“OVIDIUS” UNIVERSITY OF CONSTANTA

Ph D. SCHOOL OF MEDICINE

Field of Medicine Ph D.

THE DIAGNOSIS AND THE TERAPEUTIC ALGORITHM OF RETROPERITONEAL TUMORS

SUMMARY

COORDINATOR:

PROF.UNIV.DR. VASILE SÂRBU

CANDIDATE:

DR. RAUF OSMAN

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CONTENTS

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Summary

The anatomic space known as retroperitoneal, "a nobody's territory but also of all, gives a meeting to doctors in endocrinology, general surgery, vascular surgery, urology, neurosurgeons and orthopedics specialties, which is due either to organs located wholly or partly here, or to vascular, nerve, embryonic or ectopic tissues "wrapped" in a rich connective-fat tissue".

The paper defines "retroperitoneal space" by understanding it as a space from the diaphragm to the upper strait of the pelvis .
In the thesis is a very detailed description of this space from which can not be excluded the pelvisubperitoneal area and the extensions of this space.
Chapter II presents a classification of primitive retroperitoneal tumors especially, but also of secondary ones, their carcinogenesis, semiology and the positive diagnosis of anatomapathology and their treatement.

The diagnosis of retroperitoneal tumors is difficult due to borrowed symptoms (from the urinary system, nervous, digestive, vascular system, etc) but many retroperitoneal tumors reach large proportions due to symptom deprivation or the lack of subjective complaints from patients.
Many of the cases studied reach the doctor due to the increase in the volume of the abdomen
A major importance is given to the imaging diagnosis of retroperitoneal tumors, in particular CT and Nuclear Magnetic Resonance

Computered tomography (CT) has become the most important imagining exploration for the diagnosis and staging of retroperitoneal tumor masses. It brings not only the location of the tumor, but also the nature of the lesions (cystic or solid), the presence or absence of necorses, the invasion of the adjacent structures and the presence of intraabdominal metastases.

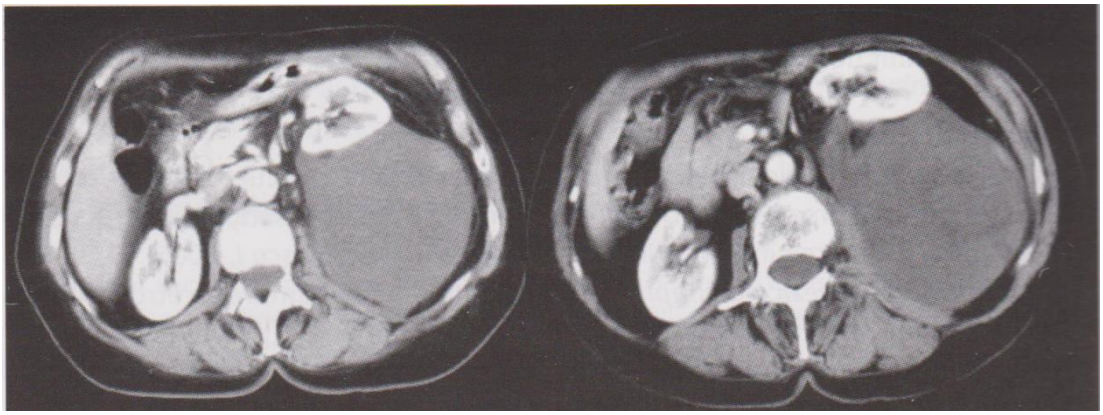

Fig. 1 Computed tomography - Voluminous left retroperitoneal tumor.
(retroperitoneal lipoma 2008–dr. Osman S collection.)

Fig.96 left paravertebral formation

Fig.97 left paravertebral formation

Diagnosis of retroperitoneal sarcomas "may be suspected by CT based on the heterogeneity of retroperitoneal tumor mases, with necrosis. CT is also important in the differential diagnosis of sarcomas from other primary or metastatic retroperitoneal malignancies as well as benign tumors developed in retroperitoneum" (50). Affecting multiple retroperitoneal lymph nodes associated with the existence of a retroperitoneal tumor formation may suggest a lymphoma, diagnosis being confirmed by lymph node biopsy. Establishing a diagnosis of lymphoma is very important because in this case the treatement is not surgical. (146)

