammation and pain, they cause prevalently vasodilatation, inhibition of thrombocyte aggregation, uterine smooth muscle contraction and have cytoprotective action upon gastric mucosa. Besides physiological effects prostaglandins participate in renal blood flow autoregulation, affect transport of NaCl, thus, playing an important role in homeostasis maintenance (Henrich and Diamond, 1989).

Prostaglandins affect the renal circulation by two ways:

1. They affect distribution of renal blood flow into various renal regions with preferential blood supply for juxtamedular nephrons (Oates, 1988). By contrast to this, prostaglandin synthesis inhibition leads to selective blood flow reduction in inner cortical

Tab. 1. Classification of analgesics.

A) Non-opioid analgesics — nonsteroidal antiflogistic agents
a) aspirin
b) ibuprofen, diclofenac, indomethacin, flurbiprofen etc.
c) paracetamol
B) Opioid analgesics (morphine, codeine, pentazocine, pethidine, benzitramide, methadone, buprenorphine, butorphanol, fentanyl, tillidine)
C) Adjuvant drugs (anticonvulsants, neuroleptic, anxiolytic drugs, corticosteroids, antidepressants, muscle relaxants, local anaesthetics, biphosphonates)

Tab. 1. Klasifikácia analgetík.

A) neopioidné analgetiká — nesteroidové antiflogistiká
a) aspirín
b) ibuprofén, diklofenak, indometacín, flurbiprofén a ďalšie
c) paracetamol
B) opioidné analgetiká (morfín, kodeín, pentayocín, benzitramid, metadon, buprenorfín, butorfanol, fentanyl, tilidín)
C) adjuvantné lieky (antikonvulzíva, neuroleptiká, anxiolytiká, kortikoidy, antidepresíva, myorelaxanciá, lokálne anestetiká, bifosfonáty)

nephrons, while the flow in outer cortex remains unchanged (Itskovitz, 1973).

2. They are the most important factors in maintenance of glomerular hemodynamics by affecting afferent arterioles and glomerular mesangium.

Functional disorder can manifest itself in form of:

a) Acute renal insufficiency

In normovolemic conditions (Muther and Benett, 1980; Favre, 1982) prostaglandins participate very little in the maintenance of renal functions. Patients suffering from systemic hemodynamic disorders are threatened by more severe consequences resulting from cyclooxygenase (COX) inhibition.

In circulatory disorders is the renal blood flow maintained by balance between vasoconstrictive factors (catecholamines, angiotensin II) and vasodilatation induced by prostaglandins. Application of NSAIDs to patients at risk, mainly those with congestive heart failure, liver cirrhosis, nephrotic syndrome, sepsis, haemorrhage, hypovolemia, and patients treated with diuretics will disturb this balance in favour of vasoconstriction, or it can lead to sudden, strong impairment of renal functions (Palmer, 1995). If NSAIDs treatment is not early enough interrupted, the prolonged renal ischemia can cause acute tubular necrosis and irreversible renal damage resulting eventually in acute renal insufficiency (Carmichael and Shankel, 1985).

b) Acute interstitial nephritis

Interstitial nephritis is a rare but severe form of NSAIDs nephrotoxicity. It has been estimated to occur in one of every 5000 to 10 000 patients and differs from acute renal insufficiency in onset, severity and duration (Brater, 1988). Although interstitial nephritis can occur within one week of NSAIDs administration, it usually occurs following several months to one year after the start of NSAIDs administration (Porile, 1990). Typically, patients present with greatly elevated serum creatinine, edema and nephrotic-range proteinuria occurs in two thirds of patients. Temporary dialysis may be necessary. Histological findings from renal biopsy specimens demonstrate diffuse interstitial edema with evidence of mild to moderate inflammation, and cellular infiltration of predominantly cytotoxic T cells with smaller numbers of B cells and eosinophils (Bender, 1984; Abt and Gordon, 1985). Affected persons are not only elderly patients, but also children who are receiving NSAIDs for the treatment of juvenile rheumatoid arthritis. Pathophysiological mechanism resides probably in the fact, that metabolites of certain NSAIDs (in 46 % of fenoprofen) are irreversibly stereoselectively bound to albumin (Volland, 1991) and the formed macromolecular complex is transported into the glomerular mesangium. Due to release of cytokins, interleukins and other substances, or by possible stimulation of macrophages and toxic leucocytes T the glomerular damage appears and interstitial nephritis is developing (Ten, 1988).

