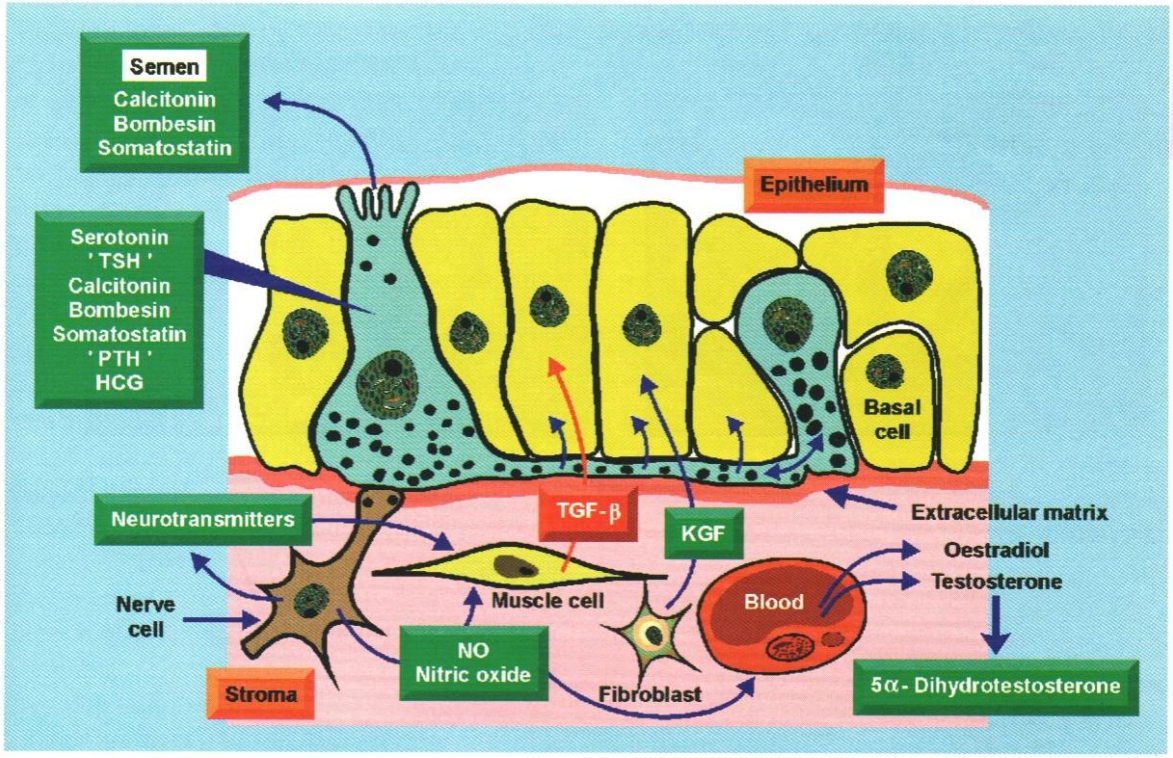
НИИ урологии и интервенционной радиологии имени Н.А. Лопаткина

Патоморфологические и моллекулярно-генетические аспекты нейроэндокринной трансформации рака предстательной железы.

Ефремов Г.Д., Михайленко Д.С., Сивков А.В., Кешишев Н.Г., Ковченко Г.А.

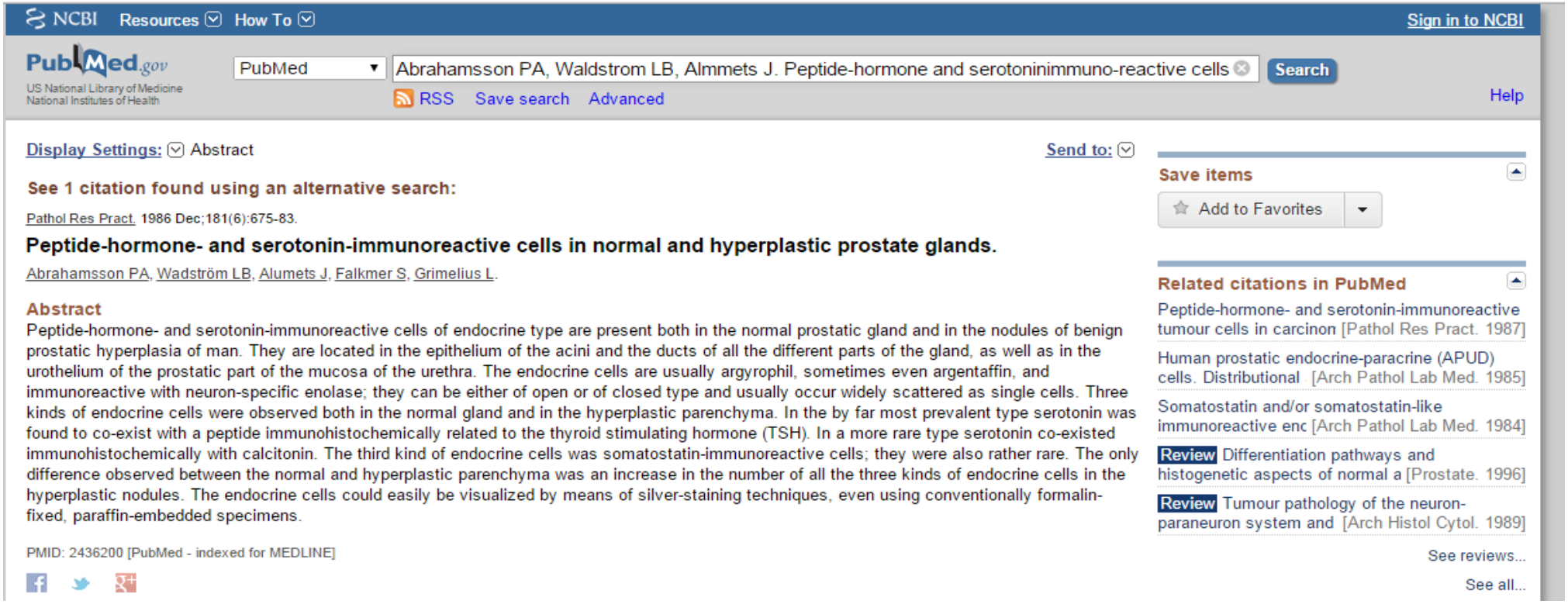
Москва, 2016

Существуют ли нейроэндокринные клетки в предстательной железе?



Нейроэндокринные клетки (НЭК) предстательной железы

В норме, наряду с клетками базального и секреторного эпителия, НЭК всегда присутствуют в предстательной железе. НЭК, базальный и секреторный эпителий имеют общее происхождение (плюрипотентные стволовые клетки).



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Pathol Res Pract. 1986 Dec;181(6):675-83.

Peptide-hormone- and serotonin-immunoreactive cells in normal and hyperplastic prostate glands.

Abrahamsson PA, Wadström LB, Alumets J, Falkmer S, Grimelius L.

Abstract

Peptide-hormone- and serotonin-immunoreactive cells of endocrine type are present both in the normal prostatic gland and in the nodules of benign prostatic hyperplasia of man. They are located in the epithelium of the acini and the ducts of all the different parts of the gland, as well as in the urothelium of the prostatic part of the mucosa of the urethra. The endocrine cells are usually argyrophil, sometimes even argentaffin, and immunoreactive with neuron-specific enolase; they can be either of open or of closed type and usually occur widely scattered as single cells. Three kinds of endocrine cells were observed both in the normal gland and in the hyperplastic parenchyma. In the by far most prevalent type serotonin was found to co-exist with a peptide immunohistochemically related to the thyroid stimulating hormone (TSH). In a more rare type serotonin co-existed immunohistochemically with calcitonin. The third kind of endocrine cells was somatostatin-immunoreactive cells; they were also rather rare. The only difference observed between the normal and hyperplastic parenchyma was an increase in the number of all the three kinds of endocrine cells in the hyperplastic nodules. The endocrine cells could easily be visualized by means of silver-staining techniques, even using conventionally formalin-fixed, paraffin-embedded specimens.

PMID: 2436200 [PubMed - indexed for MEDLINE]

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Peptide-hormone- and serotonin-immunoreactive tumour cells in carcinon [Pathol Res Pract. 1987]

Human prostatic endocrine-paracrine (APUD) cells. Distributional [Arch Pathol Lab Med. 1985]

Somatostatin and/or somatostatin-like immunoreactive enc [Arch Pathol Lab Med. 1984]

Review Differentiation pathways and histogenetic aspects of normal a [Prostate. 1996]

Review Tumour pathology of the neuron-paraneuron system and [Arch Histol Cytol. 1989]

See reviews...