Magnetic resonance imaging (MRI) provides information useful to the stage and offers the advantage of multiple-plane images, helping to establish surgical tactics. It can more accurately highlight the neighboring relationships of tumors masses

with adjacent structures, especially vascular as well as the extension of tumor invasion. It is useful to detect tumor infiltration of nerve threads and the possible invasion of spinal holes

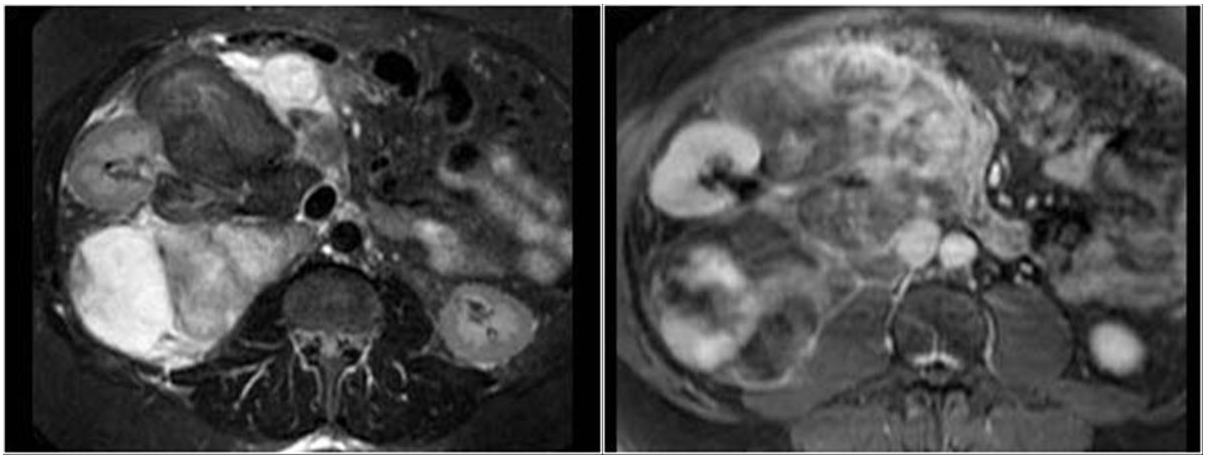

Fig. 2 A retroperitoneal mixoid tumor(liposarcoma)

fig.109 – Retroperitoneal mixed tumor with Mesenteric and retroperitoneal adenopathies

Tumor biopsy has value, especially under ultrasound or tomography.Fine needle aspiration biopsy reduces the risk of malignant cell leakage in retroperitoneal space.

Chapter III analyzes the treatament of these retroperitoneal tumors

Primary treatament should be chosen with the utmost care as there are high-grade chemo-radiosensitive tumors.

Surgical treatment is detailed starting from the staging of these tumors, from the result of the biopsy punctuation by fine or incisional adaptation to each case and which qualifies for either conservative therapy or as extensive a resection. Metastasis surgery is also analyzed.

A separate section is the one that analyzes the strategy that applies to this therapy andtheir prognosis. Early diagnosis is fundamental; this being demonstrated by the monitoring of retroperitoneal tumors.

The personal part includes the most effective methods of investigation and diagnosis « as appropriate » in retroperitoneal tumor pathology. The ultimate goal of the study is the correct and complete management of patients who have confirmed the diagnosis.

Diagnostic imaging of the studied retroperitoneal tumors, in diagnosis is illustratedwith colorful microscopic images when histopathology of tumors is

analyzed and the imagining part presents the importance of CT and MRI investigations in the diagnosis of retroperitoneal tumors

Chapter VII presents the surgical act performed in the case of the patients in the analyzed group, starting with its indications, ways of approach, tactical problems, etc The author analyzes numerous intraoperative features presenting 6 cases in practice. These cases are presented together with a rich imaging and discussion on each intervention

The problems raised by block extirpation of all these tumors have been numerous but do not seem to be related to the invasive viscera, but rather to the regional vessels, the compression of the tumor, and the effect of the sudden decompression of the inferior cave vein and its branches. The invasion of kidneys or intraabdominal viscera generally has coded surgical solutions, but other vascular implications resolve with greater difficulty, as well as the concomitant presence of other conditions such as pheochromocytoma in one case.