c) Hyponatremia

At least in 25 % of patients treated with NSAIDs sodium retention develops due to prostaglandin synthesis (PG_s) inhibition because of their natriuretic effects (Fig. 1). Clinical manifestation of salt retention depends on basal prostaglandin production degree. In healthy persons is the prostaglandin production very low, thus sodium retention will be transient and clinically insignificant. In patients with heart failure, hepatic cirrhosis, nephrosis however, can NSAIDs cause significant sodium retention with

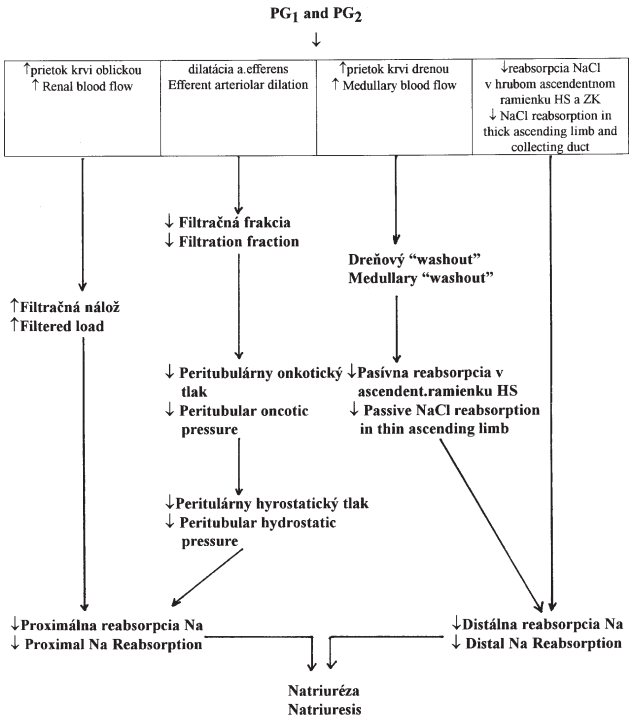

Fig. 1. The direct and indirect mechanisms by which renal prostaglandins exert a natriuretic effect.
Obr. 1. Priamy a nepriamy účinok prostaglandínov na nátriurézu.

severe consequences. 15 kg body gain has been observed in a 70 years old patient during 17 days lasting treatment with ibuprofen (Shooley, 1977).

d) Hyperkalemia

Use of NSAIDs can be accompanied with hyperkalemia especially in patients with chronic renal insufficiency, however also in those with normal renal function. The underlying cause resides in PG synthesis inhibition leading to reduction of renin release from juxtaglomerular cells with resulting hypoaldosteronism (Henrich, 1981).

Patients at risk are the diabetics due to elevated incidence of hyporenin-hypoaldosteronism (DePronzo, 1980; Nadler, 1986), and elderly people having decreased levels of circulating renin and aldosterone due to advanced age (Mimran, 1992). Caution should be used especially when NSAIDs are combined with drugs interfering with renin-aldosterone-angiotensin (RAA) system (beta-adrenergic blockers, ACE inhibitors, potassium-sparing diuretics, vasodilators) (Vane and Botting, 1996).

B) Idiosyncratic renal side effects

The most frequent form of idiosyncratic side effects associated with use of non-opioid analgesics is the so called "classic" analgesic nephropathy with characteristic papillary necrosis resulting in irreversible chronic renal failure.

Analgesic nephropathy has been originally considered to be induced by use of non-opioid analgesics containing acetylsalicy-

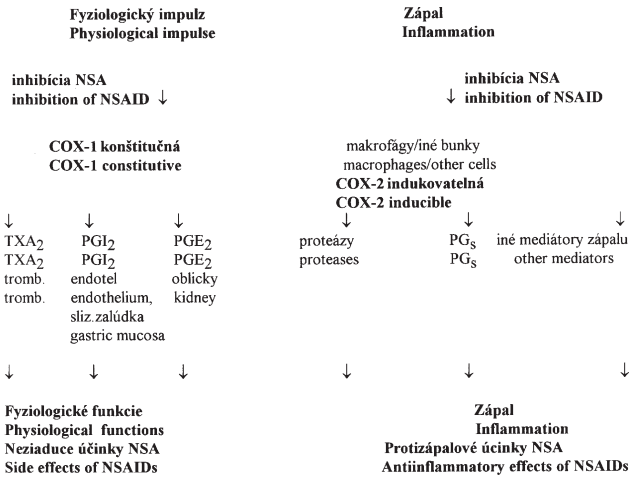

Fig. 2. Current COX-concept.
Obr. 2. Súčasný COX-koncept.

lic acid, phenacetin and caffeine (Duggin, 1980). Middle aged women using analgesics for headache and mood improving were preferentially affected. Studies appeared recently indicating that NSAIDs in monotherapy or in combination with acetylsalicylic acid can cause papillary necrosis with subsequent chronic renal insufficiency (Carmichael and Shankel, 1985).