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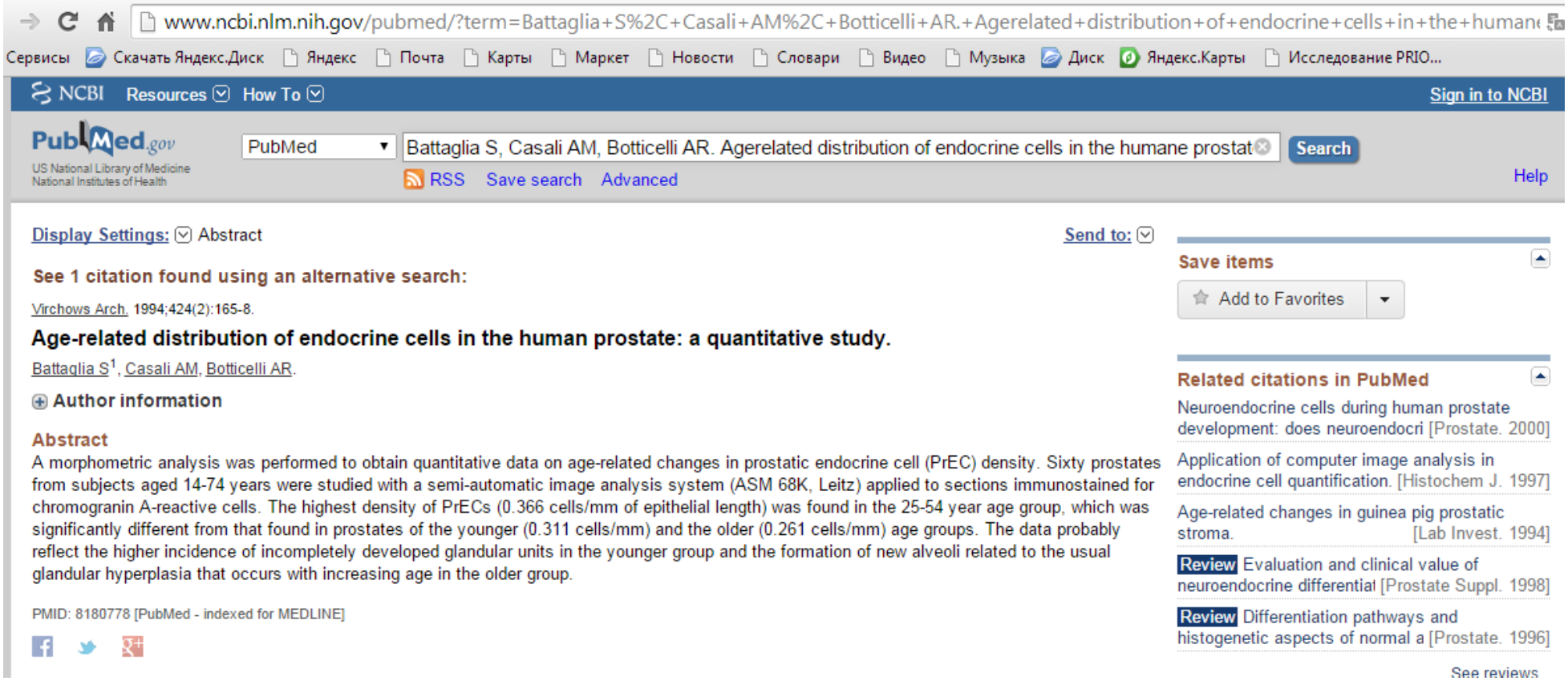
Нейроэндокринные клетки предстательной железы

Нейроэндокринные клетки (НЭК) в норме присутствуют во всех отделах предстательной железы при рождении. Их число увеличивается во время пубертатного периода.

Нейроэндокринные клетки предстательной железы

После пубертатного периода количество НЭК уменьшается, их количество остается на одном и том же уровне с 25 до 54 лет и составляет не более 1% эпителиальных клеток.



www.ncbi.nlm.nih.gov/pubmed/?term=Battaglia+S%2C+Casali+AM%2C+Botticelli+AR.+Agerelated+distribution+of+endocrine+cells+in+the+human

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Virchows Arch. 1994;424(2):165-8.

Age-related distribution of endocrine cells in the human prostate: a quantitative study.

Battaglia S[1], Casali AM, Botticelli AR.

Author information

Abstract

A morphometric analysis was performed to obtain quantitative data on age-related changes in prostatic endocrine cell (PrEC) density. Sixty prostates from subjects aged 14-74 years were studied with a semi-automatic image analysis system (ASM 68K, Leitz) applied to sections immunostained for chromogranin A-reactive cells. The highest density of PrECs (0.366 cells/mm of epithelial length) was found in the 25-54 year age group, which was significantly different from that found in prostates of the younger (0.311 cells/mm) and the older (0.261 cells/mm) age groups. The data probably reflect the higher incidence of incompletely developed glandular units in the younger group and the formation of new alveoli related to the usual glandular hyperplasia that occurs with increasing age in the older group.

PMID: 8180778 [PubMed - indexed for MEDLINE]

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Neuroendocrine cells during human prostate development: does neuroendocri [Prostate. 2000]

Application of computer image analysis in endocrine cell quantification. [Histochem J. 1997]

Age-related changes in guinea pig prostatic stroma. [Lab Invest. 1994]

Review Evaluation and clinical value of neuroendocrine differential [Prostate Suppl. 1998]

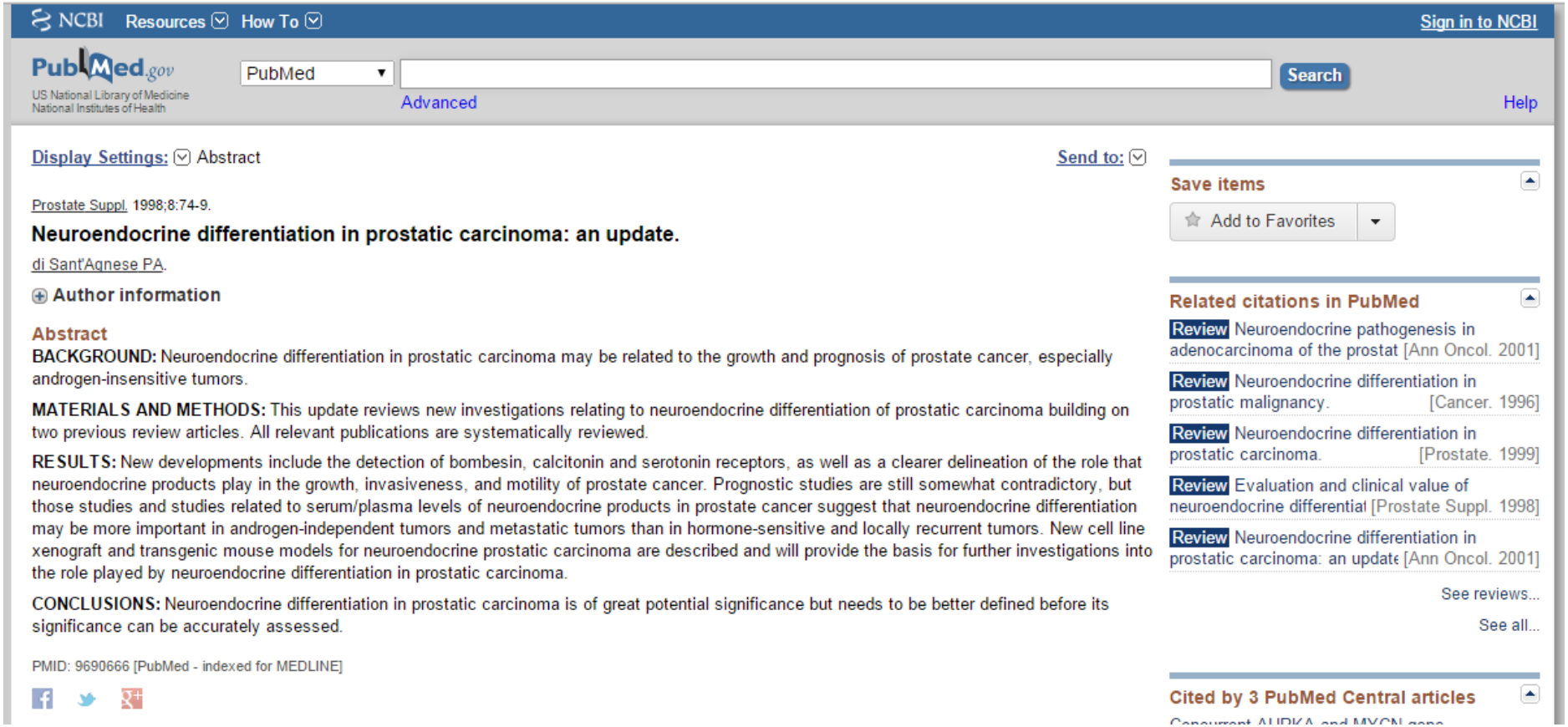
Review Differentiation pathways and histogenetic aspects of normal a [Prostate. 1996]

See reviews

Battaglia S. et al., 1994

Нейроэндокринные клетки предстательной железы

НЭК чаще всего располагаются в периуретральной зоне, нежели в периферической зоне предстательной железы.



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Prostate Suppl. 1998;8:74-9.

Neuroendocrine differentiation in prostatic carcinoma: an update.

di Sant'Agnese PA.

Author information

Abstract

BACKGROUND: Neuroendocrine differentiation in prostatic carcinoma may be related to the growth and prognosis of prostate cancer, especially androgen-insensitive tumors.

MATERIALS AND METHODS: This update reviews new investigations relating to neuroendocrine differentiation of prostatic carcinoma building on two previous review articles. All relevant publications are systematically reviewed.

RESULTS: New developments include the detection of bombesin, calcitonin and serotonin receptors, as well as a clearer delineation of the role that neuroendocrine products play in the growth, invasiveness, and motility of prostate cancer. Prognostic studies are still somewhat contradictory, but those studies and studies related to serum/plasma levels of neuroendocrine products in prostate cancer suggest that neuroendocrine differentiation may be more important in androgen-independent tumors and metastatic tumors than in hormone-sensitive and locally recurrent tumors. New cell line xenograft and transgenic mouse models for neuroendocrine prostatic carcinoma are described and will provide the basis for further investigations into the role played by neuroendocrine differentiation in prostatic carcinoma.