The postoperative evolution of the studied group starts with complications solved even intraoperatively: haemorrhages, pleurisal damage, damage to adjacent tumor organs such as colon vein, duodenum, kidney. These interventions lead to haemostasis reintervention, these complications are correlated with literature data..

A general problem of the exertion of these tumors, common to other authors, is postoperative recurrences. In the study of 40 patients there were no relapses during the follow-up period, but in 13 cases there were recurrences. Of these, only 9 were reoperated, the remaining 4 cases were surgically abandoned.

The thesis presents an extensive study on the role of surgery in the conditions of the statistical data mentioned. This study refers to an analysis of the principle of radicality, conservative surgery, techniques used (including lymphadenectomy) for palliative surgery, metastatic surgery.

Finally, there are presented discussions based on results and the conclusions. The bibliography contains over 300 titles quoted in the paper. The paper contains 35 tables and 176 images.

Material and Method

This paper aims to answer some of these questions, but, inevitably, in turn it will bring forth new ones.

The objectives pursued by this scientific study were:

1. *the primacy of imaging methods in the diagnosis of retroperitoneal tumors;*
2. *establishing the most effective method of investigating and diagnosing "case-by-case" retroperitoneal tumor pathology, highlighting the location and contribution of each imaging method;*
3. *the value of the histopathological examination extemporaneous in the intraoperative diagnosis;*
4. *correct and complete management of patients with retroperitoneal tumors to improve prognosis*

PRESENTATION OF THE CASES

Done at Constanta County Emergency Clinical Hospital, the present study includes the casuistry of the Urology and Surgery Clinics in 2005-2014 (53 patients), complemented by the casuistry of the Clinic of Oncology of SCJU Constanta in the same period and of the Urology Clinic "Prof. Dr. Theodor Burghele" Clinic Hospital, since some patients have begun investigating procedures at the Urology Clinic, continued the surgical treatment at "Th. Burghele"(6 patients) and chemotherapy treatment at the Oncology Clinic.

The necessity of such a study was due to the opportunity to present in this thesis the personal experience gained at the SCJU Urology Clinic of Constanta, supplemented by the valuable experience of Clinic Hospital "Th. Burghele "in order to obtain complete and necessary data for a statistically significant value, resulting in pertinent and relevant conclusions on the chosen topic.

Patients were followed on the basis of a card that included:

a) *Epidemiological data: sex, age, background, occupation, occupational and environmental noxes*

b) *Etiopathogenic data: family history, risk factors, co-morbidities*
c) *Clinical diagnosis: accidental, symptomatic, or by complications (intestinal occlusion, digestive haemorrhage)*
d) *Preoperative imaging diagnosis: abdominal ultrasonography, computed tomography, digestive endoscopy*
e) *Treatment: surgical – on emergency or programmed; endoscopic; adjuvant treatment*
f) *Evolution*
g) *Postoperative morbidity*
h) *Mortality*

For the evaluation of microscopic parameters, two types of tumor tissue fragments were used:

- *Fragments of tumor tissue taken from the operative parts in the cases included in the lot that were performed during the study;*
- *The paraffin blocks of the cases included in the batch that were operated before the study began.*

Tumor tissue fragments were subjected to classical histological processing techniques (fixation and inclusion in paraffin) after which serial sections of each block were performed.

- *The first section was stained with the classic H-E coloring method*
- *The following sections were used to mark the IHC.*

The sections were examined in SCJU Constanta's pathological anatomy laboratory, some of the patients being reassessed and confirmed at the "Victor Babeş" National Institute of Bucharest, where the images presented in this study also come from.

Methods and statistical analysis

The data obtained about each patient was processed using the version 11 of Stata program and the EpiInfo application. For the statistical analysis of the recorded data we used the T (Student) test which consists of a set of mathematical operations that compares the average values of two population samples or the

average of two strings of values, in this case one of the samples is the observed parameter and the other Is a random or estimated sample.
Other methods of statistical analysis were also used in the PhD thesis: Chi square test (serves to compare two distributions), the Anova test and other types of tests.

4. THE STRUCTURE OF THE SAMPLE

The clinical study performed at the Urology Clinic and Surgery Clinic of the Emergency County Clinical Hospital in Constanta is based on a group of 53 patients hospitalized and investigated in the clinic between 1 January 2005 and 31 December 2014.