The underlying mechanism is unknown till now. There are several hypotheses. Direct toxic effect of NSAIDs or of their reactive metabolites is taken into consideration. Their transport, binding, distribution may depend on factors like volume depletion, pH of urine, presence of other analgesics. In papillary necrosis development participate probably several factors. Presence of two factors at least is supposed:

1. functional or metabolic predisposition of tissues to enhanced susceptibility to blood volume reduction due to vasodilating autacoids,

2. selective concentration of drugs in papilla (Duggin, 1980).

It is not clear which drugs or components of them per se, are responsible for this pathological process.

Dubach and coworkers (Dubach, 1983; Dubach, 1991) in their study consider phenacetin and its metabolite paracetamol to be the main cause. Prescott and coworkers (Prescott, 1982) on the other hand, suppose that phenacetin and paracetamol play only minor role in development of this condition, but substances with antiflogistic effects (e.g. salicylates) are nephrotoxic (Abt and Gordon, 1985).

Comparison of effects of COX-1 and COX-2 inhibitors

The unique common point in both types of side effects seems to be renal ischemia due to prostaglandin synthesis inhibition. Key enzyme in this process is cyclooxygenase occurring in two isoforms: COX-1 and COX-2. The constitutive isoform COX-1 performs physiological functions — its activation induces production of prostacyclins with antithrombotic and antiatherosclerotic effects on endothelium, cytoprotective action on gastric mucosa, maintenance of renal blood flow with sufficient natriuresis.

Inducible isoform COX-2 is incoded at the other gene than COX-1 and is induced by inflammation and cytokins originating from macrophages and other cells. Antiinflammatory effect of NSAIDs is mediated by COX-2 inhibition, while the side effects (gastrotoxicity, nephrotoxicity) by inhibition of COX-1 (Gian, 1996) (Fig. 2).

Third isoform COX-3 is supposed to be present in brain. This assumption resides in the fact that paracetamol is an antipyretic analgesic drug with mild antiinflammatory effects, but it however decreases markedly PGs synthesis in brain.

Knowledge of single COX isoforms is only superficial till now. Current investigation is focused on influence of single NSAIDs on COX-1 and COX-2 isoforms and on pharmacological properties of highly selective COX-2 inhibitors.

It was found that neither COX-1 nor COX-2 was influenced with salicylates. COX-1 was more inhibited by indomethacin and piroxicam and COX-2 by 6-MNA (active metabolite of nabumetone), diclofenac and ibuprofen (Laneuville, 1994).

It is important to accentuate, that the specificity and selectivity two isoforms of COX disappear by use of high doses as known with beta-adrenergic blockers (Meade, 1993). Decissive factor for drug effectivity are the pharmacokinetic properties of NSAIDs in the individual patient.

The risk connected with NSAIDs application is better known concerning gastrotoxicity and nephrotoxicity. The majority of NSAIDs are nonselective COX inhibitors with little difference in the given group.

The most used antiflogistic, analgesic and antipyretic drug — acetylsalicylic acid induces in low doses antiaggregatory effect, in higher doses irreversible inhibition of COX-1 and COX-2 with dominant COX-1 inhibition. It is interesting that acetylsalicylic acid exerts only low nephrotoxicity, however its gastrotoxic effects are significant. Indomethacin is an effective inhibitor of both isoenzymes — COX-1 and COX-2. Naproxen inhibits preferentially COX-1, less COX-2. Its antiflogistic effect is equal to those of acetylsalicylic acid and indomethacin. Ibuprofen is a less effective inhibitor of COX-1 and COX-2 without evident selectivity to COX-2, with excellent analgesic effect in low doses. Piroxicam is an effective inhibitor of COX-1.

Nephrotoxicity of above mentioned NSAIDs may only be apparent in patients that are compromised and whose renal function is dependent upon prostanoid tone. This has been noted with indomethacin, naproxen, and ibuprofen. Sulindac seems to act renoprotectively (Griswold and Adams, 1996).

To the substance with favourable pharmacological properties belongs nabumetone affecting renal function in 1 % of patients only (Aronoff, 1992). Regarding its low gastrotoxicity, nephrotoxicity and antithrombotic effect is this drug classified into the group of selective COX-2 inhibitors.