CONCLUSIONS: Neuroendocrine differentiation in prostatic carcinoma is of great potential significance but needs to be better defined before its significance can be accurately assessed.

PMID: 9690666 [PubMed - indexed for MEDLINE]

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Review Neuroendocrine pathogenesis in adenocarcinoma of the prostat [Ann Oncol. 2001]
Review Neuroendocrine differentiation in prostatic malignancy. [Cancer. 1996]
Review Neuroendocrine differentiation in prostatic carcinoma. [Prostate. 1999]
Review Evaluation and clinical value of neuroendocrine differential [Prostate Suppl. 1998]
Review Neuroendocrine differentiation in prostatic carcinoma: an update [Ann Oncol. 2001]
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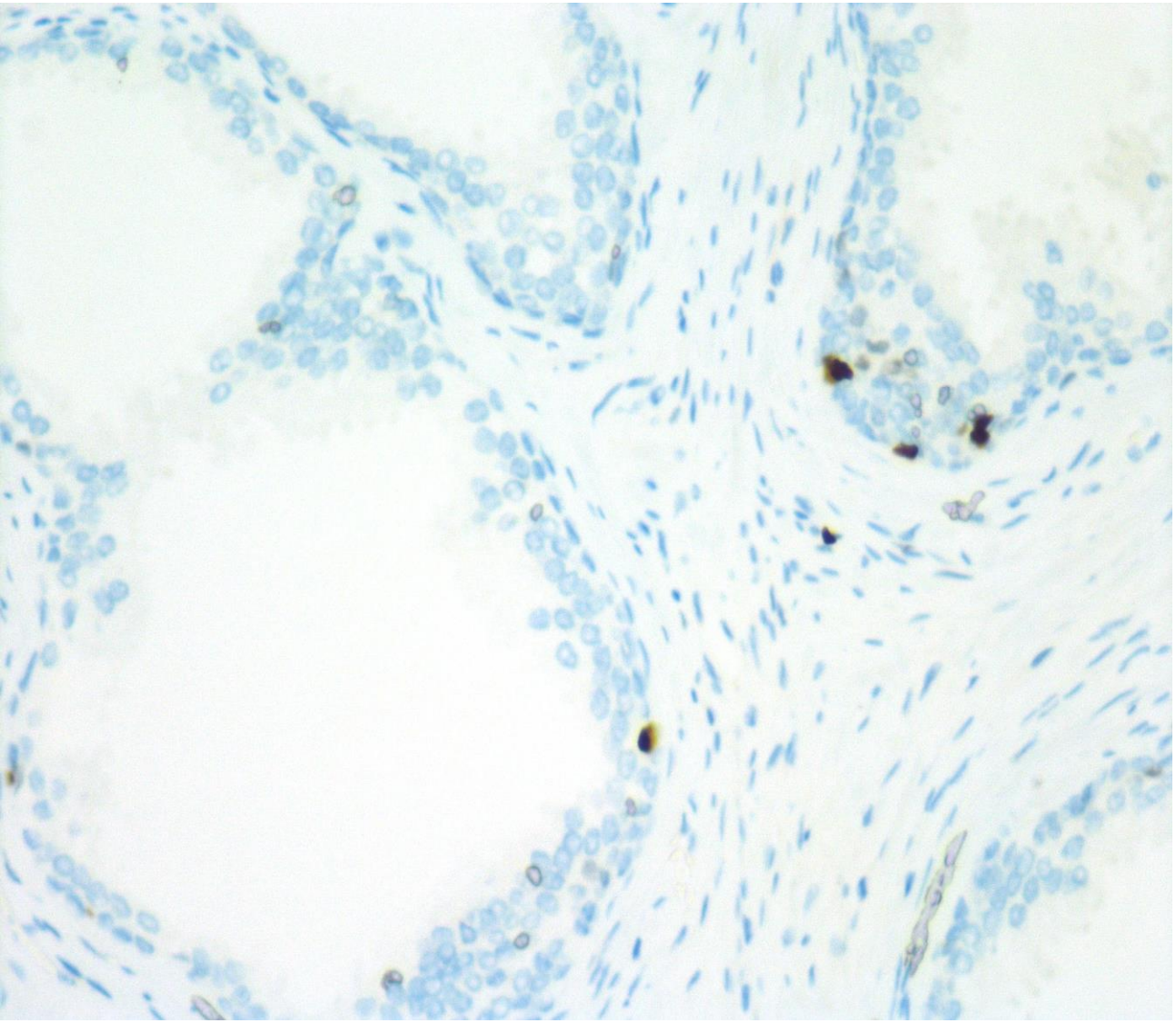
DiSant'Agnese P. A. et al., 1998

Нейроэндокринные клетки



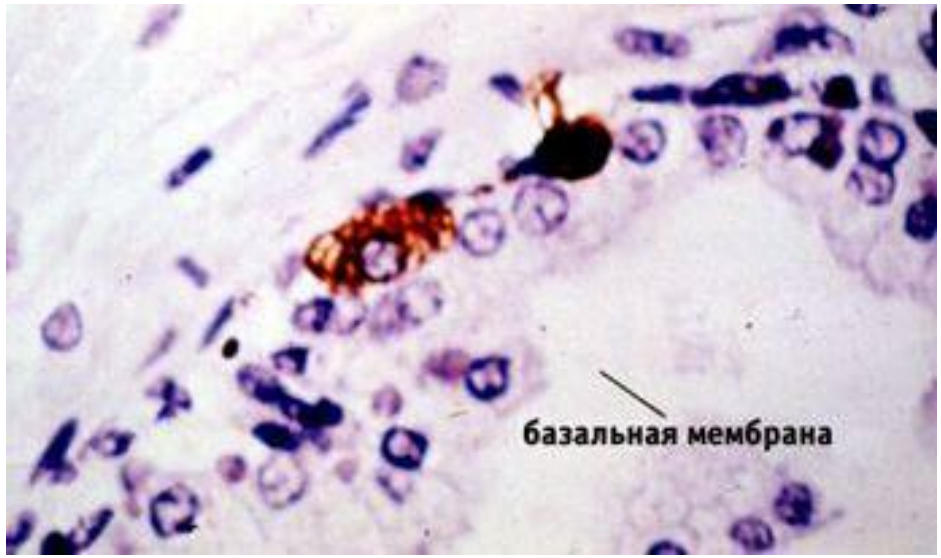
- НЭК содержат секреторные гранулы;
- НЭК обладают эндокринной секрецией;
- НЭК часто обладают аргинофильной и даже аргентофильной окраской;
- НЭК экспрессируют нейроэндокринные маркеры (хромогранин А, синаптофизин и т.д.)
- НЭК не содержат андрогеновых рецепторов.

Abrahamsson P.A., 1986; Nakada S.Y., 1993

Нейроэндокринные клетки предстательной железы

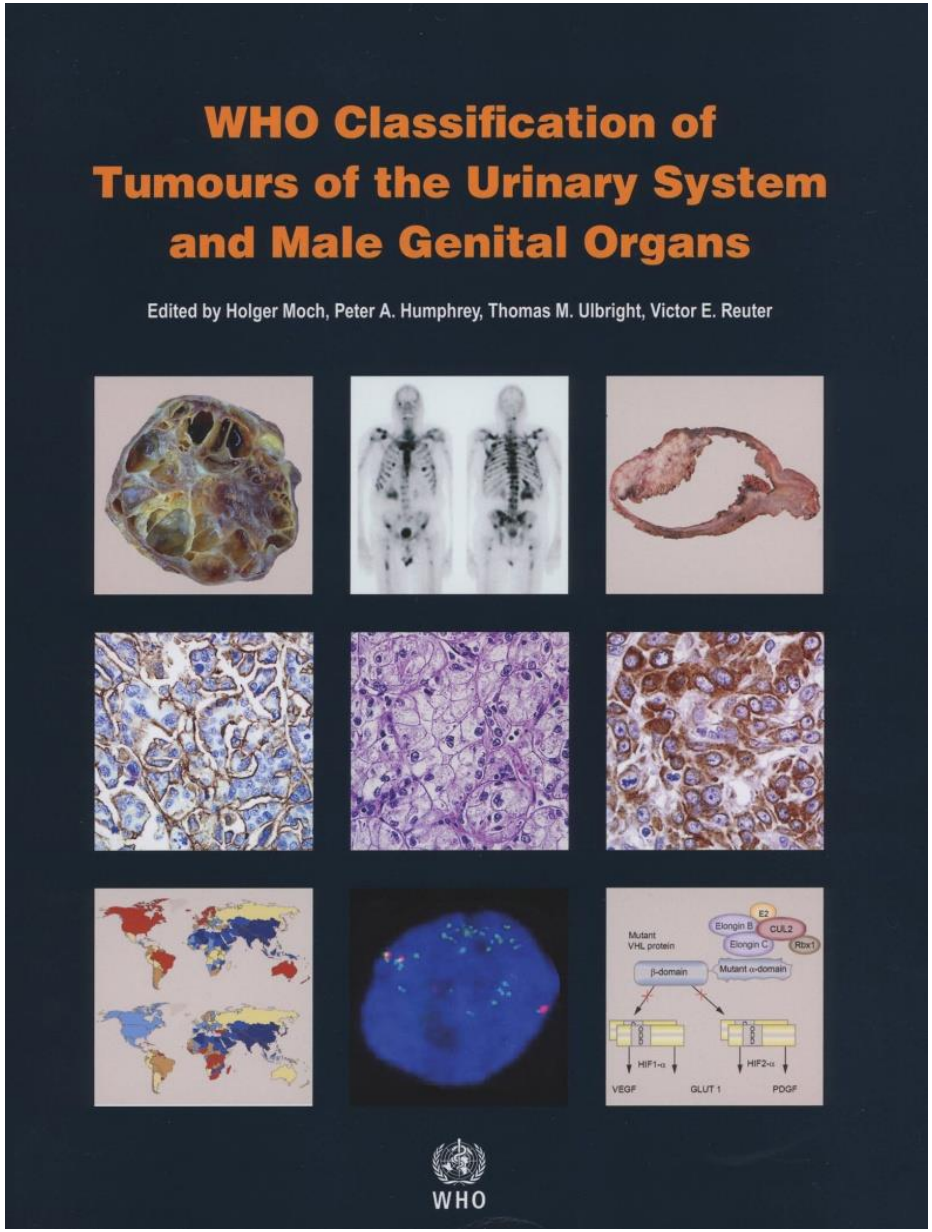
НЭК секретируют:

- Хромогранин – А (Cg-A)
- Серотонин
- Cg-B
- Секретогранин (Cg-C)
- Кальцитонин
- Катакальцин
- Бомбензин
- Соматостатин и др.



Sciarra A et al., 2011

ВОЗ


WHO Classification of
Tumours of the Urinary System
and Male Genital Organs
Edited by Holger Moch, Peter A. Humphrey, Thomas M. Ulbright, Victor E. Reuter
Mutant
VHL protein
E2
Elongin B
CUL2
Elongin C
Rbx1
β-domain
Mutant α-domain
HIF1-α
HIF2-α
VEGF
GLUT 1
PDGF
WHO

Группа нейроэндокринных опухолей

- Аденокарцинома с нейроэндокринной дифференцировкой (8574/3)
- Высокодифференцированная нейроэндокринная опухоль (8240/3)
- Мелкоклеточный нейроэндокринный рак (8041/3)
- Крупноклеточный нейроэндокринный рак (8013/3).

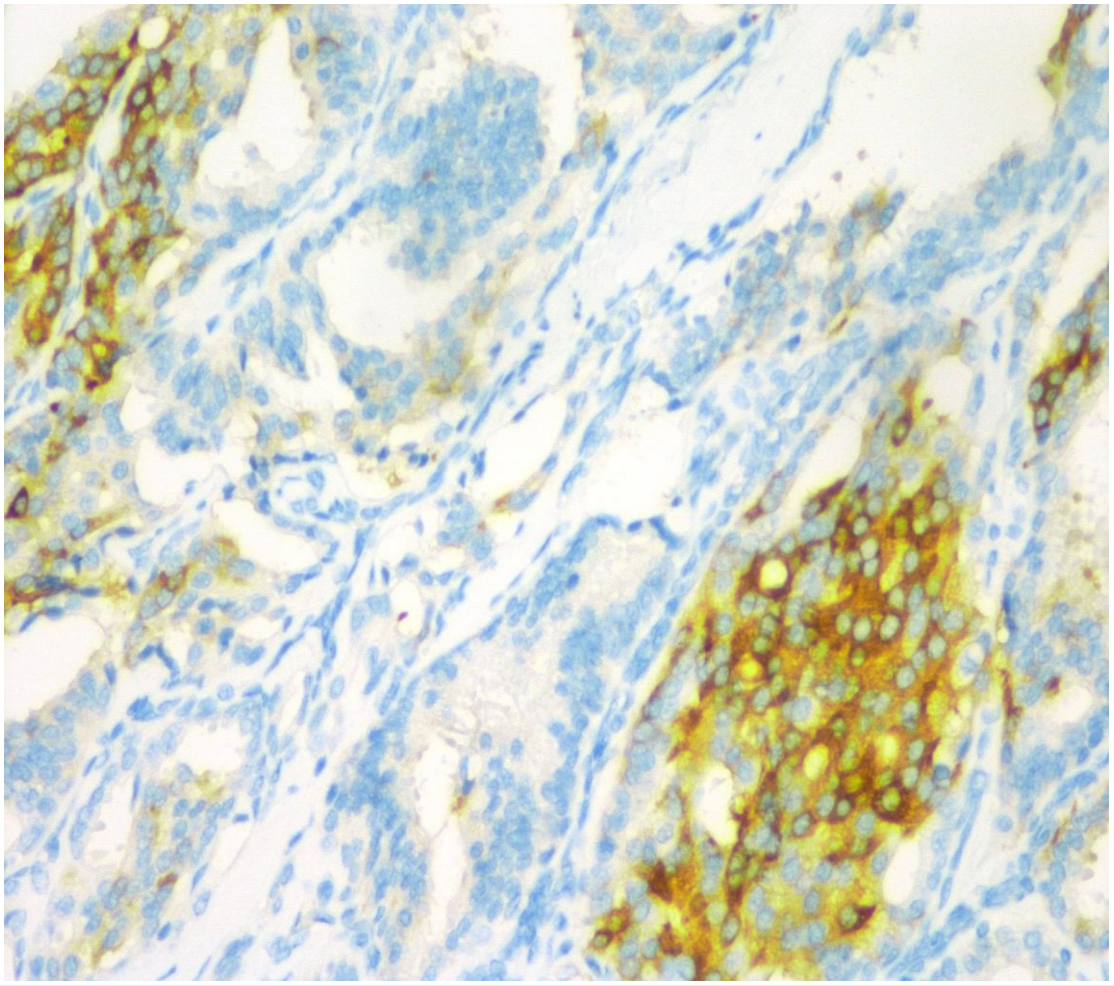
Группа нейроэндокринных опухолей

- Не замещают ткань полностью (образуют скопления – «гнезда»)
- В основном встречаются в сочетании с ацинарной аденокарциномой.
- Сложны в диагностике, т.к.
  - могут имитировать другие формы рака предстательной железы
  - использование нейроэндокринных маркеров не рекомендовано в рутинной практике.

АДЕНОКАРЦИНОМА С НЕЙРОЭНДОКРИННОЙ ДИФФЕРЕНЦИРОВКОЙ (8574/3)

- Аденокарцинома с нейроэндокринной дифференцировкой
- Аденокарцинома с клетками Панета