Considering the great symptomatic diversity that a retroperitoneal, especially malignant, tumor may have, it is extremely important to know all the symptoms of tumor pathology, the modalities of onset as well as the frequency of each such possibility encountered in practice for an early diagnosis. The capture of retroperitoneal tumors from incipient stages without clinical manifestations is an essential condition for effective therapeutic intervention and favorable prognosis.

Diagnosis in retroperitoneal tumors was based on clinical data (anamnesis, objective examination) and on paraclinical data (except for laboratory and especially imagistic). For a correct diagnosis, several steps must be taken, omission of one or superficiality may lead to an erroneous diagnosis, the prognosis of the disease being considerably prejudicial:

ANAMNESIS: - symptoms reported by a sick person, in the order of their appearance, the moment of onset of each symptom, their evolution over time, the association of several symptoms, the correlation with certain factors influencing them, the presence of significant pathological and heredocolateral personal history, eating habits, consumption of tobacco or alcohol, toxicity at work or at home.

CLINICAL EXAMINATION: - thoroughly performing all steps, without omitting a segment, with the detection of all general pathological changes.

LABORATORY TESTS AND PARACLINICAL EXAMINATIONS: laboratory screening tests and targeted investigations (tumor markers).

Full urinalysis is a test to be performed on all patients with retroperitoneal tumors, not a diagnostic test for this condition, but a screening test, important in detecting hematuria, bacteriuria, pyuria, and other biochemical parameters.

The prevalence of damage of affected retroperitoneal organs or the presence of altered blood-level values is high among the population with tumor pathology, so it is necessary to perform a battery of routine biochemical and haematological tests, to be thorough if there are alterations in physiological intervals.

Imaging explorations:

- *Standard radiography*
- *Ecography (ultrasound)*
- *Computerized axial tomography*
- *Nuclear magnetic resonance*
- *PET, intravenous urography, angiography, phflebography – less used*

Conclusions

1. *Primary tumors of the retroperitoneal space raise particular problems of diagnosis, histology, evolution, but especially therapeutic behaviour.*

The anatomical space known as retroperitoneal, a territory a nobody's territory but also of all, meets endocrinologists, surgeons, vasculators, urologists, neurosurgeons and orthopedists, due either to organs wholly or partially located here or to vascular, nervous elements, embryonic parts or ectopic tissue "packed" into a rich connective-fat tissue.

2. *The rarity of primitive retroperitoneal tumors is outlined by most data in the medical literature and confirmed in this study.*

Hence, along with the anatomical-surgical features, the diagnostic and therapeutic complexity of these cases also arises. In these conditions, primitive retroperitoneal tumors can not be related to the sex of the patients, but a statistical connection is observed between the age of the patients and certain histological types.

3. *Classification of primary retroperitoneal tumors is difficult to achieve because of tumor and intratumoral polymorphism; The 2002 WHO grading of soft tissue tumors seems to correspond to this problem at this time.*

4. *The histopathological polymorphism of retroperitoneal tumors is extremely varied and can manifest itself within the same tumor*.

Extemporaneous exam may conduct to mistakes of interpretation over the positive diagnosis, therefore the histopathological examination of paraffin will be defining. Immunohistochemistry techniques are useful in elucidating the tumor type, in TRP predominating the malignant tumors (sarcomas having the highest frequency). Invasion of lymph nodes and distant metastases are exceptions in the evolution of retroperitoneal tumors, and tumor recurrence can be accompanied by changes in the histopathological profile due to the polymorphism of these entities.

5. *The development of large tumor masses in the retroperitoneal space, without its own symptomatology or with minor "loan" signs, is one of the most important peculiarities for the direction of the positive diagnosis.*

Extremely variable symptomatology seen in patients with retroperitoneal tumors - abdominal pain, weight loss, palpation of an abdominal mass - are identified as clinically relevant data for the diagnosis of retroperitoneal tumor diagnosis. It is, however, worth mentioning that any of these signs can appear and evolve independently of the others.

6. *Imaging diagnosis is the pillar of positive diagnosis in the TRP and is based on the investigative association abdominal ultrasonography - computed abdominal tomography*.

These investigations underlie the diagnostic algorithm of primary retroperitoneal tumors, a useful diagnostic tool revealed by this study.

7. *Each histological type of retroperitoneal tumor presents intraoperative peculiarities, starting from the size, delimitation, relation with the adjacent structures*.