Nimesulide is chemically characterized by functional sulphanyl group replacing the conventional carboxyl (indomethacin, naproxen, ibuprofen) enolic (phenylbutazone, piroxicam), or hydroxylic groups. This modification seems to be important for effectivity and safety of substance in its antiinflammatory effect. Nimesulide inhibits synthesis PGE_2 by COX-2 inhibition in vitro studies (Gian, 1996).

The first drug in clinical practice, especially as selective inhibitor of COX-2 is meloxicam with excellent pharmacological properties and low incidence of gastrotoxic and nephrotoxic manifestations.

Tab. 2. Inhibitors of prostaglandin biosynthesis.

Substance	Site of action
glucocorticoids	inhibition of phospholipase A_2
acetylsalicylic acid	irreversible COX-1 inhibition
benaxoprofen	COX-1, lipogenase
indomethacin	COX-1 60 times more than COX-2
ibuprofen	COX-1 about 50 times more than COX-2
nabumetone	COX-2 about 500 times more than COX-1
nimesulid	COX-2, inhibition of leucocytic function
meloxicam	COX-2 selective inhibition
celecoxib	COX-2 selective inhibition
rofecoxib	COX-2 selective inhibition

Tab. 2. Inhibítory biosyntézy prostaglandínov.

Látka	Miesto zásahu
glukokortikoidy	inhibícia fosfolipázy A_2
kyselina acetylsalicylová	ireverzibilná blokáda COX-1
benaxoprofén	COX-1, lipoxygenáza
indometacín	COX-1 60-krát viac ako COX-2
ibuprofén	COX-1 asi 50-krát viac ako COX-2
nabumeton	COX-2 asi 500-krát viac ako COX-1
nimesulid	COX-2, inhibuje funkcie leukocytov
meloxikam	COX-2 selektívna inhibícia
celecoxib	COX-2 selektívna inhibícia$_a$
rofecoxib	COX-2 selektívna inhibícia

Conclusion

There are two types of renal damage induced by non-opiod analgesics: 1. the so called "classic" analgesic nephropathy due to long-lasting administration of drug combinations containing at least two antipyretic analgesics and usually codeine and caffeine. This condition is characterized by renal necrosis and chronic interstitial nephritis.

2. NSAID- related renal toxicity manifesting itself as acute renal insufficiency, acute interstitial nephritis and salt and fluid retention due to renal vasoconstriction.

Meanwhile the underlying mechanism "classic" analgesic nephropathy is not known till now, the main cause of NSAIDs nephrotoxicity resides in inhibition of prostaglandin synthesis. Kidneys of otherwise healthy persons are not significantly affected with NSAIDs. Patients at risk, however, are those suffering from heart failure, hepatic cirrhosis, nephrotic syndrome, sepsis, haemorrhage, hypovolemia, diabetes, or patients treated with diuretics. In these cases is recommended to prefer the selective inhibitors of COX-2, e.g. nabumetone, nimesulid, meloxicam exerting low nephrotoxic potential.

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PREDSTAVUJEME NOVÉ KNIHY

Ondruš D. a spol.: Nádory močového mechúra, diagnostika a liečba. Martin, Osveta 2000, 256 strán (ISBN 80-8063-035-6).

Monografia podáva komplexný a ucelený pohľad na problematiku nádorov močového mechúra — epidemiológiu, etiológiu, rizikové faktory, molekulovú genetiku, patológiu, diagnostické postupy, klasifikáciu a jednotlivé liečebné postupy (chirurgickú liečbu, chemoterapiu, imunoterapiu a rádioterapiu).

Štruktúra diela zodpovedá moderným požiadavkám. Autori jednotlivých častí sú významnými odborníkmi v danej problematike, skúsení aj v jej literárnom spracovaní cez početné publikácie v domácej aj zahraničnej literatúre. Spracovanie kapitol je porčné, prihliada na súčasný stav vedeckých poznatkov, ale aj na potreby ďalšieho vzdelávania príslušných odborníkov v súvislosti s modernou diagnostikou a liečbou tohto závažného ochorenia.

Autori na základe vlastných dlhoročných skúseností uvádzajú odporúčania na najvhodnejšie diagnostické a liečebné postupy v našich podmienkach.

Publikácia, ktorá je jedinečným dielom v slovenskej odbornej literatúre, by mala byť základnou príručkou urológov, patológov, onkológov, ale aj širšej lekárskej verejnosti, a v určitom slova zmysle aj pre tých, ktorí sa zaoberajú výskumom podstaty onkologických ochorení, ako aj pre študentov lekárskych fakúlt.

V. Zvara