АДЕНОКАРЦИНОМА С НЕЙРОЭНДОКРИННОЙ ДИФФЕРЕНЦИРОВКОЙ

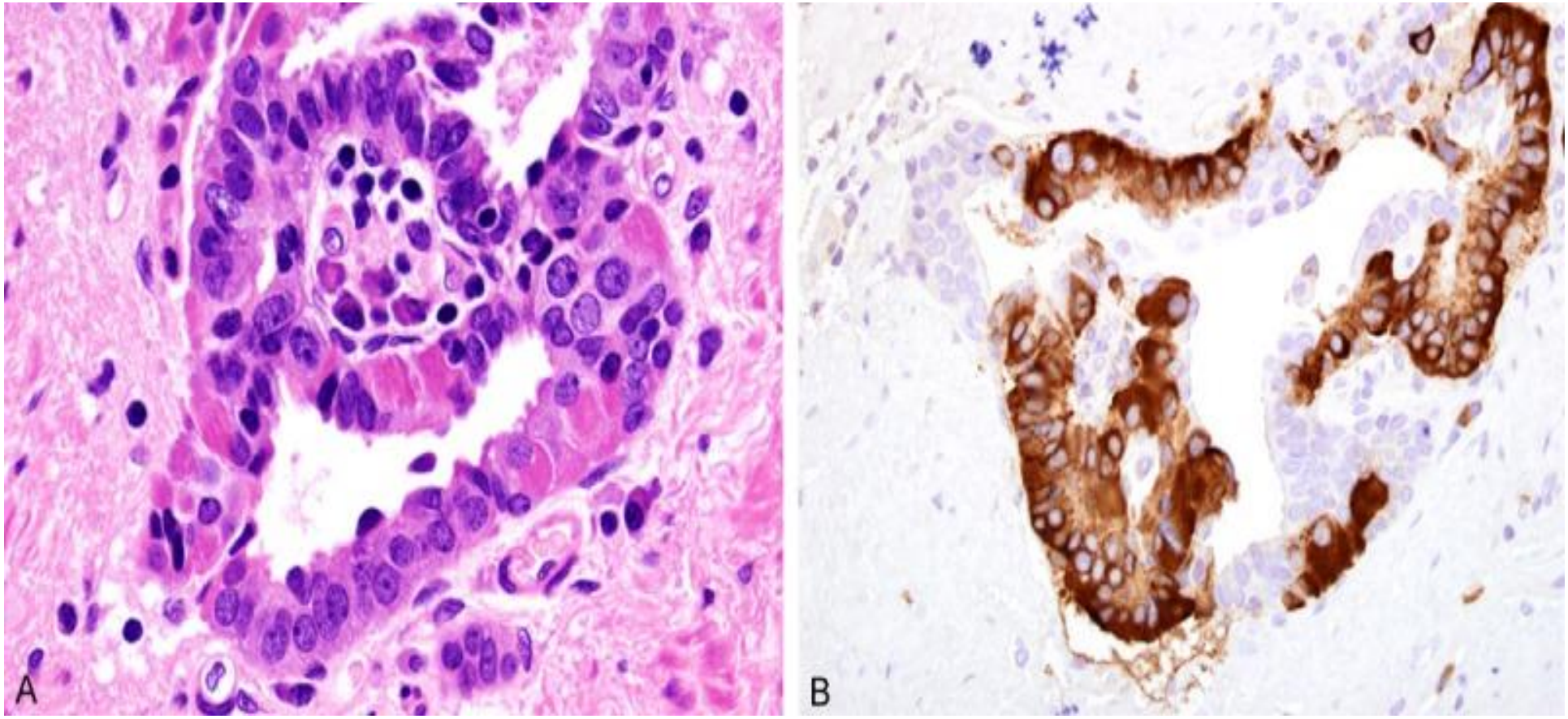


Встречается

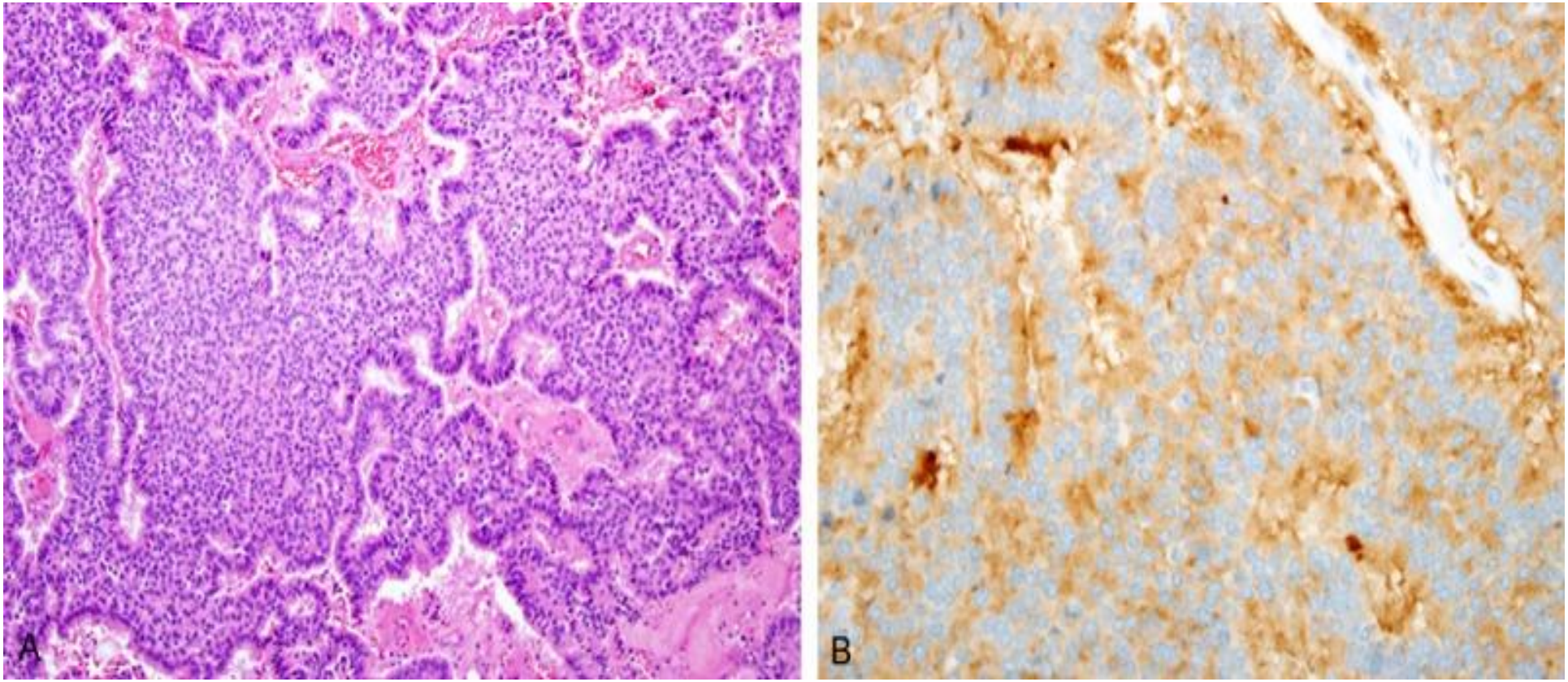
в 10 - 25%

ГРРПЖ

АДЕНОКАРЦИНОМА С КЛЕТКАМИ ПАНЕТА

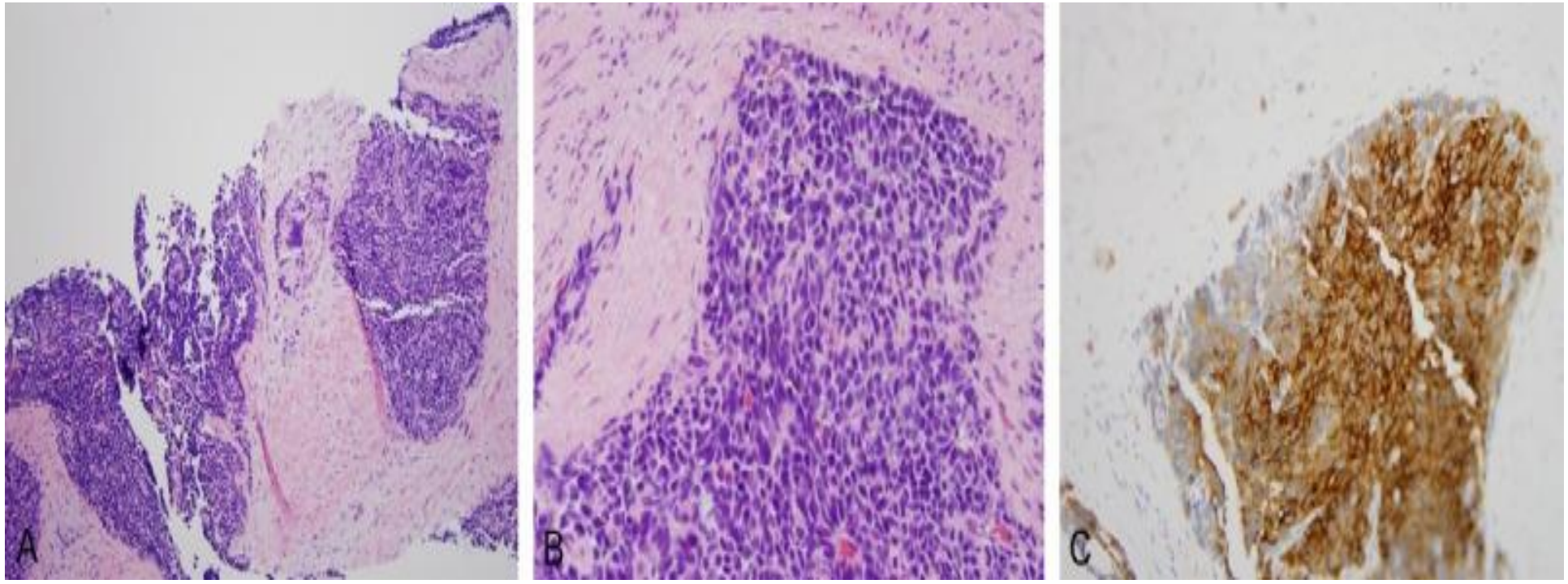


ВЫСОКОДИФФЕРЕНЦИРОВАННАЯ НЕЙРОЭНДОКРИННАЯ ОПУХОЛЬ



Термин «карциноидная опухоль» не рекомендован к использованию

МЕЛКОКЛЕТОЧНЫЙ НЕЙРОЭНДОКРИННЫЙ РАК

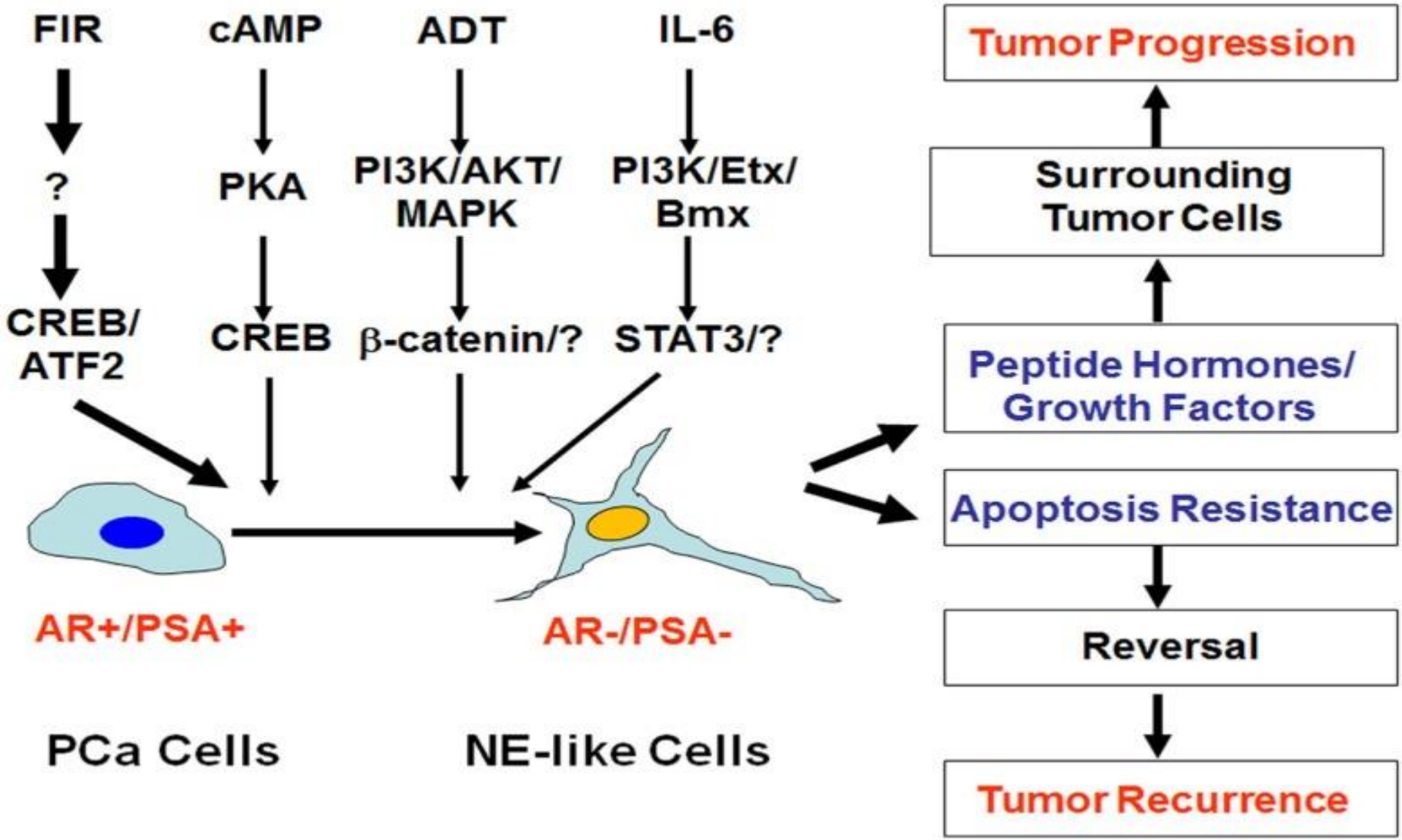


Встречается от 0,5 до 1% опухолей предстательной железы

ГИПОТЕЗЫ ВОЗНИКНОВЕНИЯ

- Пролиферация уже имеющихся нейроэндокринных клеток
- Дифференцировка de novo стволовых клеток
- Трансдифференцировка клеток первичной опухоли

ПУТИ РАЗВИТИЯ



ДИАГНОСТИКА

Основной метод диагностики ИГХ-исследование (хромогранин А, синаптофизин, CD56, TTF-1)

- **CD56 наиболее чувствительный, но наименее специфичный маркер**
- **Хромогранин А наиболее специфичный**
- **Наилучшее отношение чувствительности и специфичности отмечается у синаптофизина**
- **TTF 1 экспрессируется в более 50% случаев мелкоклеточного РПЖ.**

ПЕРСПЕКТИВЫ ДИАГНОСТИКИ

Амплификация онкогенов *AURKA* и *MYCN*

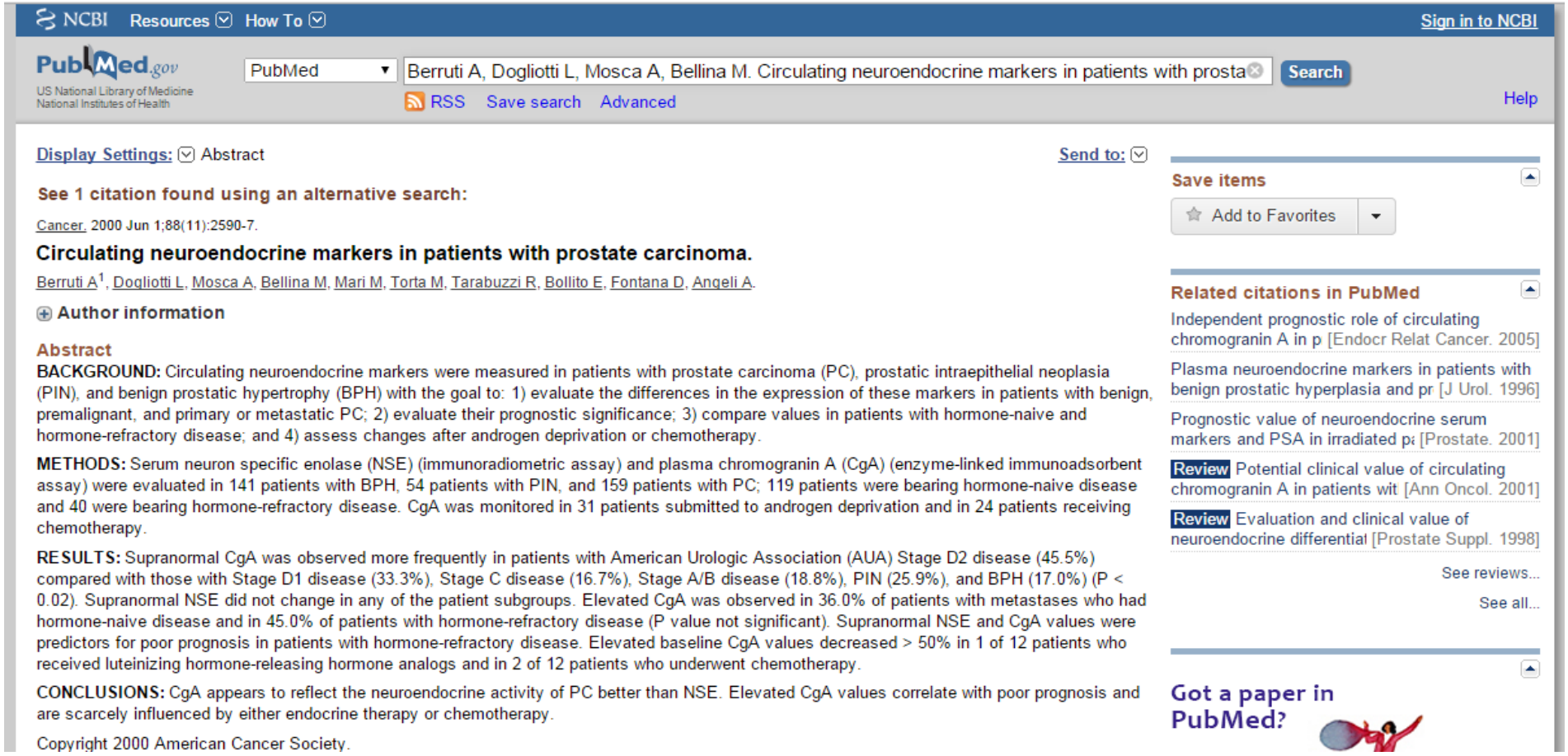
- гиперэкспрессия в 40-80% опухолей с НЭД и лишь 5% в первичных РПЖ

- не экспрессируются при доброкачественной гиперплазии

- ассоциирована с возникновением очагов НЭД в ходе дальнейшего развития РПЖ

Уровень cXrA при заболеваниях предстательной железы

Повышение уровня cXrA выявлено у 36% больных ГЧРПЖ и у 45% больных ГРРПЖ (p ‹ 0,05).



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Cancer. 2000 Jun 1;88(11):2590-7.

Circulating neuroendocrine markers in patients with prostate carcinoma.

Berruti A[1], Dogliotti L, Mosca A, Bellina M, Mari M, Torta M, Tarabuzzi R, Bollito E, Fontana D, Angeli A.

Author information