Often, the intraoperative aspect may be different from the preoperative diagnostic image of a retroperitoneal tumor, the intraoperative exploration being important for defining its primitive character, but also for adopting appropriate surgical tactics.

8. Histological diagnosis should be made according to the World Health Organization classification, the degree of malignancy (G) should be established whenever possible.

A biopsy puncture can underestimate the degree of malignancy; When preoperative treatment is an option, imaging examinations can provide the clinician with useful information in estimating malignancy. Anatomo-pathological diagnosis is based on histology and immunohistochemistry. It should be supplemented with molecular histology (FISH, RT-PCR) performed in a laboratory with external quality assurance program (especially when the histological form is rarely encountered or histological diagnosis is in doubt). The piece has to be fixed with formalin (fixation with Bouin solution should be avoided, this may diminish the feasibility of the molecular analysis). Collecting frozen tissue samples or tumor fingerprints should be encouraged, as new histopathological analysis methods may be available that may be used for the benefit of the patient.

9. *Surgical ablation is the standard treatment for patients with localized disease, surgery should be performed by a specialized surgeon in the treatment of this condition*.

The standard procedure is broad excision, followed by radiotherapy and / or chemotherapy as a standard treatment for deep-to-medium-high malignant tumors with a diameter of less than 5 cm [II, A]. This involves excision of the tumor with a normal tissue area around it, as a benchmark was set a 1 cm safety margin; it is important to realize that this can be minimal in the case of the presence of anatomical barriers such as muscle fascia, periost or perinerv. A marginal excision may be acceptable in selected cases, particularly for non-parathymic atypical lipomatous tumors.

10. *For retroperitoneal tumor recurrence, surgical reintervention should be considered if safety margins can be achieved without major morbidity, taking into account tumor extension and tumor biology (may be omitted in intrapartum atypical lipomatous tumors).*

In case of relapses, reintervention may be performed with pre-operative treatment if the safety limits can not be obtained or surgery would be too mutilating. In the latter case, the use of multimodal treatment followed by less radical surgery requires a joint decision (doctor-patient), if uncertain. When plastic surgery and vascular grafts are needed, the surgical team should be expanded with field specialists if needed.

11. Complete or partial resection of the retroperitoneal tumor directly benefits the patient by increasing the postoperative survival rate and lowering the rate of tumor recurrence. In the case of partial excretion, there is the advantage of increasing the quality of life by temporarily resolving complications arising from the invasion of the adjacent structures and gaining continuity of adjuvant oncology treatament.

The quality of the exertion is controlled by the histopathological examination of the operative part. The presence of tumor invasion in the resection sections is a local recurrence factor and justifies indicating a wider reintervention or postoperative radiotherapy. Surgical resection of solid

tumors determines excellent results in local control if the tumor is truly located and is currently the only curative option in most retroperitoneal solid tumors.

12.The laparoscopic approach of retroperitoneal tumors, which is still in the beginning, is generally only indicated if tumor carcinoma has been excluded.

Solid tumors up to 10 cm are rarely approached based on their position and size (lower), as well as by the relatively more precise character of the tumor delineation. Avoiding peritumoral metastatic seeding during preparation and exertion seems to be feasible through the use of a laparoscopic procedure without a mechanical retractor (laparolift).

13.*The benefits of surgical treatment of primary retroperitoneal tumors are evidenced by the low rate of postoperative complications in these tumors (haemorrhage, lymphoma), especially in patients with associated conditions, but also by lower mortality than in WHO statistics*.

The data from this study outlines the idea of beneficial results through the surgical treatment of retroperitoneal tumors.

14. Recurrence risk assessment, based on the degree of differentiation, size and location of the retroperitoneal tumor may guide the choice of the follow-up strategy.

Patients who have been identified with high-risk tumors generally recur in the first 2-3 years, while low-risk patients may relapse much later. Early detection of relapses may have prognostic implications, metastasis being asymptomatic at the stages in which they are resolved. Thus, control investigations can focus on relapsing sites (liver, lung, kidneys).

15. The rational approach of the patient with retroperitoneal tumor is one multidisciplinary. Potential benefits will be appreciated by tumor growth and realistic targets of care will be set to primarily seek quality of life.

Although the patient is the final referee, the family and therapist have to participate and communicate during the therapeutic decision-making process. When healing or diminishing disease progression can not be achieved, competent palliative treatment must become the goal of the physician.