Abstract

BACKGROUND: Circulating neuroendocrine markers were measured in patients with prostate carcinoma (PC), prostatic intraepithelial neoplasia (PIN), and benign prostatic hypertrophy (BPH) with the goal to: 1) evaluate the differences in the expression of these markers in patients with benign, premalignant, and primary or metastatic PC; 2) evaluate their prognostic significance; 3) compare values in patients with hormone-naive and hormone-refractory disease; and 4) assess changes after androgen deprivation or chemotherapy.

METHODS: Serum neuron specific enolase (NSE) (immunoradiometric assay) and plasma chromogranin A (CgA) (enzyme-linked immunoadsorbent assay) were evaluated in 141 patients with BPH, 54 patients with PIN, and 159 patients with PC; 119 patients were bearing hormone-naive disease and 40 were bearing hormone-refractory disease. CgA was monitored in 31 patients submitted to androgen deprivation and in 24 patients receiving chemotherapy.

RESULTS: Supranormal CgA was observed more frequently in patients with American Urologic Association (AUA) Stage D2 disease (45.5%) compared with those with Stage D1 disease (33.3%), Stage C disease (16.7%), Stage A/B disease (18.8%), PIN (25.9%), and BPH (17.0%) (P < 0.02). Supranormal NSE did not change in any of the patient subgroups. Elevated CgA was observed in 36.0% of patients with metastases who had hormone-naive disease and in 45.0% of patients with hormone-refractory disease (P value not significant). Supranormal NSE and CgA values were predictors for poor prognosis in patients with hormone-refractory disease. Elevated baseline CgA values decreased > 50% in 1 of 12 patients who received luteinizing hormone-releasing hormone analogs and in 2 of 12 patients who underwent chemotherapy.

CONCLUSIONS: CgA appears to reflect the neuroendocrine activity of PC better than NSE. Elevated CgA values correlate with poor prognosis and are scarcely influenced by either endocrine therapy or chemotherapy.

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Independent prognostic role of circulating chromogranin A in p [Endocr Relat Cancer. 2005]

Plasma neuroendocrine markers in patients with benign prostatic hyperplasia and pr [J Urol. 1996]

Prognostic value of neuroendocrine serum markers and PSA in irradiated pa [Prostate. 2001]

Review Potential clinical value of circulating chromogranin A in patients wit [Ann Oncol. 2001]

Review Evaluation and clinical value of neuroendocrine differential [Prostate Suppl. 1998]

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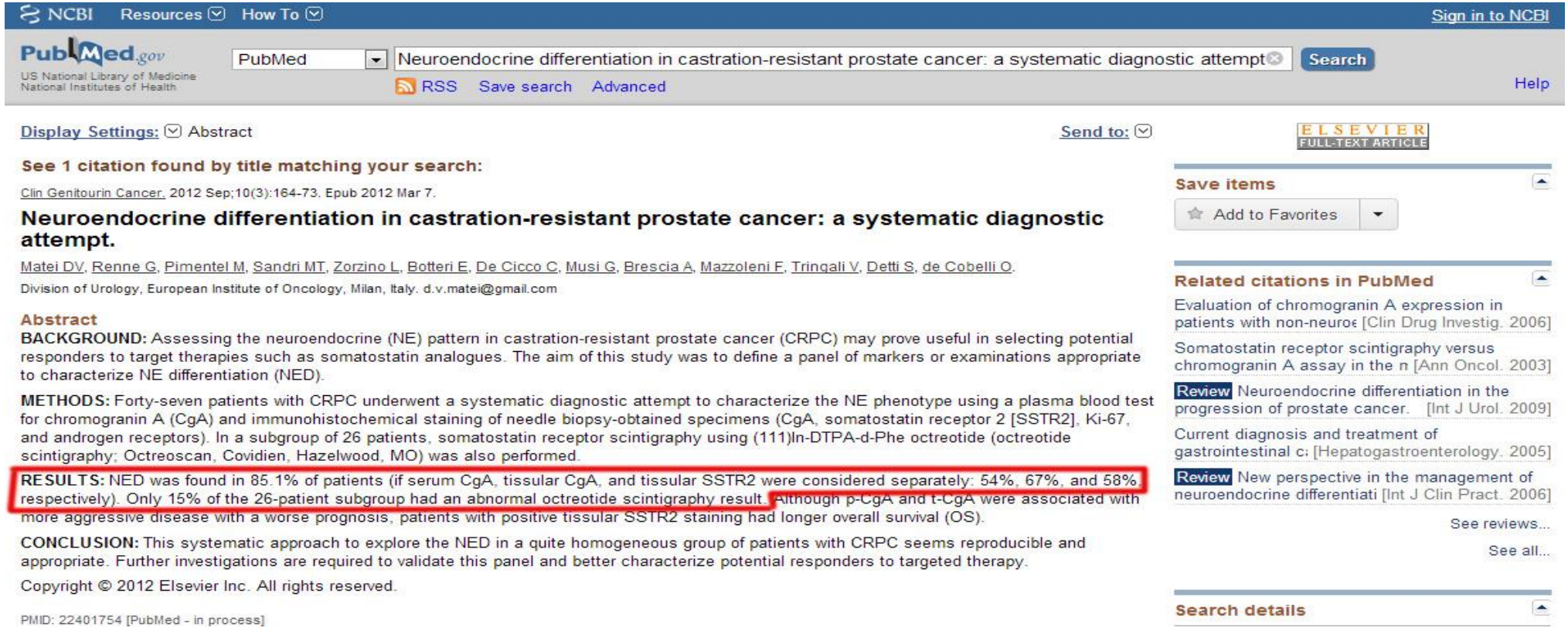
Кастрационно-резистентный РПЖ и нейроэндокринная дифференцировка

НЭД выявлена у 85,1% при КРРПЖ: повышение ХгА в сыворотке крови (54%), тканевого ХгА (67%) и рецепторов к соматостатину SSTR2 (58%)



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PubMed | Neuroendocrine differentiation in castration-resistant prostate cancer: a systematic diagnostic attempt | Search

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Clin Genitourin Cancer. 2012 Sep;10(3):164-73. Epub 2012 Mar 7.

Neuroendocrine differentiation in castration-resistant prostate cancer: a systematic diagnostic attempt.

Matei DV, Renne G, Pimentel M, Sandri MT, Zorzino L, Botteri E, De Cicco C, Musi G, Brescia A, Mazzoleni F, Tringali V, Detti S, de Cobelli O.

Division of Urology, European Institute of Oncology, Milan, Italy. d.v.matei@gmail.com

Abstract

BACKGROUND: Assessing the neuroendocrine (NE) pattern in castration-resistant prostate cancer (CRPC) may prove useful in selecting potential responders to target therapies such as somatostatin analogues. The aim of this study was to define a panel of markers or examinations appropriate to characterize NE differentiation (NED).

METHODS: Forty-seven patients with CRPC underwent a systematic diagnostic attempt to characterize the NE phenotype using a plasma blood test for chromogranin A (CgA) and immunohistochemical staining of needle biopsy-obtained specimens (CgA, somatostatin receptor 2 [SSTR2], Ki-67, and androgen receptors). In a subgroup of 26 patients, somatostatin receptor scintigraphy using (111)In-DTPA-d-Phe octreotide (octreotide scintigraphy; Octreoscan, Covidien, Hazelwood, MO) was also performed.

RESULTS: NED was found in 85.1% of patients (if serum CgA, tissular CgA, and tissular SSTR2 were considered separately: 54%, 67%, and 58%, respectively). Only 15% of the 26-patient subgroup had an abnormal octreotide scintigraphy result. Although p-CgA and t-CgA were associated with more aggressive disease with a worse prognosis, patients with positive tissular SSTR2 staining had longer overall survival (OS).

CONCLUSION: This systematic approach to explore the NED in a quite homogeneous group of patients with CRPC seems reproducible and appropriate. Further investigations are required to validate this panel and better characterize potential responders to targeted therapy.

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PMID: 22401754 [PubMed - in process]

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Evaluation of chromogranin A expression in patients with non-neuroe [Clin Drug Investig. 2006]

Somatostatin receptor scintigraphy versus chromogranin A assay in the n [Ann Oncol. 2003]

Review Neuroendocrine differentiation in the progression of prostate cancer. [Int J Urol. 2009]

Current diagnosis and treatment of gastrointestinal c: [Hepatogastroenterology. 2005]

Review New perspective in the management of neuroendocrine differentiati [Int J Clin Pract. 2006]

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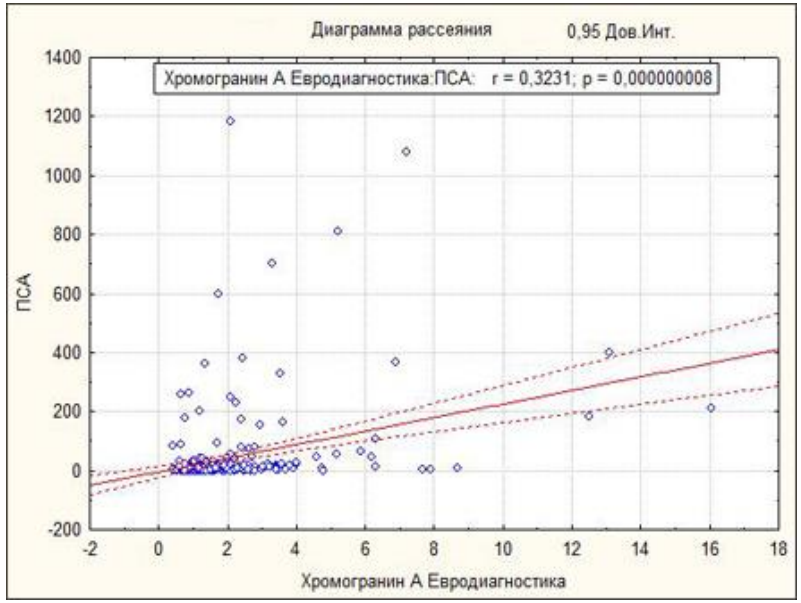
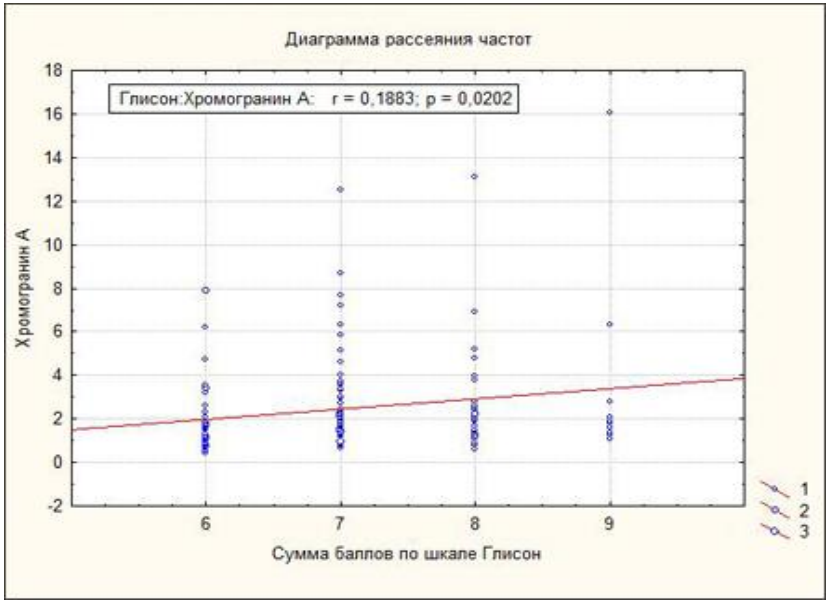
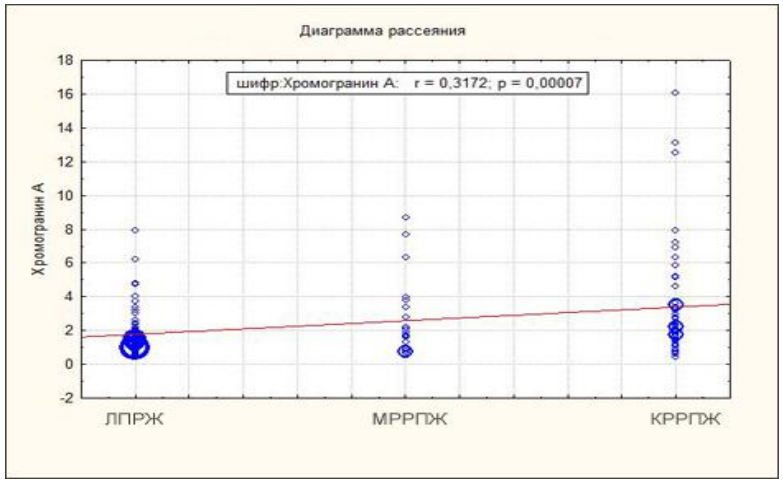
Matei D. et al. 2012

Эпидемиологическое исследование уровня cXгA в зависимости от диагноза, нмоль/л

Корреляция ХгА с ПСА, показателем Глисона и стадией РПЖ



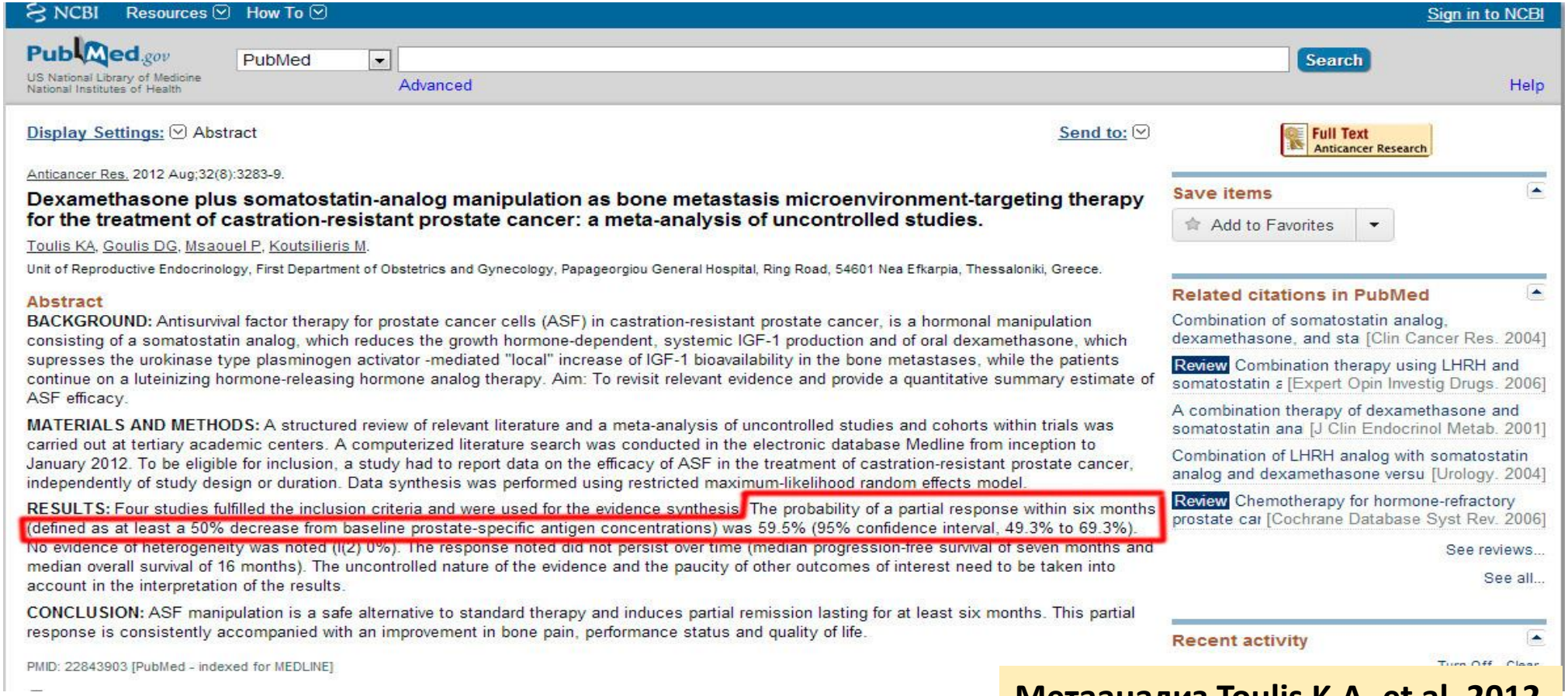




Выявлена корреляция сывороточного ХгА с уровнем ПСА, суммой баллов по шкале Глисоном и стадией РПЖ

Аналоги соматостатина

Гормональная терапия метастатического КРРПЖ в комплексе с аналогами соматостатина в течение 6 мес. позволяет добиться частичного (снижение ПСА на 50%) ответа в 59,5% (49,3-69,3%) случаев.



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Anticancer Res. 2012 Aug;32(8):3283-9.

Dexamethasone plus somatostatin-analog manipulation as bone metastasis microenvironment-targeting therapy for the treatment of castration-resistant prostate cancer: a meta-analysis of uncontrolled studies.

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Abstract

BACKGROUND: Antisurvival factor therapy for prostate cancer cells (ASF) in castration-resistant prostate cancer, is a hormonal manipulation consisting of a somatostatin analog, which reduces the growth hormone-dependent, systemic IGF-1 production and of oral dexamethasone, which supresses the urokinase type plasminogen activator -mediated "local" increase of IGF-1 bioavailability in the bone metastases, while the patients continue on a luteinizing hormone-releasing hormone analog therapy. Aim: To revisit relevant evidence and provide a quantitative summary estimate of ASF efficacy.

MATERIALS AND METHODS: A structured review of relevant literature and a meta-analysis of uncontrolled studies and cohorts within trials was carried out at tertiary academic centers. A computerized literature search was conducted in the electronic database Medline from inception to January 2012. To be eligible for inclusion, a study had to report data on the efficacy of ASF in the treatment of castration-resistant prostate cancer, independently of study design or duration. Data synthesis was performed using restricted maximum-likelihood random effects model.

RESULTS: Four studies fulfilled the inclusion criteria and were used for the evidence synthesis. The probability of a partial response within six months (defined as at least a 50% decrease from baseline prostate-specific antigen concentrations) was 59.5% (95% confidence interval, 49.3% to 69.3%). No evidence of heterogeneity was noted (I(2) 0%). The response noted did not persist over time (median progression-free survival of seven months and median overall survival of 16 months). The uncontrolled nature of the evidence and the paucity of other outcomes of interest need to be taken into account in the interpretation of the results.

CONCLUSION: ASF manipulation is a safe alternative to standard therapy and induces partial remission lasting for at least six months. This partial response is consistently accompanied with an improvement in bone pain, performance status and quality of life.

PMID: 22843903 [PubMed - indexed for MEDLINE]

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Метаанализ Toulis K.A. et al. 2012

Повышение ХгА при заболеваниях, не связанных с предстательной железой

- НЭД опухоли желудочно-кишечного тракта
  - В 92% случаев при активной гастриноме;
  - В 60% случаев у больных с синдромом множественной эндокринной неоплазии 1 типа;
- Секретирующая/несекретирующие гормоны и амины НЭО поджелудочной железы
- Больные с синдромом множественной эндокринной неоплазии 1 типа
- Пациенты со сниженной функцией почек
- Атрофический гастрит
- Лечение ингибиторами протоновой помпы
- Опухоль мозгового слоя надпочечников
- Опухоль паращитовидных желез

Выводы

1. НЭД при РПЖ может быть одной из причин развития КРРПЖ;
2. ХгА является важным показателем выбора, прогнозирования и контроля эффекта лечения больных КРРПЖ, направленного на подавление активности нейро-эндокринных клеток опухоли с использованием пролонгированной формы октреотида-депо;
3. Назначение аналогов соматостатина у больных КРРПЖ с повышенным ХгА сыворотки крови является патогенетически обоснованным и позволяет добиться снижения ПСА у 71% пациентов.
4. Целесообразно включить в алгоритм обследования больных КРРПЖ определение ХгА сыворотки крови.

НИИ урологии и интервенционной радиологии имени Н.А. Лопаткина

Спасибо за внимание!